筑　波　大　学

博　士（医学）学　位　論　文

Long-term Outcomes of Patients with Unresectable Benign Meningioma Treated with Proton Beam Therapy

（手術治療が困難であった良性髄膜腫に対する陽子線治療の長期予後についての検討）

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Long-term Outcomes of Patients with Unresectable Benign Meningioma Treated with Proton Beam Therapy

Short Running: Proton beam therapy for benign meningioma

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Contets

Introduction

Meningioma is the most common nonglial primary intracranial tumor, accounting for approximately 30% of all primary central nervous system tumors [1-3]. Its incidence increases with age, with a peak at 40 years of age and a female-to-male ratio of approximately 2:1 [4, 5]. Regarding the location of tumors, 90% are within the supratentorial compartment; the sagittal sinus, the falx, the convexity, and the sphenoid ridge are the most common sites in descending order [4, 5].

Most meningiomas are benign; however, up to 15% are atypical and 2% are anaplastic according to the World Health Organization (WHO) histological criteria [6]. Surgical removal is the mainstay treatment [7,8]; however, it is sometimes difficult to achieve complete removal because of its complex shape or difficult location, especially given that it may involve vital structures such as the brain stem, cranial nerves, or major vessels [7,8,9]. Actually, cranial nerve deficits have been reported in 22-91% of patients who underwent surgical removal for petroclival meningiomas [10, 11, 12]. For the preservation of neurological functions in these difficult cases, intentional subtotal resection may be performed; however, it has been reported that the local recurrence rates are approximately 10%, 20%, and 25% at 5, 10, and 15 years after complete resection, and approximately 50%, 60%, and 70% at 5, 10, and 15 years after subtotal resection, respectively [13,14].

Postoperative radiotherapy has been reported to improve local control and overall survival rates in patients who undergo incomplete resection [15, 16, 17]. However, the long-term effects are not yet clear. It has been reported that proton beam therapy (PBT) can provide an excellent dose localization for relatively large or irregularly shaped tumors with a higher rate of preservation of healthy brain tissue compared to other photon therapies [18,19]. Here, we analyzed the clinical data of patients with unresectable benign meningiomas treated with PBT at our institute to verify its long-term efficacy.

Treatment Methods and Patients

Proton beam therapy

From 1986 to 1998, 10 patients with benign meningiomas were treated at the Particle Radiation Medical Science Center (PRMSC) where a booster synchrotron for physics research was used to generate 250 MeV proton beams [20]. Following that, from 2002 to 2017, 17 patients were treated at the Proton Medical Research Center (PMRC) using proton beams of 155–250 MeV generated by a synchrotron dedicated to medical use [21].

At the PRMSC, the accelerated proton beams were taken to the treatment rooms on demand; each was equipped with a horizontal or vertical beamline. The machine availability for PBT at this institute

was 3-3.5 hours per day, 27-30 weeks, with clustered periods of 9-10 weeks [20]. Based on this limited machine availability for PBT, we had to change the fraction size from 2.5 Gy to 4.0 Gy. When the total dose was insufficient conventional x-ray therapy was used for compensation. For treatment planning, computed tomographic (CT) images were obtained at 5 mm intervals in the treatment position. The contours of the target volume including tumor attachment (corresponding to clinical target volume: CTV) were manually outlined on serial CT sections displayed on a monitor, and the planned target volume (PTV) was made by overwriting on the same images by adding 2-3 mm margins to cover set-up errors. The proton beams were spread out and shaped with a ridge filter, double-scattering, multi-leaf collimators, and a custom-made bolus covering the target volume. The patient's irradiation position was adjusted using fluoroscopy before every treatment.

At the PMRC, the beams were delivered using a rotating gantry through one to three ports with coplanar angles [21]. Treatment planning for PBT was performed using CT images at 3-mm intervals in the treatment position. Similarly, the proton beams were spread out and shaped with a ridge filter, double-scattering, multi-leaf collimators, and a custom-made bolus covering the target volume. The proton beam was generally delivered from 2 directions, and all the fields were treated daily. The gross target volume (GTV) was defined as the area of contrast enhancement plus the tumor attachment on MRI, and the CTV was made by adding 5 mm margins to the tumor attachment to cover the area

where tumor cells are supposed to be infiltrated. In patients who received surgical resection, the CTV did not enclose the entire area of the initial tumor, but only the residual or recurrent site and the attachment. Finally, the PTV was obtained by adding 3 mm margins to the CTV to cover the setup error. Dose prescription to PTV was determined based on the following dose constraint on the organ at risk at our institute; D_{max}<6GyE at the lens, D_{max}<44GyE at the retina, D_{max}<50GyE at the optic nerve, the optic chiasm, and the whole brain stem (up to 60GyE when the irradiated volume is smaller in the pons).

Patients

The present clinical studies at the PRMSC and the PMRC were conducted according to the principles of the Helsinki Declaration [22] and approved by the Ethics Committee of our university. All patients provided written informed consent.

Reviewing the medical records, we identified 27 patients with benign meningiomas treated with PBT between 1986 and 2017 at both facilities. It was confirmed that none of them previously received any kind of cranial radiotherapy including stereotactic radiosurgery. Their characteristics are detailed in Table 1. In this study, we excluded pathologically diagnosed WHO grade II and III meningiomas

mainly because they were few and partly because we focused on the evaluation of long-term tumor control and the occurrence of malignant transformation or secondary malignancy after PBT.

At the PRMSC, the male-to-female ratio was 2:8, and the ages ranged from 31-74 years with a median of 54 years. Of 10 patients, 5 had recurrent cases after subtotal or total resection in whom a median interval between surgery and PBT ranged from 0.4 to 251.9 months with a median of 18.2 months, 3 had biopsy alone, and 2 did not undergo surgical intervention. Consequently, 8 patients had a histological diagnosis of meningioma of WHO grade I, and 2 cases were diagnosed as benign based on clinical observation and imaging by neurosurgeons and radiation oncologists. Seven patients were treated with PBT alone, and 3 patients were treated with PBT and conventional x-ray therapy for dose compensation. The tumor maximum diameter ranged from 15-100 mm, with a median of 38 mm. The anatomical sites were as follows: falx/parasagittal area in 2, parasellar in 1, tuberculum sellae in 1, optic nerve sheath in 3, sphenoidal ridge in 1, cerebellopontine angle in 1, middle cranial fossa in 1, and petroclival in 1. One patient had 2 lesions at different sites. The total dose ranged from 50.4 Gy to 66 Gy, and a median of 54 Gy was delivered to the target. The doses per fraction ranged from 1.8 Gy to 3.96 Gy, with a median of 2.27 Gy because the treatment schedule was based on the accelerator machine availability. For the same reason, the total dose was compensated by linear accelerator with a dose ranging from 10.8 Gy to 18.0 Gy in 3 patients. The relative biological effectiveness value (RBE)

for ^{60}Cobalt in the institute was determined as 1.0, based on biological experiments [23]. The treatment details are shown in Table 2.

