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Risk group-adapted adjuvant radiotherapy for WHO grade I and II skull base meningioma

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Abstract

Purpose Salvage treatment including surgery and radiotherapy (RT) for recurrent or progressive meningioma is not an easy task, especially for the skull base location. And yet, criteria for adjuvant radiotherapy after initial surgery are not clearly defined for WHO grade I/II meningioma. We determined prognostic factors for recurrence and evaluated the benefit of risk group-adapted adjuvant RT for WHO grade I/II meningioma in the skull base.

Methods We reviewed 272 patients who underwent surgery and were pathologically confirmed with WHO grade I or II skull base meningioma between January 2000 and July 2017. Subgroup analyses were performed for WHO grade I (259 patients) and WHO grade II (13 patients) meningiomas to evaluate the benefit of RT in each subgroup.

Results Patients with WHO grade II meningiomas tended to present more neurologic symptoms and to receive RT more frequently. In prognostic factor analysis, tumor size ($p = 0.039$), surgical extent ($p < 0.001$), and RT ($p = 0.005$) were associated with recurrence-free survival (RFS). In subgroup analysis of WHO grade I, RFS was significantly better in RT group after matching other variables. The risk stratification was performed using three risk factors (petroclival location, tumor size, Simpson grade) in WHO grade I patients, and significantly different RFS was observed according to the risk group in non-RT patients.

Conclusions Tumor size, Simpson grade, and adjuvant RT were prognostic factors. The risk group-adapted approach can facilitate the selection of patients who may benefit from adjuvant RT for WHO grade I/II skull base meningiomas.

Keywords Meningioma · WHO grade I/II · Skull base neoplasm · Adjuvant radiotherapy · Surgical extent · Risk factors

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Introduction

Meningioma is the most common primary brain tumor, accounting for 33.8% of all brain tumors, and approximately 25% of all intracranial meningiomas occur in the skull base (Mathiesen et al. 1996; Ostrom et al. 2013). Meningioma is classified as grade I–III according to the WHO grading system; higher grade meningiomas are known to have higher rates of recurrence and thus poorer prognoses (Yang et al. 2008).

For small and asymptomatic meningioma, observation may be an option; however, published data suggest a tendency for either radiologic or neurological progression in 60–76% of untreated cases (Sughrue et al. 2010; Van Havenbergh et al. 2003). Therefore, the current treatment objectives for skull base meningioma consist of achieving maximum tumor resection while preserving the patient's function and quality of life. Adjuvant radiotherapy (RT) is recommended for WHO grade III meningioma because of

the frequent recurrences even after maximal tumor removal (Adeberg et al. 2012; Aghi et al. 2009; Perry et al. 1999); however, the indications for adjuvant RT for low-grade meningioma have not yet been clearly defined, especially for WHO grade I meningioma. In particular, surgery for meningioma arising from the skull base such as the petroclival area remains a formidable challenge, and repeated surgeries after recurrence lead to higher rates of morbidity and mortality than in non-skull base meningiomas (Wayhs et al. 2017). Therefore, adjuvant RT after initial surgery may potentially play an important role in lowering the risk of recurrence while maintaining the quality of life for patients with skull base meningioma, provided patients with high risk of recurrence can be pre-selected.

We evaluated the prognostic factors associated with recurrence and the efficacy of the risk group-adapted adjuvant RT after surgery for WHO grade I/II skull base meningiomas.

Materials and methods

Study population

This study was approved by the institutional review board (IRB) (3-2018-0024). All protocols were carried out in accordance with the Helsinki Declaration of 1975 (revision in 1983). For this retrospective study, obtaining patients' written consent forms have been waived by the IRB. The medical records of 291 consecutive patients with newly diagnosed skull base meningiomas who were treated with surgical resection between January 2001 and July 2017 were reviewed. After excluding ineligible patients (WHO grade III, other brain tumor or cancer history at least 5 years, prior treatment, no image available), a total of 272 patients with WHO grade I/II skull base meningiomas were qualified and included for analysis.

Treatment protocol

All patients underwent surgical resection, and histology was confirmed by experienced neuropathologists. The decision to undergo adjuvant RT or radiosurgery was made during a multidisciplinary team conference. In general, adjuvant RT or radiosurgery was recommended for patients with adverse features such as a WHO grade II tumor, gross residual disease, and the presence of tumor-related symptoms. When determining whether to perform radiosurgery or adjuvant RT, patients with small-sized (≤ 3 cm) grossly remaining tumors were considered as candidates for radiosurgery, while adjuvant RT was preferred for other circumstances.

