Brain Tumor Pathology (2019) 36:7–13
https://doi.org/10.1007/s10014-018-0332-1

ORIGINAL ARTICLE

The clinicopathological analysis of receptor tyrosine kinases in meningiomas: the expression of VEGFR-2 in meningioma was associated with a higher WHO grade and shorter progression-free survival

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Received: 24 September 2018 / Accepted: 26 November 2018 / Published online: 5 December 2018

Abstract

WHO grade II/III meningiomas recur frequently and there is currently no established molecular target therapy for meningioma. No previous studies have revealed the association between receptor tyrosine kinases (RTKs) and the recurrence of meningiomas. This study aims to elucidate the association between RTKs and the clinicopathological characteristics and recurrence of meningioma. We investigated the immunohistochemical expression of RTKs (VEGFR-1/2/3, PDGFR-alpha/beta and c-Kit) in 81 meningiomas (WHO grade I, $n=64$, WHO grade II/III, $n=17$) in 74 patients. Immunohistochemistry revealed that 29 WHO grade I (45%), 10 WHO grade II (77%), and 4 WHO grade III (100%) tumors were VEGFR-2-positive, and that the VEGFR-2 expression was significantly correlated with the WHO grade. In univariate analyses to investigate the clinicopathological factors associated with recurrence, Simpson grade IV/V resection, a larger tumor size, a high VEGFR-2 expression level, WHO grade II/III, a high Ki-67 expression level, and the non-expression of PgR were identified as significant factors. Furthermore, patients with VEGFR-2-positive meningiomas showed significantly shorter progression-free survival. In the multivariate analysis, WHO grade II/III and the location were significantly associated with recurrence. In conclusion, our study suggests that VEGFR-2 inhibitors might be one of the best candidates for molecular therapy against recurrent meningiomas.

Keywords Meningioma · Recurrence/regrowth · WHO grade · Receptor tyrosine kinase · VEGFR-2

Introduction

Meningioma is most common type of brain tumor. Most meningiomas are benign and are classified as WHO grade I; however, 20–25% and 1–6% of meningiomas are classified as WHO grade II and III, respectively [1]. WHO grade II/III meningiomas frequently recur and rarely metastasize to the extracranial organs. Malignant meningiomas are mainly treated by surgery with additional radiotherapy. At the time of writing, there are no effective chemotherapeutic or molecular targeted agents for meningioma. Reported risk factors for recurrent meningioma include clinical factors (the extent of resection [Simpson grade], tumor location, age, sex, preoperative neurologic deficit, tumor size) and pathological factors (WHO grade, a high Ki-67 labeling index) [1–3].

Receptor tyrosine kinases (RTKs) such as VEGFR, PDGFR, and KIT are well known for their involvement in

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angiogenesis, lymphangiogenesis, proliferation, cell survival, and cell migration in the development of vascular systems and tumors [4]. Regarding RTKs in meningiomas, Tuchen et al. reported that the inhibition of receptor tyrosine kinases such as VEGFR, PDGFR, KIT and FGFR1 by regorafenib and sorafenib inhibits the growth and invasion of meningioma cells through the RAF/MEK/ERK and/or PI3K/AKT pathways [5]. There have also been reports of a clinical trial phase II using RTK inhibitors such as erotinib, imatinib, sunitinib, vatalanib, and anti-VEGF antibodies such as bevacizumab; however, no randomized studies have been performed [6], and there have been no reports of the immunohistochemical analysis of RTKs in large cohorts that include all WHO grades of meningioma, and there have been no clinicopathological examinations to investigate the association between the expression of RTKs and the prognosis of patients treated without molecular therapy. In this study, we analyzed the expression of these RTKs in meningiomas by immunohistochemistry and determined clinicopathological factors, including the expression of RTKs, associated with recurrence.