At the PMRC, all 17 patients were treated with PBT alone. The male to female ratio was 6:11, and the age ranged from 8 to 78 years with a median age of 53 years. Of the 17 patients, 9 had recurrent cases after subtotal resection in whom a median interval between surgery and PBT ranged from 3.1 to 127.1 months with a median of 21.6 months, 1 had a biopsy, and 7 did not undergo a surgical procedure. Thus, 10 patients had a histological diagnosis of meningioma WHO grade I, and 7 were diagnosed as benign from clinical observation and imaging by both neurosurgeons and radiation oncologists. The tumor maximum diameter ranged from 20 to 95 mm with a median of 50 mm. The anatomical sites were as follows: falx/parasagittal area in 2, cavernous sinus in 2, parasellar in 1, olfactory groove in 1, sphenoidal ridge in 3, cerebellopontine angle in 1, middle cranial fossa in 3, tentorial in 3, and petroclival in 1. The CTV ranged from 5.8 to 295.5 cc, with a median of 46.3 cc. The administered doses to the target ranged from 45.0 to 61.2 GyE, with a median of 50.4 GyE. The doses per fraction ranged from 1.8 GyE to 2.0 GyE, with a median of 1.8 GyE. The RBE for 10 MV X-rays in the institute was determined to be 1.1 based on our biological experiments [24].

Evaluation and statistical analyses

The patients were followed-up through hospital visits, mail, or telephone calls to patients or their referring physicians. SPSS II for Windows (IBM, Chicago IL) was used for the statistical analysis. The overall survival and local control rates were calculated using the Kaplan-Meier method. The acute reactions were scored according to the Common Terminology Criteria for Adverse Events version 4.0 [25]. The late toxicities were scored according to the late effects of normal tissues-subjective, objective, management, and analytic scoring system [26].

Results

PRMSC

During the follow-up lasting between 3.8 and 31.6 years, with a median of 25.1 years, 4 patients were alive and 5 died of disease unrelated to treatment at the PRMSC. In August 2020, 4 patients had been followed-up for over 20 years, including 3 for over 30 years. The pre-existing symptoms improved in 4 patients, were stable in 5 patients, and deteriorated in 1 patient. One asymptomatic patient also showed no change. The clinical responses of the patients are summarized in Table 3.

One patient died of pneumonia 5.1 years after the occurrence of brainstem radiation necrosis that was observed 1.3 years after PBT. The death of the remaining 5 patients was not associated with PBT; one died of colon cancer at 29.7 years, one died of suffocation at 27.8 years, one died of femoral fracture at 21.8 years, one died of pneumonia at 13.8 years, and one died of acute myocardial infarction 3.8 years after PBT. Consequently, the 5-, 10-, 15-, 20-, and 30-year local control rates were 100%, and the 5-, 10-, 15-, 20-, and 30-year survival rates were 90.0, 80.0, 70.0, 70.0, and 36.0%, respectively (Fig 1, 2).

Concerning treatment-related toxicities, 10 types of grade I or II acute adverse effects were observed at the PRMSC as shown in Table 4; however, no patient needed to discontinue the treatment. For late toxicity greater than grade III, one patient suffered from brainstem radiation necrosis. This patient was a 68-year-old woman who had a right petroclival meningioma with a maximum diameter of 52 mm significantly compressing the brainstem. PBT was performed with 58 Gy (RBE = 1.0) in 29 fractions. Although the tumor was controlled, brainstem radiation necrosis developed 1.3 years after PBT. The patient suffered from the gradual progression of consciousness and cranial nerve disorders and died of pneumonia 5.1 years after PBT.

PMRC

During the follow-up lasting between 3.0 and 17.0 years at the PMRC, with a median of 10.5 years, 16 patients were alive and one died of disease unrelated to the treatment. Nine patients were followed-up for more than 10 years, including 4 with more than 15 years, in August 2020. The pre-existing symptoms improved in 5 patients, and they were stable in 12 patients. None of the patients showed deterioration including 2 patients who were asymptomatic before PBT. Their clinical responses are shown in Table 3. One died of pneumonia 10.5 years after PBT. Consequently, the 5-, 10-, and 15-year local control rates were all 94.1%. The 5-, 10-, and 15-year survival rates were 100, 100, and 88.9%, respectively (Fig 1, 2).

Concerning the treatment-related toxicities, 7 types of acute adverse effects were observed, as shown in Table 4; however, no patient needed to discontinue the treatment. To date, no late toxicity has been observed in this cohort.

One patient was not locally controlled by PBT. A sixty-year-old woman underwent partial resection of the right sphenoid wing meningioma spreading from the right middle fossa to the pterygopalatine fossa. Three years later, she underwent a second partial resection due to local recurrence followed by PBT of 50.4 GyE in 28 fractions using two oblique beams overlapping on the PVT which was set-upped by the same method mentioned above. At the time of PBT, the size of CTV was 122.5 cc including the infiltrative portion in the skull base. However, the tumor regrew mostly in the

pterygopalatine fossa. Thereafter, tumor resection was performed 3 times, and stereotactic radiotherapy with a Cyberknife (28Gy / 7Fr) was performed once. The pathological diagnosis of the tumor removed by these four surgeries was WHO grade I transitional meningioma, and malignant changes were not observed (Fig 3 a, b, c, d). Immunohistochemical stainings were also performed. EMA staining responds to epithelial tumors such as meningioma. It was positive in this case. MIB-1 index is a measure of proliferative capacity. It was 3.8% before PBT, 5.8% 2 years after PBT, 1.0% 3 years after PBT, 2.0% 5 years after PBT. And 5 years after PBT, hot spots showing 15% were observed for the first time. EMA staining and MIB-1 indexes are shown in Fig 4 a, b. In the last surgery, radical resection of the tumor in the right cavernous sinus including the carotid artery was performed, which unfortunately resulted in the ipsilateral massive cerebral infarction. This patient is now being hospitalized and the tumor was under observation.

Representative Cases

Case 1

A fifty-year-old woman with decreased visual acuity and right exophthalmos due to a tumor extending from the right sphenoid wing to the orbit was treated at the PRMSC (Fig 5 a) . Only the planning of PBT is shown in Fig 5 b. After a combination treatment of 48 Gy (RBE=1) in 24 fractions of PBT

using two orthogonal beams and 18 Gy in 10 fractions of linear accelerator (LINAC) using the similar two orthogonal x-ray beams, the tumor gradually decreased in size and enhancement effect (Fig 5 c). Although right blindness was unchanged, exophthalmos gradually improved, and the left visual acuity and visual field were maintained during the 22.4 years of follow-up. No adverse effects were observed.