Adjuvant RT was performed either by three-dimensional conformal RT (3D-CRT) or by intensity-modulated RT (IMRT). Planning target volume was defined as the volume including both the gross residual tumor and the postoperative tumor bed plus 10–20 mm margin to account for microscopic tumor extent and setup errors. The Pinnacle system (Philips Healthcare, Andover, MA) and the TomoTherapy Hi-Art system (TomoTherapy, Madison, WI, USA) were used for 3D-CRT and IMRT planning, respectively. Adjuvant radiosurgery was performed by gamma-knife surgery (GKS). The GammaPlan system (version 5.30, Elekta, Sweden) was used for treatment planning, and a single-fraction dose was prescribed to the 50% isodose line encompassing the tumor margin on postoperative MR images (Chang et al. 2003; Iwai et al. 2008).

Evaluation of surgical extent and treatment outcome

On postoperative MRI, the extent of tumor removal was evaluated using the Simpson grading system on postoperative MRI (Simpson 1957). Patients were followed up clinically 1 month after treatment, every 3 months for the first 2 years, and every 6–12 months thereafter. MRI was performed 1–3 months after surgery and 6–12 months thereafter on clinical basis. Treatment outcome was evaluated with respect to the control of the tumor. No change in tumor size or no evidence of recurrence in follow-up MRI was defined as "stable disease"; "tumor progression" covered all other circumstances (Park et al. 2006).

Statistical analysis

To compare the differences in characteristics between the two groups, χ^2-tests and Fisher's exact test were used. Recurrence-free survival (RFS) was measured from the time of surgery to recurrence or death, or the date of last image follow-up. Overall survival (OS) was measured from the time of surgery to death or last follow-up visit. Cumulative probabilities of survivals were calculated using the Kaplan–Meier method and compared using the log-rank test. To determine prognostic factors for RFS, Cox proportional hazards regression analysis was performed at both univariate and multivariate levels. The factors shown to be significant in univariate analysis, as well as the clinically relevant factors independent of their significance in univariate analysis, were considered for multivariate analysis. To adjust for covariates and determine if RT improves RFS, we used propensity score matching (PSM) approach with logistic regression to balance the patient characteristic variables. We carried out nearest-neighbor PSM on a one-to-one basis, without replacement, and without caliper between patients who received RT and those who did not. All p values were two-sided, and p values less than 0.05 were considered statistically significant. All analyses were performed using SPSS version 23.0 (IBM Inc., Armonk,

NY, USA); the "psmatching" program that uses the SPSS R-plugin (SPSS R Essentials) was used to perform all analysis in R (Thoemmes 2012).

Results

Patient and treatment characteristics

Patient and treatment characteristics according to WHO grades are summarized in Table 1. Among the 272 patients included in the current study, WHO grade I and II meningiomas were identified in 259 (95.2%) and 13 (4.8%) patients. The patients with WHO grade II tumors tended to present more neurologic symptoms ($p = 0.044$) and to receive adjuvant RT more frequently ($p < 0.001$) than WHO grade I patients. In the whole study cohort, 33 (12.1%) patients received adjuvant RT (RT group), while the remaining 239 (87.9%) patients did not (non-RT group). A total dose of 54 Gy in 30 fractions was used for two patients who received 3D-CRT. The median total dose for 22 patients treated with IMRT was 54.6 Gy (range 49.4–60.9 Gy) in 30 fractions (range 24–30 fractions), and

the median marginal and tumor doses for nine patients treated with GKS were 14 Gy (range 11–14 Gy) and 28 Gy (range 22–28 Gy).

Survival outcomes and prognostic variables for RFS in whole study cohort

At a median follow-up of 63.8 months (range 11.3–224.7 months), Kaplan–Meier estimation of 5-year RFS rate was 87.5% (Fig. 1a), and 5-year OS rate was 99.5%. There was no significant difference in RFS (5-year RFS, 100% vs. 85.9%, $p = 0.163$, Fig. 1b) and OS (5-year OS, 100% vs. 99.4%, $p = 0.727$) between RT and non-RT groups.

The results of the Cox proportional hazard regression analysis for RFS are shown in Table 2. In univariate analysis, tumor location ($p = 0.009$), tumor size ($p = 0.019$), and the extent of resection ($p < 0.001$) showed significant association with RFS, while RT did not ($p = 0.195$). In multivariate analysis, tumor size ($p = 0.039$), the extent of resection ($p < 0.001$) and RT ($p = 0.005$) were shown to be independently associated with RFS.