Materials and methods

This study investigated 81 tumors in 74 patients who underwent tumor resection at the neurosurgery department of Kanazawa Medical University from 2001 to 2014. This study was approved by the Research Ethics Committee of Kanazawa Medical University. Patient data were obtained from electronic medical records, which included radiology reports, operation reports, and pathology reports. The Simpson grade, location, size of each tumor, and recurrence/regrowth were reviewed by neurosurgeons (YS, OT and HI). Regrowth was considered present if the size of the residual tumor on the MRI images was larger than the previous one. And the histopathology, based on the WHO 2016 Classification of Tumors of the Central Nervous System, was reviewed by pathologists (SN, NK and SY). The pathological review included immunohistochemical staining of STAT6 (Rabbit, mono, YE361, abcam, ab32520, Tokyo, Japan) for the differential diagnosis of solitary fibrous tumor/hemangiopericytoma.

For immunohistochemistry, a representative 5-mm core of each tumor was collected in a tissue microarray. The antibodies included progesterone receptor (PgR) (Rabbit, mono, 1E2, Roche Tissue Diagnostics, 87746, Tokyo, Japan), Ki-67 (Mouse, mono, MIB-1, BioGenex, AM297-UC, Fremont, USA), VEGFR-1 (Rabbit, mono, Y103, abcam, ab32152), VEGFR-2 (Flk-1, Mouse, mono, Santa Cruz Biotechnology, sc-6521, Texas, USA), VEGFR-3 (Mouse, mono, #54703, R&D systems, MAB3491, Minneapolis, USA), PDGFR-alpha (Mouse, mono, #35248, R&D systems, MAB322), PDGFR-beta (D-6, Mouse, mono, Santa Cruz, sc-374573), c-Kit (Rabbit, poly, DAKO, A4502, Tokyo, Japan). Immunohistochemistry was performed using an autoimmunostainer (Leica Biosystems, Bond-MAX, Nussloch, Germany). Colon cancer tissue was used as a positive control for RTKs. Immunohistochemical staining of RTKs was evaluated using the Allred score [7]. The intensity was classified into 4 groups: 0 (negative), 1 (weakly positive), 2 (moderately positive), and 3 (strongly positive). The percentage was classified into 6 groups: 0 (negative), 1 (< 1%), 2 (1–10%), 3 (11–33%), 4 (34–66%), 5 (67–100%). The immunohistochemistry score (IHC score) was calculated as the sum of the intensity score and the percentage score. The immunohistochemistry data were assessed by two pathologists (SN and SY) and the reproducibility of methods was checked. The tumors with no staining for most antibodies, such as tumors with calcification, were excluded from this study.

All statistical analyses were performed using the EZR software program on R commander (Version 1.37) [8]. Each IHC score of the RTKs, and the percentage of PgR and Ki-67, tumor size, and age were included in a receiver operating characteristic (ROC) curve analysis to determine the optimal cutoff values that predicted recurrence. Univariate log-rank tests were performed to evaluate the association between recurrence and each variable, then Kaplan–Meier curves were drawn to compare the progression-free survival of meningiomas with and without the expression of VEGFR-2. Variables with p values of < 0.2 in the univariate log-rank test were included in a subsequent Cox multivariate analysis. Fisher's test was used to examine the association between WHO grade and the expression of VEGFR-2. p values of < 0.05 were considered to indicate statistical significance.

Results

Clinical features

The clinical data are summarized in Table 1. The median age at the first operation was 64 years (range 27–83 years). The median duration of follow-up after the diagnosis of meningioma was 60.4 months (range 1.5–196.3 months). There were 52 (70%) female patients and 22 (30%) male patients. Forty-nine (60%) tumors were located in the skull base. The median tumor size was 32 mm (range 13–70 mm). Gross total resection was achieved for 52 (64%) tumors, the Simpson grades of which were I, II and III. Out of the 11 tumors that were treated with adjuvant radiotherapy and/or chemotherapy, 5 of the 8 WHO grade II/III meningiomas recurred, while none of the 3 WHO grade I meningiomas, which were located in skull base and treated with Simpson grade IV resection, recurred.