Case 2

A fifty-one-year-old woman with a tentorial meningioma underwent partial tumor resection. However, she had reduced right visual acuity and sub-optimal ocular movement due to the regrowth of the tumor 10.6 years after the surgery (Fig 6 a, b). At the time of PBT at the PMRC, size of the CTV was 148.6 cc. Initially, 50.4 GyE in 28 fractions was delivered to the PTV, then the irradiation field was focused on the attachment part and irradiated up to 61.2 GyE in 34 fractions using one port. Only the initial planning of PBT is shown in Fig 6 c, d. The tumor gradually shrank and her visual field defect improved (Fig 6 e, f). She has been stable for 12.7 years after PBT.

Case 3

A fifty-three-year-old man with a tentorial meningioma spreading from the left middle fossa to the pterygopalatine fossa underwent partial intracranial tumor resection. However, he developed a left ocular movement disorder and left trigeminal neuralgia 1.9 years after surgery (Fig 7 a, b). At the time of PBT at the PMRC, size of the CTV was 158.6 cc. He was treated with PBT of 50.4 GyE in 28 fractions using two oblique beams overlapping on the PTV. After PBT (Fig 7 c, d), the intracranial tumor gradually shrank, and the trigeminal neuralgia improved remarkably (Fig 7 e, f), and the tumor has been controlled for the next 7.0 years.

Discussion

Although surgery is the gold standard therapy for meningioma, radical resection may not be possible because of the technical difficulty and high risk of morbidity and mortality [8-12]. Condra et al. reported that radiotherapy after subtotal resection improved cause-specific survival and the quality of life [13]. Later, Rogers et al. reviewed the results of external-beam radiation therapy (EBRT) either as an adjuvant or a primary therapy for meningiomas [27]. They mention that 5- to 10- year progression free survival (PFS) rates have ranged 80 to 100% with fractionated EBRT and from 75 to 100% with stereotactic radiosurgery (SRS). Although the results were comparable, fractionated EBRT appeared

to carry smaller risk of side effects compared with SRS [27]. Among various kinds of modalities of EBRT, PBT is advantageous for treating large or complex-shaped tumors especially for those adjacent to critical regions [19]. IMRT also gives excellent dose distribution with the avoidance of surrounding healthy organs [28, 29]; however, Kosaki et al reported PBT was superior to IMRT in reducing dose in the brainstem in patients with complex-shaped skull base meningiomas [30].

Studies on IMRT and PBT for benign meningiomas, from the literature, are summarized in Table 5. Although the number of patients included and the follow-up period vary, the treatment outcomes in these reports are similarly favorable. The descriptions on clinical observations including appearance of toxicities are as follows. In IMRT, Pirzkall et al. showed that pre-existing neurologic symptoms improved in 12 patients after a median follow-up of 3 years; the pre-existing pituitary dysfunction worsened in 1 patient, and preoperative low vision worsened in 1 patient [17]. Milker-Zabel et al. mention that worsening of preexisting neurologic symptoms was seen in 4.3%, and 2 patients developed new clinical symptoms such as worsening of hearing or trigeminal dysesthesia [28].

As for PBT, Wenkel et al. reported that 1 patient died of brainstem necrosis 22 months after treatment, and 8 patients suffered from late treatment-related toxicities of grade 3 or 4, including 4 patients with ophthalmologic toxicities. From these experiences, the optic apparatus constraints were determined to be 54 GyE [15]. Also, Weber et al. reported that 2 patients suffered from late visual

toxicities [31]. Noël et al. reported that 1 patient presented with complete hypophysis insufficiency after receiving a maximal dose of 60.6 GyE, and 1 patient experienced severe hearing loss after receiving a maximal dose of 59.4 GyE in the internal ear and cochlea [32]. Weber et al. reported that the cumulative 5-year grade 3 late toxicity-free survival rate was 84.5% [33]. Murray et al. reported that only 1 experienced acute grade 3 brain edema, and the 5-year grade 3 late toxicity-free survival rate was 89.1% [34]. Finally, El Shafie et al. reported that 2 patients had late side effects of grade 3 radio-necrosis, and 1 patient had late side effects of grade 3 asthenia secondary to hypopituitarism [35].

The treatment outcome of my study is almost comparable to other reports; however, the follow-up period of median 25.1 years at the PRMSC was significantly longer than others. Although the pre-existing symptoms improved in 4 patients and remained stable in 5 patients. One female patient with a large petroclival meningioma developed brainstem radiation necrosis 1.3 years after PBT of 58 Gy in 29 fractions with an RBE value of 1.0, as mentioned above. Retrospectively, the RBE might be higher in human brain tissue. In addition, it might have been even higher than expected because the distal end of the peak was located at the boundary between the tumor and brainstem [36]. At present, we treat patients using an RBE of 1.1, and a maximum dose of 60 GyE in 30 fractions and 54 GyE in 27 fractions at the surface and the center of the brainstem, respectively.

The induction of malignant transformation or secondary malignancy after radiotherapy for “benign” meningiomas is of great concern. Pollock et al. reported that malignant transformation occurred in 7 of 316 patients with meningiomas (2.2%) after single-fraction SRS with a median follow-up of 9 years. They insist that the risk of secondary tumors or malignant transformation after SRS is very low [37]. However, Ichimura et al. warned recently that postoperative radiotherapy using a gamma-knife or a linear accelerator induces malignant transformation during the recurrence of skull base meningiomas. They reported that the rate of malignant transformation in the patients with recurrence who received both radiotherapy and surgery was 57.1%, which was higher than that for surgery alone (18.2%) [38]. Regarding the induction of radiation-related secondary malignancies, Schneider et al. showed that the use of spot-scanned protons could reduce secondary cancer incidence by as much as 50% [39]. In addition, Dennis et al. reported that IMRT has a two-fold higher risk of secondary intracranial tumors as compared with proton therapy, and the benefit of proton therapy over IMRT may be more substantial in patients with tumors close to critical structures [40]. These findings are in good agreement with my results; there was no therapy-related malignancy or malignant transformation at the PRMSC and the PMRC with significantly longer follow-ups. These results may indicate that PBT may be a suitable modality for patients with unresectable large meningiomas with predictable long-term survival.

The risk of secondary cancer due to radiation induction depends on factors such as the modality and dose of radiation, the irradiation field, the irradiated part of the body, the inherent tissue sensitivity, the age at the time of irradiation, and so on. By using a physical property called Bragg peak that stops at the lesion site, radiation therapy localized to the lesion site becomes possible. Therefore, I consider that PBT can reduce the risk of therapy-related malignancy.

Regarding the difference in malignant transformation, I presume as follows. Tsuboi reviewed that protons have greater effects on gene expression compared to photons both in number of genes responding and the magnitude of the response [41]. According to his review, most significant differences were seen for genes related to apoptosis [42] and cell cycle and DNA damage response [43,44]. In addition, it has been reported that protons and photons differentially regulate gene expressions of pro-angiogenic genes [45], core genes involved in stem cell differentiation [44,46], extracellular matrix, and adhesion molecules [44,47], showing distinctly different transcriptome profiles between protons and photons. I consider that differences in gene expressions like those may suppress malignant transformation.