Table 1 Patient and treatment characteristics according to WHO grades

	All patients ($n = 272$)		WHO grade I ($n = 259$)		WHO grade II ($n = 13$)		p value
	No	(%)	No	(%)	No	(%)	
Age (median, range)	52	22–81	52	22–81	48.8	23–72	0.294
Sex							
Female	219		211	81.5	8	61.5	0.141
Male	53		48	18.5	5	38.5	
KPS							
≥ 90	84		79	30.5	5	38.5	0.548
< 90	188		180	69.5	8	61.5	
Neurologic symptoms							
Absent	115		113	43.6	2	15.4	0.044
Present	157		146	56.4	11	84.6	
Location							
Petroclival	45		42	16.2	3	23.1	0.457
Non-petroclival	227		217	83.8	10	76.9	
Tumor size (cm)							
< 3.4	132		128	49.4	4	30.8	0.189
≥ 3.4	140		131	50.6	9	69.2	
Resection (Simpson grade)							
GTR (G1-3)	212		202	78	10	76.9	1
STR (G4-5)	60		57	22	3	23.1	
Adjuvant RT							
No RT	239		235	90.7	4	30.8	< 0.001
RT	33		24	9.3	9	69.2	

No number, *KPS* Karnofsky performance score, *GTR* gross total removal, *G* grade, *STR* subtotal removal, *RT* radiotherapy
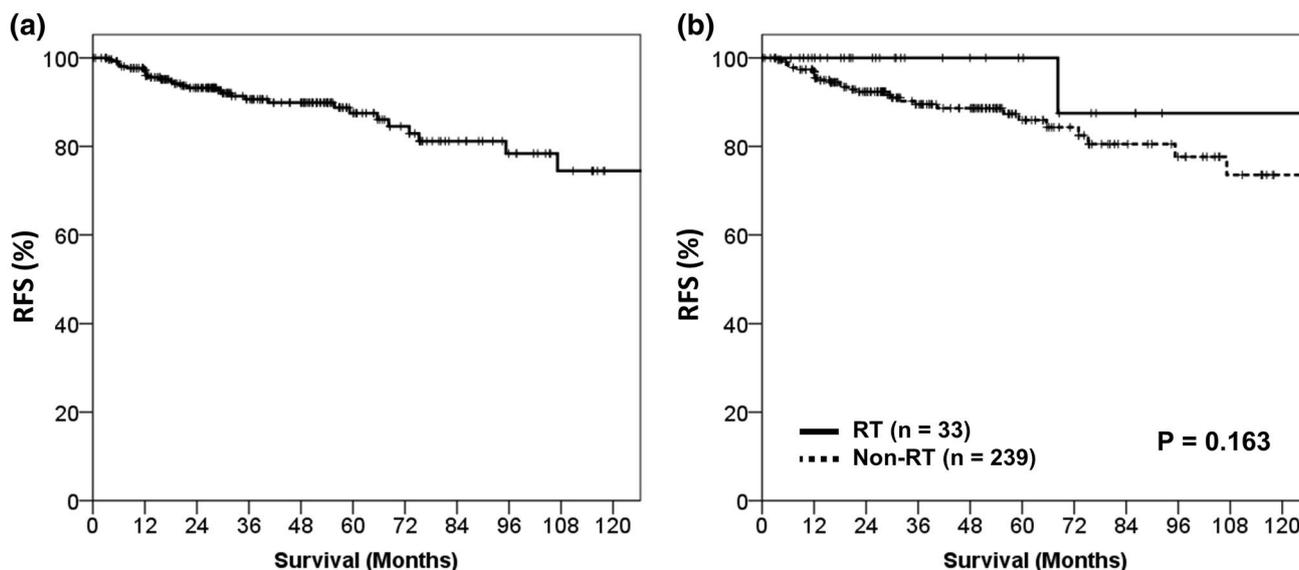
Fig. 1 **a** Recurrence-free survival (RFS) for the whole study cohort and comparison of **b** RFS between radiotherapy (RT) and non-RT groups

Table 2 Univariate and multivariate analysis for RFS

Variable	UVA			MVA		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
Age	0.994	(0.962–1.028)	0.724			
Sex						
Female	1					
Male	1.288	(0.552–3.006)	0.558			
KPS						
≥ 90	1					
< 90	1.307	(0.530–3.222)	0.561			
Neurologic symptoms						
Absent	1					
Present	1.228	(0.583–2.587)	0.589			
Location						
Non-petroclival	1			1		
Petroclival	2.757	(1.287–5.905)	0.009	1.743	(0.749–4.057)	0.197
Tumor size (cm)						
< 3.4	1			1		
≥ 3.4	2.640	(1.174–5.937)	0.019	2.417	(1.047–5.580)	0.039
WHO grade						
Grade I	1					
Grade II	1.009	(0.136–7.491)	0.993			
Simpson grade						
Grade 1–3	1			1		
Grade 4–5	5.501	(2.666–11.352)	< 0.001	9.298	(3.983–21.708)	< 0.001
RT						
Non-RT group	1			1		
RT group	0.267	(0.036–1.964)	0.195	0.052	(0.007–0.407)	0.005