Table 1 Clinical characteristics

Variable	Value
Number of patients	74
Number of tumors	81 (R 7)
Median age of 1st operation in years (range)	64 (27–83)
Median follow-up after diagnosis in months (range)	60 (1.5–196)
Sex	
Female	52
Male	22
Location	
Skull base	49 (R 7)
Optic nerve sheath	3 (R 1)
Anterior fossa	1
Olfactory groove	6 (R 2)
Planum sphenoidale	2
Tuberculum sellae	11 (R 1)
Sphenoidal ridge	9
Falcotentorial	3 (R 2)
Petroclival	3
Petrous	1
Tentorial	8 (R 1)
Posterior fossa	2
Non-skull base	32
Convexity	18
Falx	6
Parasagittal	7
Intraventricular	1
Median tumor size in mm (range)	32 (13–70)
Simpson grade	
I	16
II	24
III	12
IV	29
V	0
Adjuvant radiotherapy and/or chemotherapy	11

R number of tumors with recurrence/regrowth

Table 2 Pathological characteristics

Variable	WHO grade		
	I ($n=64$)	II ($n=13$)	III ($n=4$)
Histological features			
High mitotic index (≥ 4)	0	4	3
Brain invasion	0	2	2
Increased cellularity	30	13	4
Small cells with high N/C	4	6	3
Prominent nucleoli	15	8	3
Sheeting	0	7	2
Necrosis	0	8	3
Immunohistochemistry			
PgR	53	5	1
Ki-67	1	8	4
VEGFR-1	24	7	2
VEGFR-2	29	10	4
VEGFR-3	46	9	3
PDGFR-alpha	9	3	0
PDGFR-beta	51	9	3
c-Kit	43	9	3

The numbers represent the number of the tumors that met the conditions. Regarding immunohistochemistry, the listed numbers are the number of positive tumors classified by each cutoff value. The cutoff values for each antigen are described in the results

Pathological features

The revision of all meningiomas based on the WHO 2016 Classification of Tumors of the Central Nervous System led to the reclassification of two meningiomas. One rhabdoid meningioma (WHO grade III) was changed to atypical meningioma with rhabdoid features (WHO grade II) because the tumor had focal rhabdoid cells, increased cellularity, prominent nucleoli, sheeting, foci of spontaneous necrosis, but a low mitotic index (1/10 high-power field). One meningothelial meningioma (WHO grade I) was changed to atypical meningioma (WHO II) due to the presence of brain invasion. All meningiomas, including angiomatous meningiomas, were immunohistochemically negative for STAT6.

The histological and immunohistochemistry data are summarized in Table 2 and representative photos are shown in Fig. 1. Sixty-four tumors were WHO grade I meningiomas (meningothelial meningioma, $n=35$; transitional meningioma, $n=13$; fibrous meningioma, $n=11$; psammomatous meningioma, $n=3$; angiomatous meningioma, $n=2$), 13 were WHO grade II (atypical meningiomas), and 4 were WHO grade III (anaplastic meningiomas). The histological features necessary for grading are shown in Table 2. The average mitotic index values in WHO grade I, II, and III tumors were 0.2, 3.2, and 24.0, respectively. The average percentage of PgR on IHC of WHO grade I, II and III tumors were 48.7%, 13.9%, and 22.5%, respectively. Ki-67 labeling index values of WHO grade I, II, and III tumors were 2.1%, 11.4%, and 35.6%, respectively.

The immunohistochemical analysis of RTKs (Fig. 1) revealed VEGFR-1/2 and PDGFR-beta positivity in the cytoplasm and/or membrane, and VEGFR-3, PDGFR-alpha, and c-Kit positivity in the cytoplasm. The expression of VEGFRs was seen in endothelial cells and the expression of c-Kit was seen in inflammatory cells in tumors. Normal meninges were not included in the specimens. The average IHC score of VEGFR-1 in WHO grade I, II and III tumors was 6.5, 7.1, and 7.3, respectively. The average IHC score of VEGFR-2 in WHO grade I, II and III tumors was 4.8, 6.2, and 7.3, respectively. The average IHC score of VEGFR-3 in WHO