In my study at the PMRC, one female patient was not locally controlled by PBT, and she underwent multiple surgeries as mentioned above. Commins et al. reported that routine histological examination may fail to identify the subset of WHO grade I tumors that behave aggressively. They also mentioned

that an understanding of the genetic changes that underlie tumor progression will help in predicting the behavior of meningiomas [6]. Therefore, reliable biomarkers at the genome level have been sought because of incongruence between the clinical course and WHO grades. Mirian et al. reported that TERT-alt is an important biomarker for significantly higher risks of recurrence and death from meningiomas [48]. Further investigation is required.

Regarding the limitations of my study, the patients were reviewed retrospectively, and the number of cases was limited. It has been proposed that large prospective randomized trials are still needed to assess the clinical advantages of PBT in comparison with SRT, SRS, or IMRT for surgically unresectable meningiomas [19, 33]. However, Maclean et al. stated that randomized studies have proved challenging to carry out, and research strategies similar to those undertaken for other rare tumors should be adopted [49]. As for "resectability" of meningiomas, it is determined mainly based on technical difficulty of surgery; however, it may depend not only on the technical standard of each neurosurgeon or institute, but also on the patient's background or wish. In my study, 9 cases did not undergo any surgical procedure including biopsy; however, some of them were considered to be technically resectable and pathological diagnosis could have been obtained. Among these, 2 refused surgery because of a religious reason and 1 had hypertrophic cardiomyopathy. In other 6 patients, many of them selected PBT as an alternative at the presentation of treatment options.

Conclusion

It was indicated that fractionated PBT may be effective for benign unresectable meningioma even for the lifelong period of time. Particularly, 50.4 GyE/28frac may be sufficient and safe.

Table 1. Patient characteristics

		Our old facility (n=10)	Our new facility (n=17)
Gender			
	Male	2	6
	Female	8	11
Age (years)			
	Median	54	53
	Range	31-74	8-78
Tumor maximum diameter (mm)			
	Median	38	50
	Range	15-100	20-95
Anatomical site (number of patient)			
	Falx/Parasagittal	2	2
	Cavernous sinus		2
	Parasellar	1	1
	tuberculum sellae	1	
	Optic nerve sheath	3	
	Olfactory groove		1
	Sphenoidal ridge	1	3
	Cerebellopontine angle	1	1
	Middle cranial fossa	1	3
	Tentorial		3
	Petroclival	1	1
Surgery (number of patient)			
	None	3	7
	Biopsy	3	1
	Removal	5	9

	Simpson grade*		
	I	1	
	II	2	
	III	1	
	IV	1	9
Interval between surgery (removal) and PBT (months)			
	Median	18.2	21.6
	Range	0.4-251.9	3.1-127.1
Histology WHO grade I (number of patient)			
	Meningothelial	4	5
	Fibrous	2	1
	Transitional		3
	Not documented	2	1

* Simpson Grade Meningioma Removal

Grade	Tumor Resection
I	Macroscopically complete removal of dura, bone
II	Macroscopically complete removal, dural coagulation
III	Complete tumor resection, dura not coagulated
IV	Partial removal

Table 2. PBT details

		Our old facility（n=10）	Our new facility (n=17)
CTV (cc)			
	Median	not measurable	46.3
	Range	not measurable	5.8-295.5
Proton beam dose			
	Median	51.2 Gy (RBE=1)	50.4 GyE (RBE=1.1)
	Range	43-60 Gy (RBE=1)	45-61.2 GyE (RBE=1.1)
Fraction number			
	Median	21	28
	Range	14-29	25-34
Treatment duration (Day)			
	Median	39	44
	Range	24-57	30-53
Combined case using LINAC* (number of patient)			
10.8 Gy (6 fractions)		1	-
12.0 Gy (6 fractions)		1	-
18.0 Gy (10 fractions)		1	-
Total dose (PBT + LINAC)			
	Median	54 Gy (RBE=1)	50.4 GyE (RBE=1.1)
	Range	50.4-66 Gy (RBE=1)	45.0-61.2 GyE (RBE=1.1)

*LINAC; Linear Accelerator

Table 3. Clinical responses of patients

	Our old facility (n=10)			Our new facility (n=17)	
Clinical symptoms (number of patient)	Improved	Unchanged	Worsened	Improved	Unchanged
Visual disturbance	2	2			6
Narrowing of visual field	2	3		1	2
Trigeminal neuralgia	2			2	2
Exophthalmus	2	1			1
Epilepsy		1			3
hemiparesis			1		3
Headache				2	1
Double vision		1			2
Asymptomatic		1			2
Hoarseness		1			1
Hyposmia					2
Sensory disturbance		1			
Hearing loss					1
Orbital pain					1
Tinnitus					1
Parotid swelling					1
Ocular motility disorder					1
4th cranial nerve palsy					1
6th cranial nerve palsy					1

Table 4. Acute and late treatment-related toxicity

Side effect (number of patient)	Acute toxicity		Late toxicity	
	Our old facility (n=10)	Our new facility (n=17)	Our old facility (n=10)	Our new facility (n=17)
Low grade (CTCAE I - II)				
Radiation dermatitis	1	7		
Conjunctivitis	3			
Vomiting	2	1		
Alopecia	2	2		
Middle ear inflammation		2		
Headache	1	1		
White blood cell decreased	1			
Dizziness	1			
Eye pain	1			
Facial pain	1			
Anorexia	1			
Mucositis oral		1		
Gastritis		1		
High grade (CTCAE III)				
Radionecrosis			1	

Table 5. Summary of results on main published studies on the IMRT and PBT for benign meningiomas

Authors, year [ref.]	Modality	Number of patient	Median dose (Gy or GyE)	Median fraction number	Median volume (cc)	Local control rate (%)	Overall survival rate (%)	Median follow up (years)
Pirzkall et al., 2003 [17]	IMRT	20	55.8-58.2 Gy	32	TV 108	NA	NA	3
Milker-Zabel et al., 2007 [28]	IMRT	51	57.6 Gy	32	TV 81.4	96.3 (5 years)	97 (5 years)	4.4
Wenkel et al., 2000 [15]	combined PBT	46	59 GyE	PBT 25 Ph 6	CTV 76.5	100 (5 years) 88 (10 years)	93 (5 years) 77 (10 years)	4.4
Weber et al., 2004 [31]	PBT	11	56 GyE	28	PTV 107.7	91.7 (3 years)	92.7 (3 years)	2.8
Noël et al., 2005 [32]	combined PBT	51	60.6 GyE	PBT 15 Ph 17	GTV 17	98 (4 years)	100 (4 years)	2.1
Weber et al., 2012 [33]	PBT	23	56 GyE	28	GTV 21.5	100 (5 years)	NA	5.2***
Murray et al., 2017 [34]	PBT	61	54 GyE	NA	GTV 21.4	95.7 (5 years)	92.1 (5 years)	4.7
EL Shafie et al., 2018 [35]	PBT	102	54 GyE	27	CTV 31.5	PFS 96.6 (5 years)	96.2 (5 years)	4.8
Our study (old facility, 1986-1998)	PBT*	10	54 Gy	21	**	100 (5 years) 100 (10 years)	90 (5 years) 80 (10 years)	25.1
Our study (new facility, 2002-2017)	PBT	17	50.4 GyE	28	CTV 46.3	93.3 (5 years) 93.3 (10 years)	100 (5 years) 100 (10 years)	10.5