RFS recurrent-free survival, *UVA* univariate analysis, *MVA* multivariate analysis, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance score, *WHO* world health organization, *RT* radiation therapy

Subgroup analysis of WHO grade I meningioma patients

The considerable differences in the risk for recurrence between WHO grade I and II meningiomas led us to perform the subgroup analysis in each WHO grades (Yang et al. 2008). In patients with WHO grade I meningioma, the 5-year RFS and OS were 89.8% and 99.5% with median follow-up of 68.1 months. The RFS was not significantly different between the RT and non-RT patients of WHO grade I subgroup as in whole cohort (5-year RFS, 100% vs. 86.2%, $p = 0.289$. Fig. 2a). However, after PSM to adjust for systematic differences in the baseline characteristics between the RT and non-RT group (Table 3), the RT group showed significantly better RFS than non-RT group (5-year RFS, 100% vs. 44.1%, $p = 0.001$, Fig. 2b).

The results of prognostic factors analysis for RFS are shown in Table 4. Similar to that of the whole cohort, tumor location ($p = 0.005$), tumor size ($p = 0.008$), and the extent of resection ($p < 0.001$) were significant factors in univariate analysis, while tumor size ($p = 0.020$), the extent of resection ($p < 0.001$) and RT ($p = 0.006$) remained significant in multivariate analysis.

To determine the subset who would benefit from adjuvant RT among patients with WHO grade I meningioma, patients in non-RT group were stratified into three risk-groups according to the number of risk factors associated with recurrence: petroclival location, tumor size ≥ 3.4 cm, and Simpson grade $\geq$ IV. Low-risk group consisted of 0–1 risk factors, intermediate-risk group of two risk factors, and high-risk group of three risk factors (Fig. 3). The 3-year RFS for low-, intermediate-, and high-risk groups were

97.2%, 57.7%, and 34.6%, respectively (low vs. intermediate, $p < 0.001$; low vs. high, $p < 0.001$; intermediate vs. high, $p = 0.196$) (Fig. 4).

Subgroup analysis of WHO grade II meningioma patients

Among 13 patients diagnosed with WHO grade II meningioma, 9 patients (69.2%) received adjuvant RT. Four patients who did not undergo RT were at lower risk for recurrence (all grossly total removal and only one patient had a tumor larger than 3.4 cm) compared to the other nine patients. Nevertheless, among the four patients, one experienced recurrence 6 months after surgery, even with his few risk factors for recurrence. On the other hand, no recurrence was observed in the nine patients who underwent adjuvant RT.

Outcome of salvage treatment after recurrences

Supplementary table 1 shows detailed outcomes of salvage treatment among the patients who experienced tumor recurrence. During follow-up period, treatment failure occurred in one (3%) and 29 (12.1%) patients in the RT and non-RT groups, respectively. In RT group, the only patient who experienced recurrence was a 62-year-old woman treated with GKS after subtotal resection of the tumor extending through the optic fissure. Five years after GKS, MR images showed a growing tumor along the optic pathway, and reconstruction of the GKS plan revealed that the tumor growth was at the margin of the GKS target delineation where the initial tumor may have been under-dosed to prevent the optic nerve from falling into a high ablative dose region (Fig. 5a,
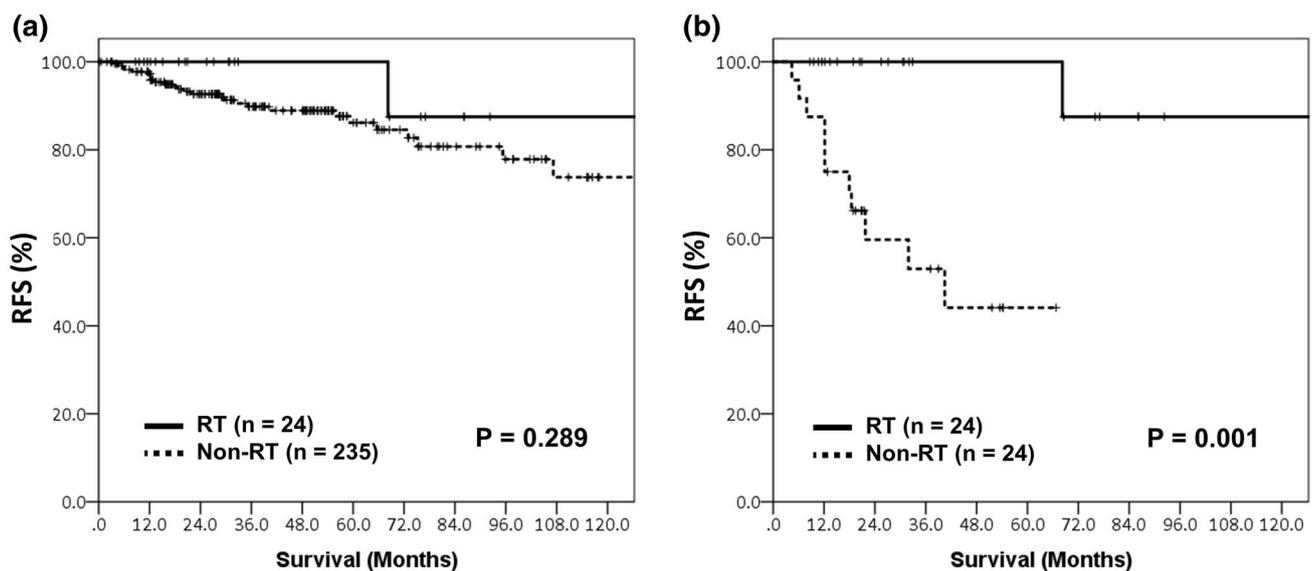