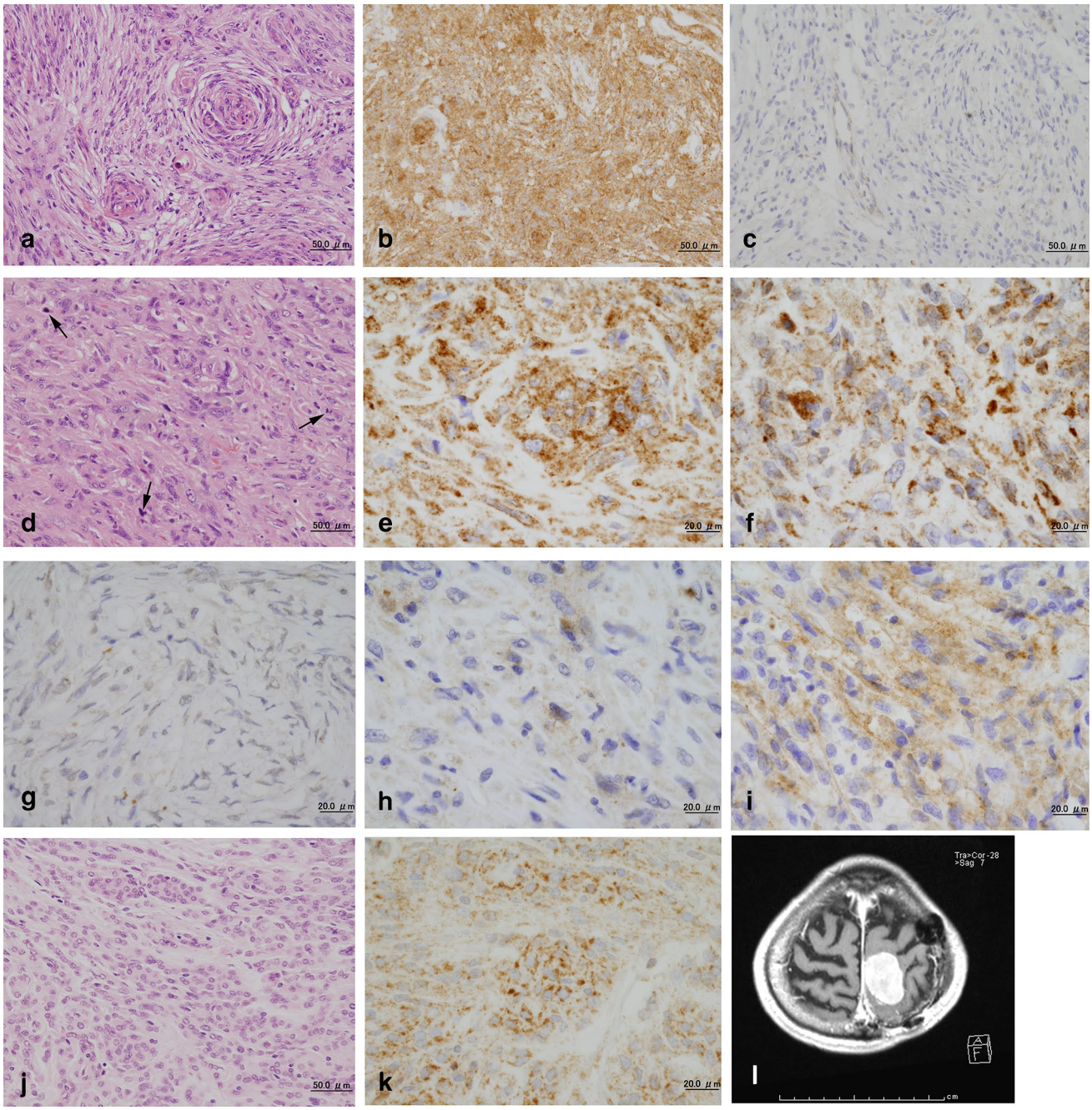

Fig. 1 The histology and immunohistochemical staining of receptor tyrosine kinases in meningiomas and MRI imaging of VEGFR-2-positive recurrent WHO grade I meningioma. **a** The histological examination of a representative case of WHO grade I meningioma (HE staining). **b** VEGFR-1 was expressed with moderate intensity in a representative case of WHO grade I meningioma. **c** A representative case of VEGFR-2-negative WHO grade I meningioma. **d** The histological examination of a representative case of WHO grade III meningioma (HE staining). Arrows indicate mitosis. **e** VEGFR-1 was expressed with high intensity in a representative case of WHO grade III meningioma. **f** VEGFR-2 was expressed with high intensity in the cytoplasm and cell membrane in a representative case of WHO grade III meningioma. **g** A representative case of VEGFR-3-negative WHO grade III meningioma. **h** PDGFR-alpha was weekly positive in a representative case of WHO grade III meningioma. **i** PDGFR-beta was expressed with moderate intensity in the cytoplasm and cell membrane of a representative case of WHO grade III meningioma. **j** The histological examination of a recurrent WHO grade I meningioma. **k** The expression of VEGFR-2 was detected in the same case as **j**. l T1-weighted MRI with contrast enhancement shows recurrence in the same case as **j**