IMRT; Intensive Modulated Radiotherapy, PBT; Proton Beam Therapy, GyE; proton Gy × 1.1 RBE, RBE; Relative Biologic Effectiveness, Ph; Photons, TV; Target Volume, CTV; Clinical Target Volume, PTV; Planning Target Volume, GTV; Gross Tumor Volume, PFS; Progression-free Survival, NA; Not Available

* series includes 3 cases by combined PBT, ** not measurable, *** mean

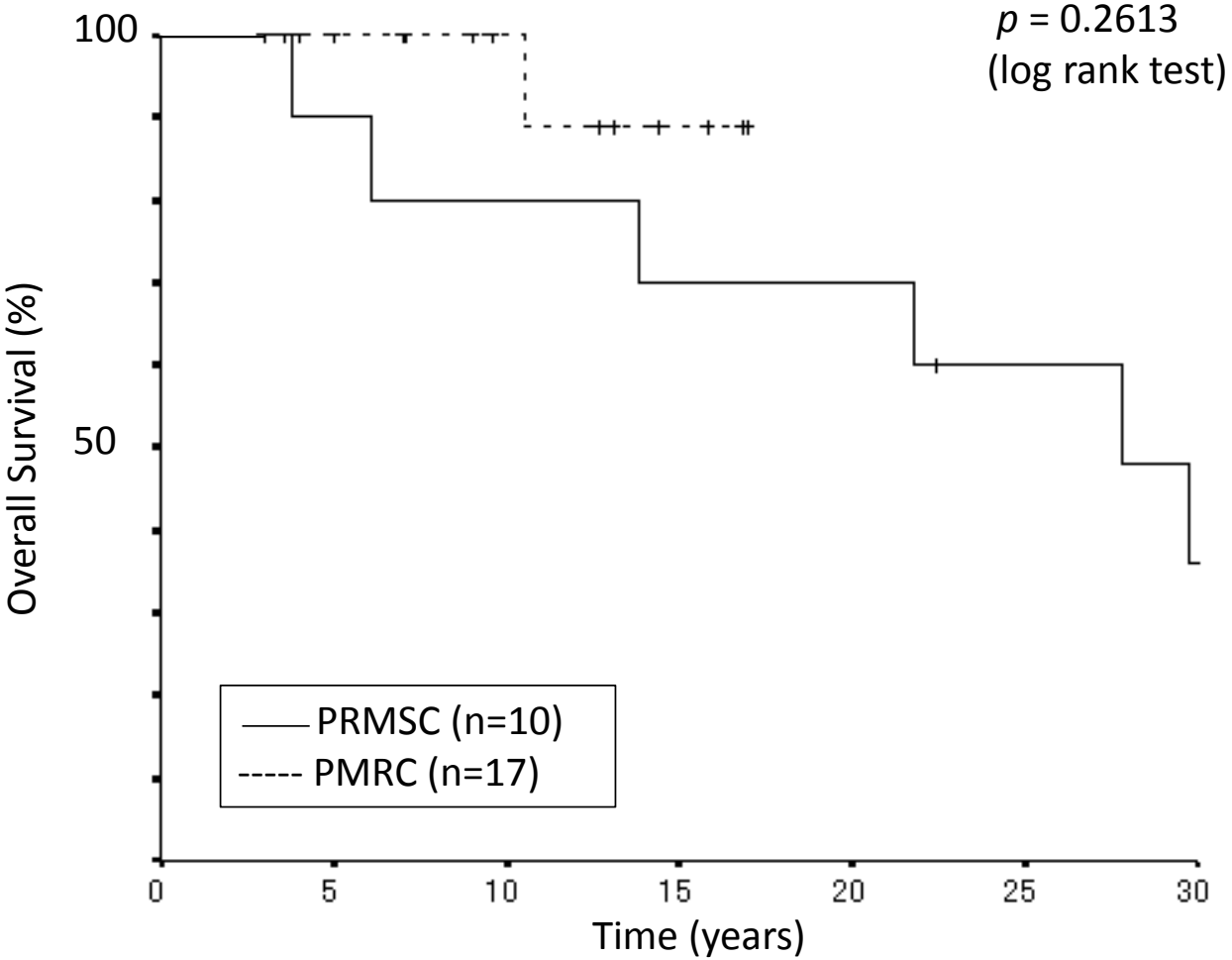


Fig.1: Kaplan-Meier curves of overall survival as a function of time (years).