(a)

(b)

Fig. 2 Comparison of RFS between RT and non-RT group (**a**) before and (**b**) after propensity score matching in WHO grade I patients

Table 3 Patient and treatment characteristics before and after propensity score matching in WHO grade I patients

Variable	Unmatched cohort (n = 259)					Propensity score matched cohort (n = 48)				
	Non-RT (n = 235)		RT (n = 24)		p value	Non-RT (n = 24)		RT (n = 24)		p value
	No	(%)	No	(%)		No	(%)	No	(%)	
Age (median, range)	52	22–81	50.5	24–69	0.455	50	33–70	50.5	24–69	0.903
Sex										
Female	187	79.6	24	100	0.011	24	100	24	100	1.000
Male	48	20.4	0	0		0	0	0	0	
KPS										
≥ 90	74	31.5	5	20.8	0.280	5	20.8	5	20.8	1.000
< 90	161	68.5	19	79.2		19	79.2	19	79.2	
Neurologic symptoms										
Absent	108	46.0	5	20.8	0.018	5	20.8	5	20.8	1.000
Present	127	54.0	19	79.2		19	79.2	19	79.2	
Location										
Petroclival	30	87.2	12	50	< 0.001	11	45.8	12	50	0.773
Non-petroclival	205	12.8	12	50		13	54.2	12	50	
Tumor size (cm)										
< 3.4	118	50.2	10	41.7	0.425	10	41.7	10	41.7	1.000
≥ 3.4	117	49.8	14	58.3		14	58.3	14	58.3	
Resection (Simpson grade)										
GTR (G1–3)	198	84.3	4	16.7	< 0.001	4	16.7	4	16.7	1.000
STR (G4–5)	37	15.7	20	83.3		20	83.3	20	83.3	

RT radiation therapy, *No* number, *KPS* Karnofsky performance score, *GTR* gross total removal, *STR* subtotal removal

b). The last outcome assessment for this patient revealed that the remaining tumor has been increasing in size, even after salvage surgery for the progressive tumor.

Discussion

In this study, though not definite in a crude comparison, the benefit of adjuvant RT was observed in the prognostic factor analysis and the subgroup analyses of WHO grade I/II patients. We also showed that tumor location, tumor size, and Simpson grade may be used as risk factors in determining the group of patients who may benefit from adjuvant RT.

Although the malignant potential of skull base meningioma has been reported to be low in the existing literature (Cornelius et al. 2013; Kane et al. 2011), the subtotal resection rate is substantial, which indicates a high risk for recurrence. Therefore, delivering adjuvant RT may be beneficial to improve RFS and quality of life. Several retrospective studies showed the safety and efficacy of RT for skull base meningioma (Combs et al. 2018; Gorman et al. 2008; Hamm et al. 2008; Iwai et al. 2008; Milker-Zabel et al. 2007; Pirzkall et al. 2003). In a largest single-institution study, Combs et al. reported long-term results for high-precision FSRT

and IMRT in 507 patients with skull base meningiomas (Combs et al. 2013). Approximately half of the patients underwent prior surgical interventions, and low-grade meningiomas accounted for 50% of cases. With a median total dose of 57.6 Gy, local control was 95% at 5 years and 88% at 10 years. Regarding SRS, Kreil et al. reviewed the outcome of 200 patients with skull base meningiomas evenly divided between adjuvant radiosurgery and primary radiosurgery with a median margin dose of 12 Gy (Kreil et al. 2005). They reported a 10-year PFS rate of 97% and observed neurologic deterioration in 4.5% of patients. In the current study, we evaluated the role of adjuvant RT in skull base meningiomas, using either conventionally fractionated RT or SRS. The 5-year RFS rate was not significantly different between the RT and non-RT groups, but the benefit was evident after PSM in WHO grade I patients, which means that other factors (e.g., WHO grade, extent of removal, tumor size, location) should also be considered to determine whether adjuvant RT is beneficial or not.

Adjuvant RT is often indicated for high-grade meningioma (irrespective of removal extent) (Dziuk et al. 1998; Rosenberg et al. 2009). However, the benefit of adjuvant RT in low-grade (especially WHO grade I) meningiomas has not been clearly defined. In previous studies, various

Table 4 Univariate and multivariate analysis for RFS in WHO grade I patients

Variables	UVA			MVA		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
Age	0.997	(0.962–1.028)	0.881			
Sex						
Female	1					
Male	1.11	(0.552–3.006)	0.821			
KPS						
≥ 90	1					
< 90	1.241	(0.530–3.222)	0.641			
Neurologic symptoms						
Absent	1					
Present	1.213	(0.583–2.587)	0.615			
Location						
Non-petroclival	1			1		
Petroclival	3.002	(1.287–5.905)	0.005	1.758	(0.749–4.057)	0.196
Tumor size (cm)						
< 3.4	1			1		
≥ 3.4	3.178	(1.174–5.937)	0.008	2.853	(1.047–5.580)	0.020
Simpson grade						
Grade1–3	1			1		
Grade4–5	5.996	(2.666–11.352)	< 0.001	10.385	(3.983–21.708)	< 0.001
RT						
Non-RT group	1			1		
RT group	0.356	(0.036–1.964)	0.311	0.054	(0.007–0.407)	0.006

RFS recurrent-free survival, *UVA* univariate analysis, *MVA* multivariate analysis, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance score, *WHO* world health organization, *RT* radiation therapy

Fig. 3 Risk group stratification by recurrence-risk scoring in WHO grade I patients
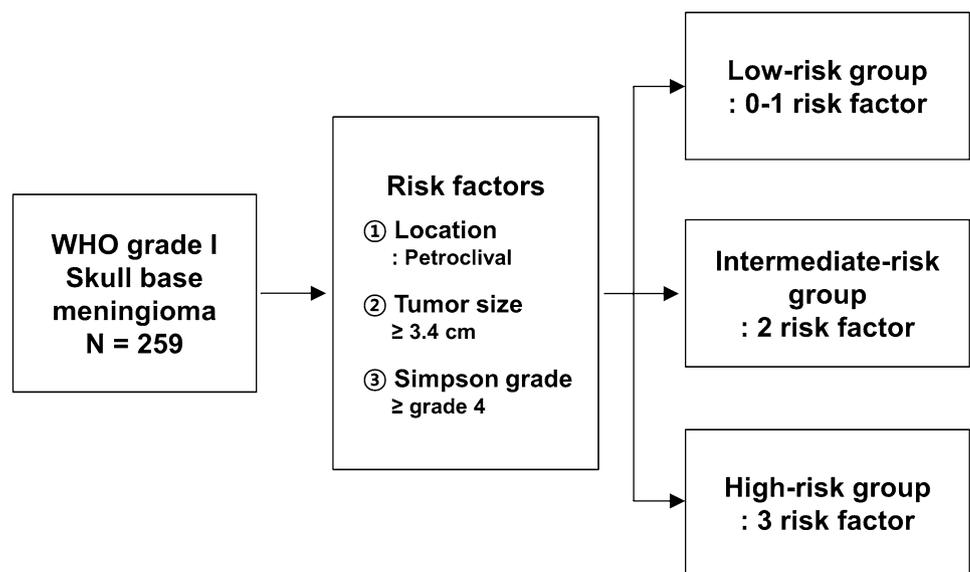

forms of RT, including external beam RT, fractionated stereotactic RT (FSRT), and stereotactic radiosurgery (SRS), have been shown to achieve durable local control in grade I and II meningiomas when used as an adjunct to surgery (Condra et al. 1997; Huffmann et al. 2005; Hug et al. 2000; Milker-Zabel et al. 2005; Park et al. 2013). Nevertheless, because a substantial proportion of low-grade meningiomas can be observed following surgery, it is necessary to determine the group of patients who may benefit from adjuvant RT. Several studies have attempted to select the