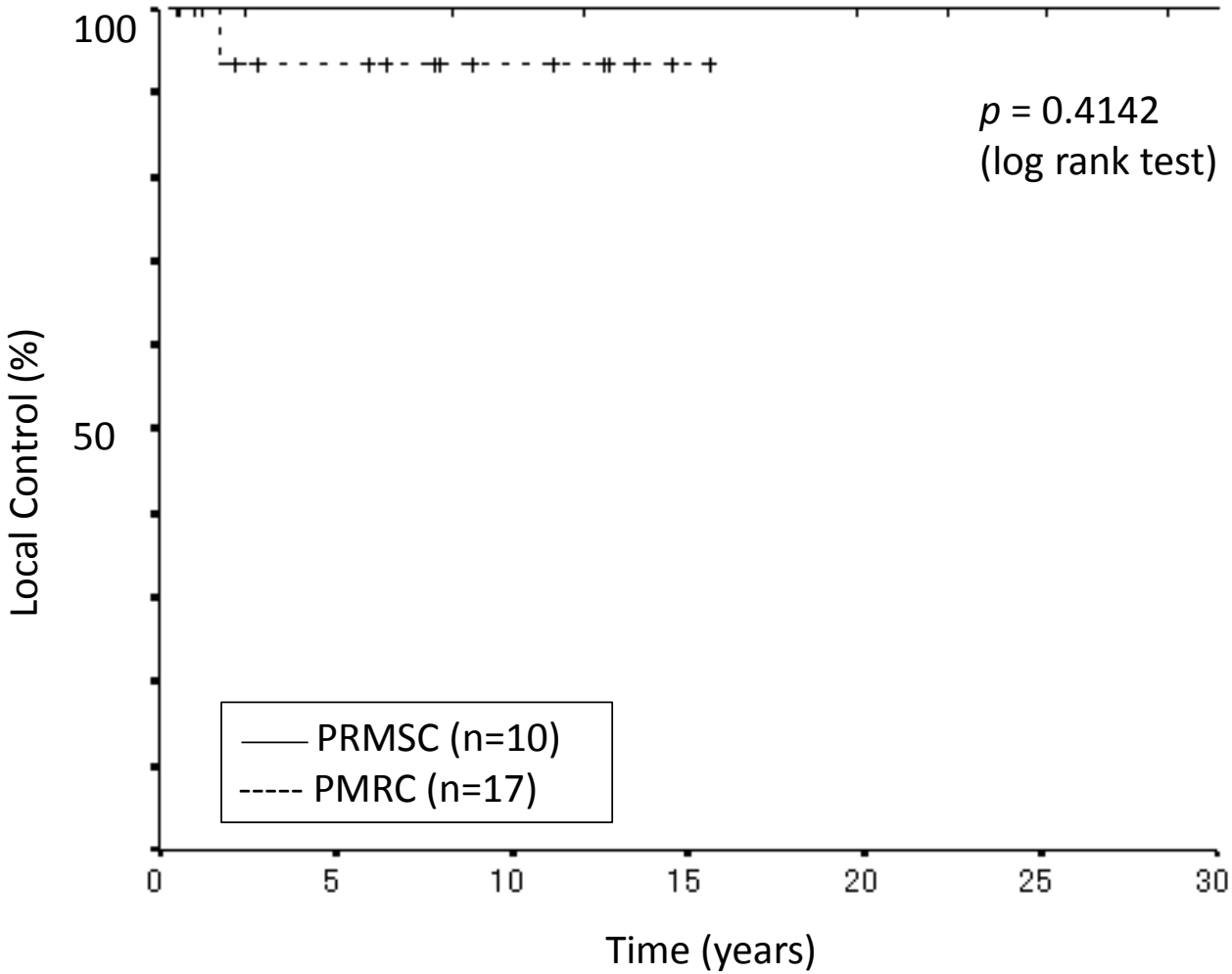
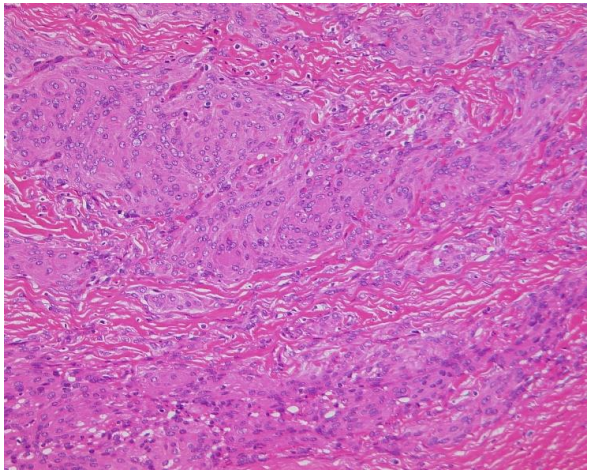
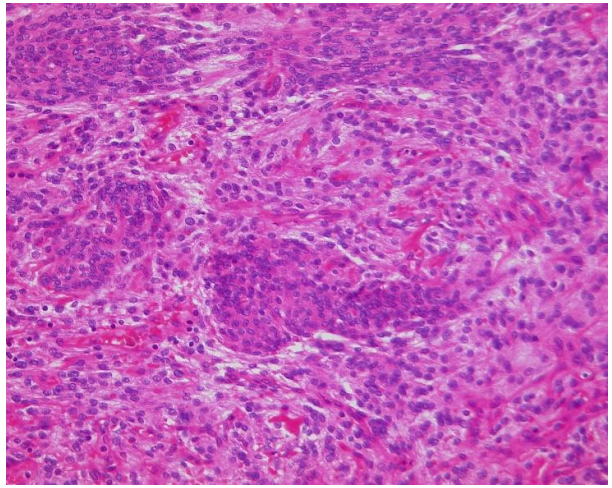


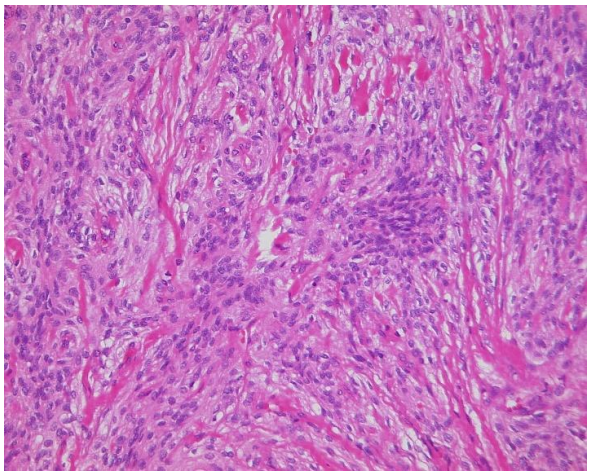
Fig.2: Kaplan-Meier curves of local control rate as a function of time (years).