Fig. 4 Comparison of RFS according to risk groups in non-RT patients with WHO grade I meningiomas
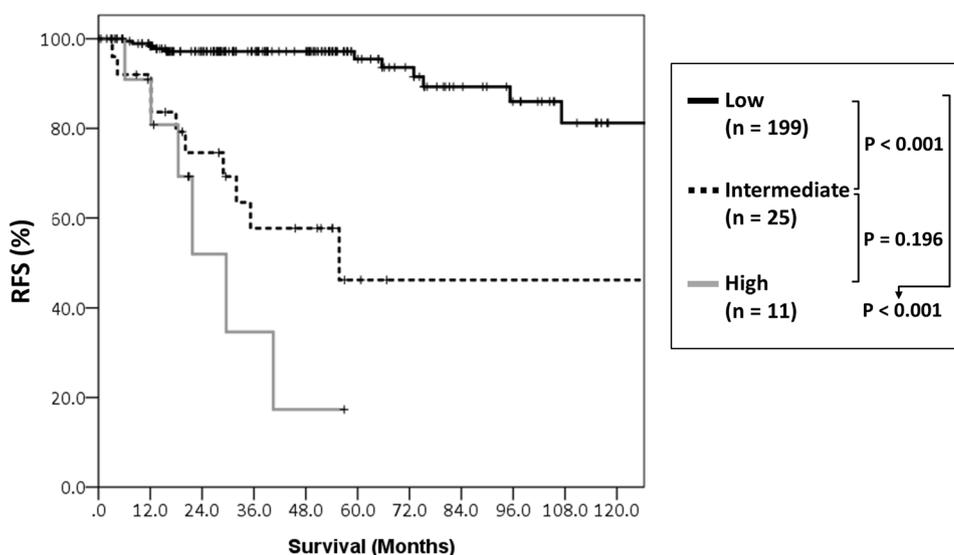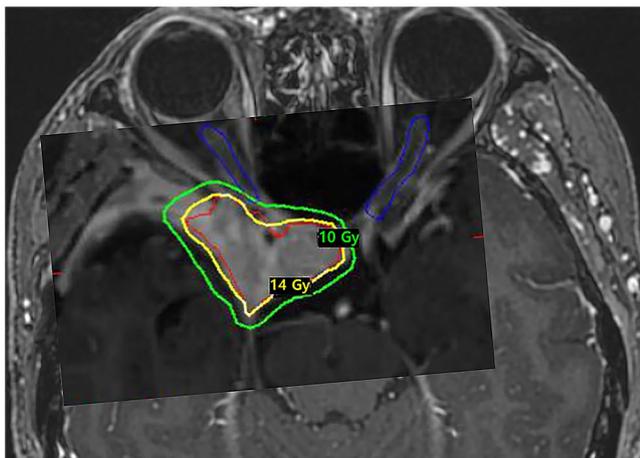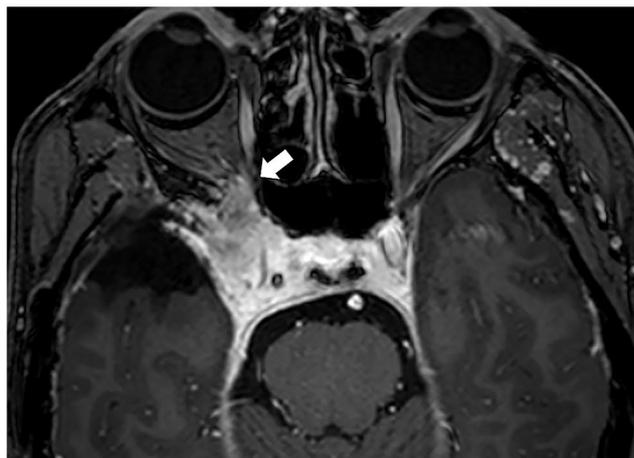