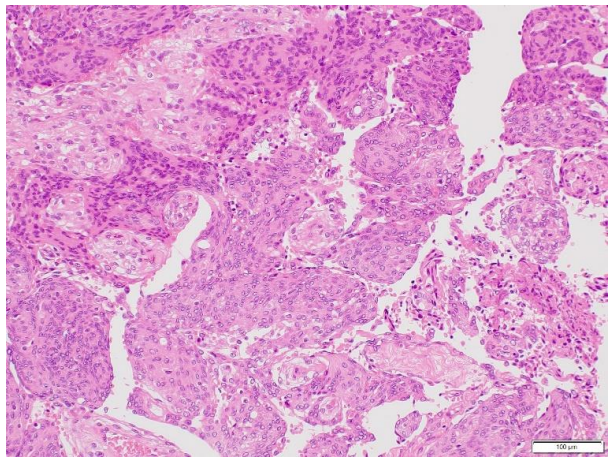
a ; Before PBT*



c; 3 years after PBT



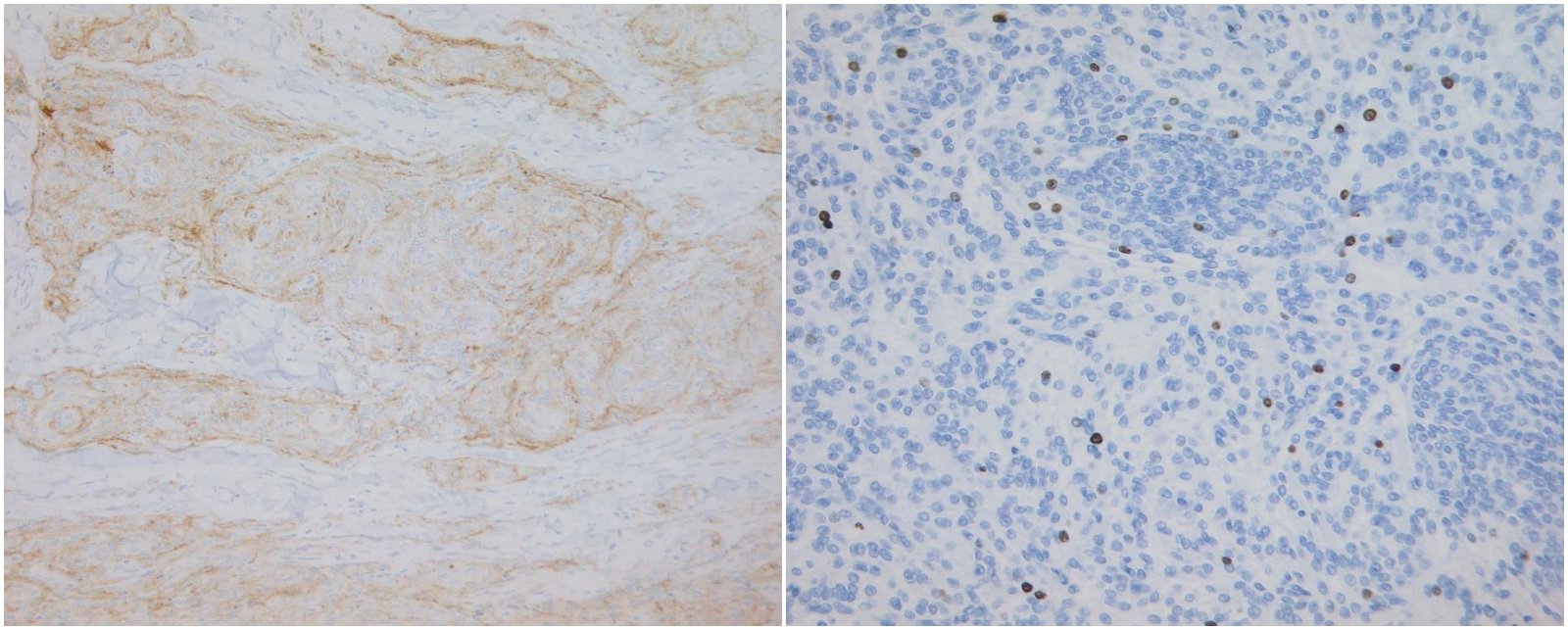
b; 2 years after PBT



d; 5 years after PBT

* PBT: proton beam therapy

Fig. 3　Recurrence case of meningioma, HE stain（×200）

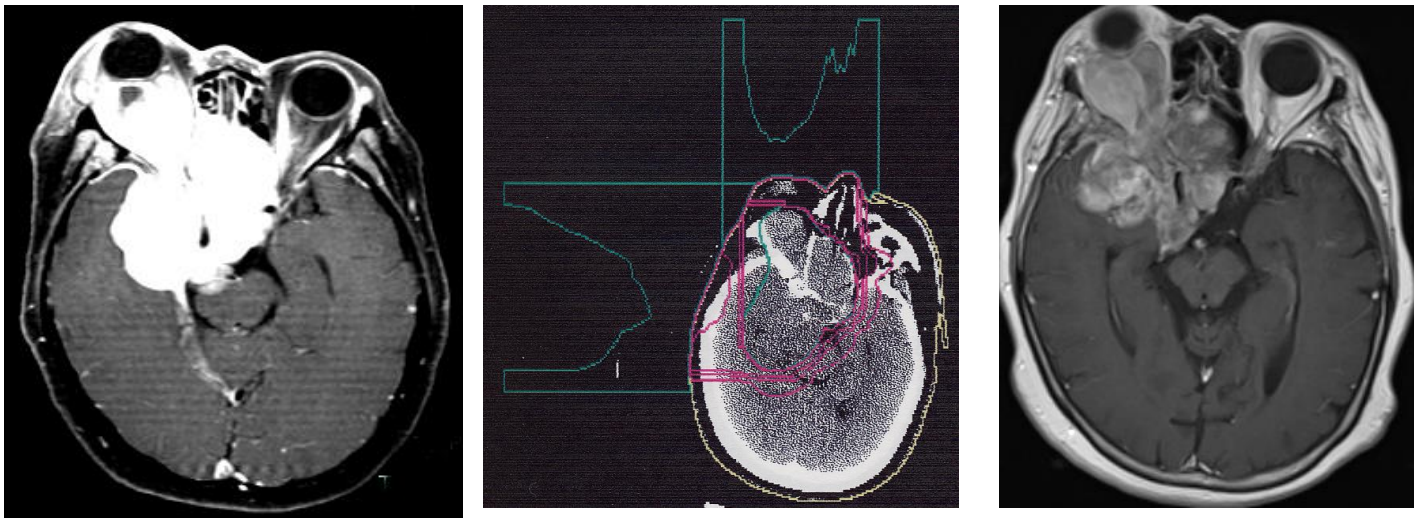


a ; EMA stain（Before PBT）

b; MIB-1 stain（Before PBT）

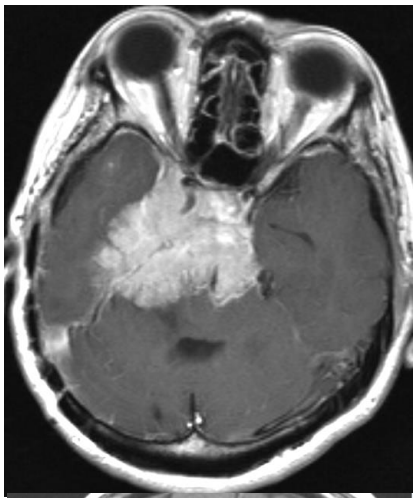
MIB-1 index： Before PBT 3.8%
2 years after PBT 5.8%
3 years after PBT 1.0%
5 years after PBT 2.0%
(hot spot; 15.0%)

Fig. 4 Recurrence case of meningioma,
Immunohistochemical staining: EMA stain, MIB-1 stain（×200）

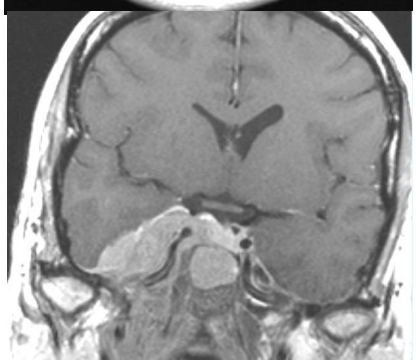


a; Before PBT　　b; Treatment plan　　c; 22.4 years after PBT

Fig. 5　Case 1; 50 y/o Female (PRMSC)