Fig. 5 Case of failure in RT group. **a** Residual tumor and RT field for gamma-knife surgery (GSK) and **b** re-growing tumor along the optic nerve 68 months after GKS

subgroup of patients with meningiomas who can benefit most from RT using prognostic factor analysis (Ayerbe et al. 1999; Yamaguchi et al. 2014). In a prospective trial of the radiation therapy oncology group (RTOG) 0539, patients with meningioma were risk-stratified into three arms: low risk for all WHO grade I regardless of extent of surgery, intermediate risk for recurrent WHO grade I and WHO grade II with grossly total removal, high risk for WHO grade II with subtotal removal, recurrent WHO grade II and all WHO grade III tumors. Although the final results have not been reported, recently reported results from intermediate-risk group showed excellent progression-free survival (PFS) rate of 96% with few toxicities above grade 2 (Rogers et al. 2017), suggesting the validity

of risk group-adapted approach for RT in meningiomas. Likewise, we used a risk group-adapted approach to determine which subgroup of patients would benefit most from adjuvant RT. Using the variables identified in the prognostic factor analysis, WHO grade I patients were divided into three risk groups (Fig. 3). Among non-RT patients, intermediate- and high-risk groups showed significantly poor 3-year RFS of 57.7% and 34.6%, respectively, compared to that of 97.2% in low-risk group. This result indicated that performing adjuvant RT may be of greatest benefit for these intermediate and high-risk groups. In WHO grade II patients, the fact that the only recurrence observed in this subgroup occurred in non-RT patient is noticeable. Even with more risk factor (e.g., subtotal removal, large tumor),

Fig. 6 Summary of risk group-adapted approach for adjuvant RT suggested by the study
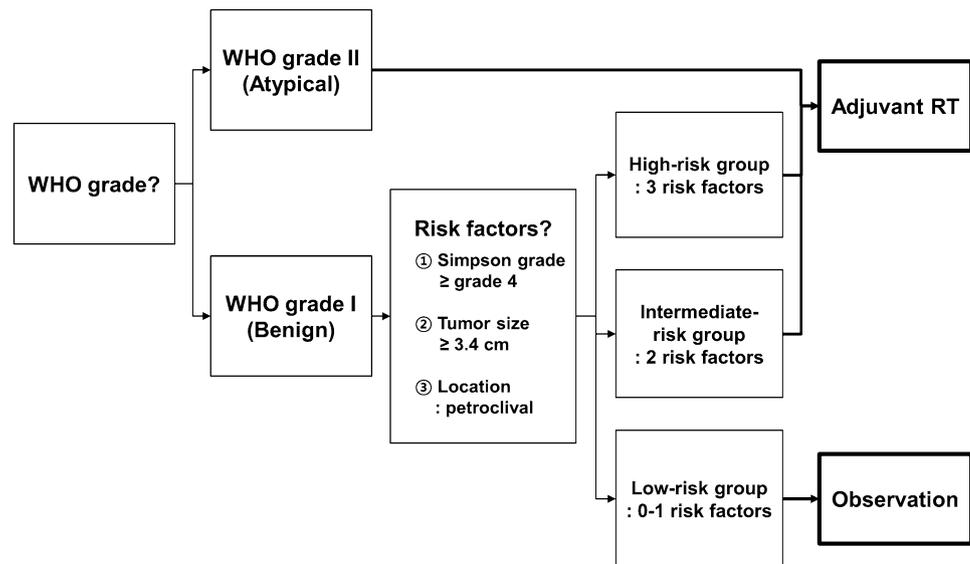
no recurrence was observed in patients who received RT. Though it is difficult to derive any statistical significance with only 13 patients, the results suggest that adjuvant RT may be beneficial for WHO grade II skull base meningioma irrespective of the risk factors. Consequently, the risk group-adapted approach for adjuvant RT suggested by our study can be summarized as Fig. 6. To the best of our knowledge, our study is the first to evaluate the benefit of adjuvant RT with adapting the risk group-based approach to identify the subgroup of patients who may benefit from RT, exclusively for skull base meningioma.

Several limitations should be considered, stemming from the retrospective nature of this study. The major limitations are the small numbers of patients who received RT (33 patients) and who were diagnosed as WHO grade II meningioma (13 patients), which were somewhat insufficient to derive robust statistical results. The heterogeneous RT modality used in the current study can also be considered a limitation. Various forms of RT were used as adjuvant treatment, including GKS and fractionated RT, which showed considerable variations in RT schemes and doses.

Despite the limitations, in the absence of a randomized controlled trial, this is one of the largest single-institution studies to evaluate the benefit of adjuvant RT using risk group-adapted approach, especially for skull base meningioma. The prognostic factor analysis showed that adjuvant RT, tumor size, and the extent of surgical resection were significant predictors, and the results of subgroup analyses suggest that risk group-based adjuvant RT may be beneficial for WHO grade I/II skull base meningiomas. However, these data are hypothesis-generating rather than confirming and need to be validated in a separate series of patients.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest concerning the materials or methods in this study or the findings specified in this paper.

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