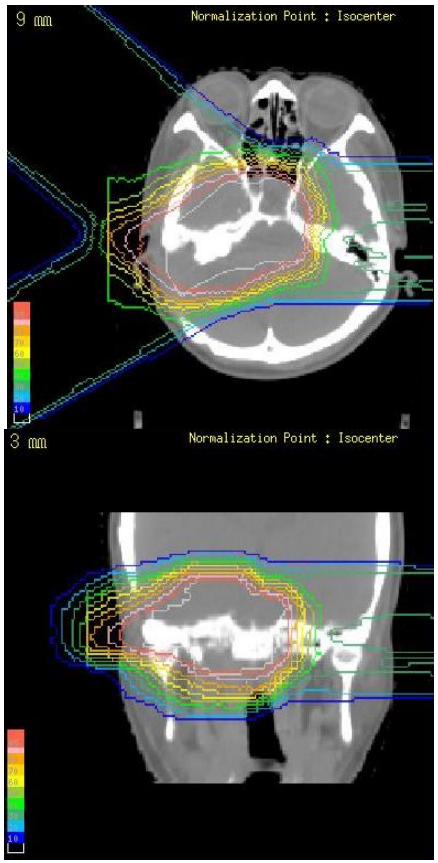


a



b

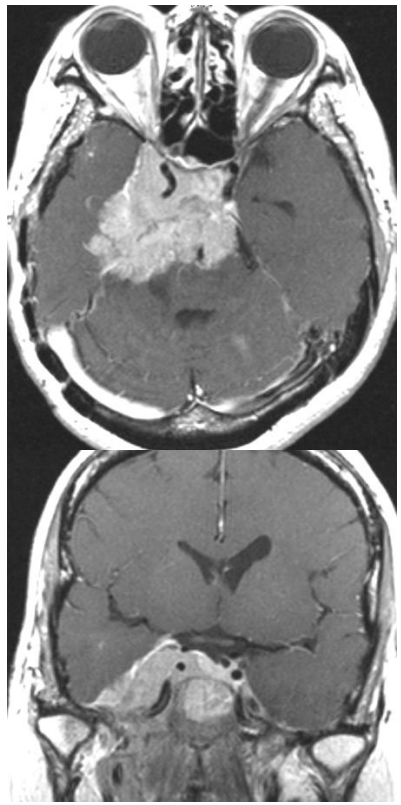
Before PBT



c

d

Treatment plan



e

f

3.5 years after PBT

Fig. 6　Case 2; 51 y/o Female (PMRC)

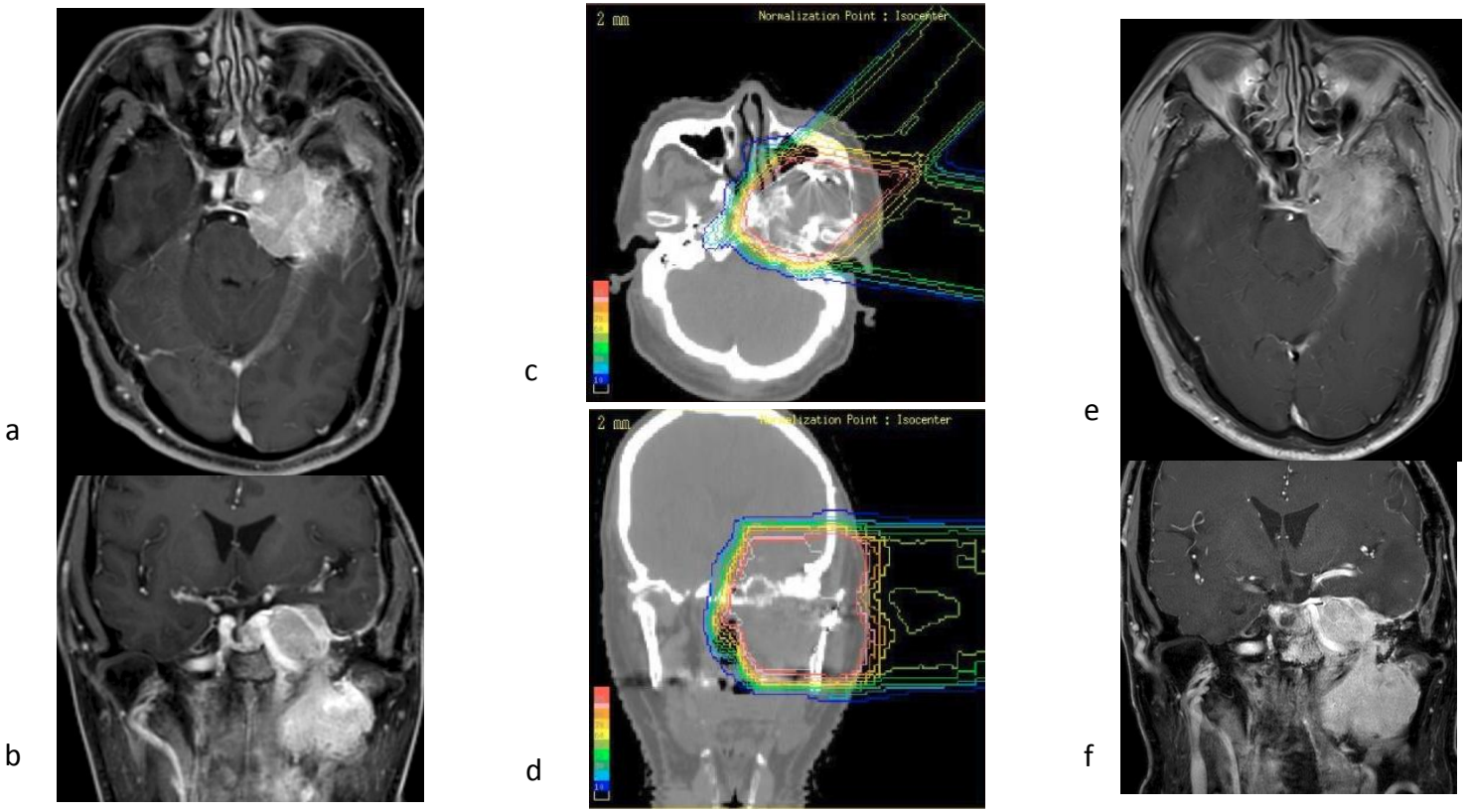


Fig. 7　Case 3; 53 y/o Male (PMRC)

Figure legends

Fig. 1: Kaplan-Meier curves of overall survival as a function of time (years).

Fig. 2: Kaplan-Meier curves of local control rate as a function of time (years).

Fig. 3: Recurrence case, HE stain（×200）

a: Before PBT

b: 2 years after PBT

c: 3 years after PBT

d: 5 years after PBT

Fig. 4: Recurrence case, EMA stain, MIB-1 stain（×200）

a: EMA stain（Before PBT）

b: MIB-1 stain（Before PBT）

Fig. 5: Case 1 (The clinical course was written in the text.)

a: Contrast enhanced MRI (axial view). Before PBT

b: Treatment plan

c: Contrast enhanced MRI (axial view). 22.4 years after PBT

Fig. 6: Case 2 (The clinical course was written in the text.)

a, b: Contrast enhanced MRI (axial and coronal views). Before PBT

c, d: Treatment plan

e, f: Contrast enhanced MRI (axial and coronal views). 3.5 years after PBT

Fig. 7: Case 3 (The clinical course was written in the text.)

a, b: Contrast enhanced MRI (axial and coronal views). Before PBT

c, d: Treatment plan

e, f: Contrast enhanced MRI (axial and coronal views). 7.0 years after PBT

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Source

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