grade I, II and III tumors was 3.5, 3.4, and 3.5, respectively. The average IHC score of PDGFR-alpha in WHO grade I, II and III tumors was 4.8, 4.1, and 5.5, respectively. The average IHC score of PDGFR-beta in WHO grade I, II and III tumors was 4.1, 4.4, and 4.5, respectively. The average IHC score of c-Kit in WHO grade I, II and III tumors was 3.3, 3.3, and 3.5, respectively.

In the ROC curve analysis for recurrence, the areas under the curve (AUCs) of PgR, Ki-67, VEGFR-1/2 and PDGFR-alpha/beta were 0.5–0.7, while AUCs of VEGFR-3 and c-Kit were < 0.5. The cutoff values for PgR, Ki-67, VEGFR-1/2/3, PDGFR-alpha/beta, and c-Kit were 0, 9, 8, 6, 4, 7, 3, and 3, respectively. The numbers of positive tumors using the cut-off values for each antibody are listed in Table 2. VEGFR-1 was detected in 24 (38%) WHO grade I tumors, 7 (54%) WHO grade II tumors, and 2 (50%) WHO grade III tumors. VEGFR-2 was detected in 29 (45%) WHO grade I tumors, 10 (77%) WHO grade II tumors, and 4 (100%) WHO grade III tumors. VEGFR-3 was detected in 46 (72%) WHO grade I tumors, 9 (69%) WHO grade II tumors, and 3 (75%) WHO grade III tumors. PDGFR-alpha was detected in 9 (14%) WHO grade I tumors, 3 (8%) WHO grade II tumors, and 0 (0%) WHO grade III tumors. PDGFR-beta was detected in 51 (80%) WHO grade I tumors, 9 (69%) WHO grade II tumors, and 3 (75%) WHO grade III tumors. c-Kit was detected in 43 (67%) WHO grade I tumors, 9 (69%) WHO grade II tumors, and 3 (75%) WHO grade III tumors.

Statistical analyses

In the log-rank univariate analysis to investigate the clinical and pathological factors associated with recurrence/regrowth (Table 3), the expression of VEGFR-2 was identified as a significant factor ($p = 0.035$), along with WHO grade II/III ($p < 0.001$), a higher Ki-67 labeling index ($p < 0.001$), the absence of PgR expression ($p = 0.008$), larger tumor size ($p = 0.002$) and non-gross total resection ($p < 0.001$). The Kaplan–Meier curves for progression-free survival of meningiomas with and without the expression of VEGFR-2 are shown in Fig. 2. Because the p values of male sex and skull base (location) were 0.100 and 0.172, respectively, these factors were included in the subsequent multivariate analysis. The p value of adjuvant radiotherapy and/or chemotherapy in the log-rank univariate analysis was 0.002, but adjuvant radiotherapy and/or chemotherapy were excluded from the subsequent multivariate analysis because it was evident that adjuvant radiotherapy and/or chemotherapy depended on WHO grade and/or Simpson grade.

In the Cox multivariate analysis (Table 4), only WHO grade II/III ($p = 0.002$) and skull base (0.042) were independent risk factors for progression; the expression of VEGFR-2 was not ($p = 0.364$). Based on the results of the IHC data of VEGFR-2 and the results of univariate and multivariate analyses to investigate the association between progression and VEGFR-2, we performed Fisher's test to investigate the association between VEGFR-2 and the WHO grades.

Table 3 The univariate analysis of risk factors for recurrence/regrowth

Variable	Recurrence	No recurrence	p value
Sex			
Male	7	19	0.100
Female	7	48	
Age			
< 60 years	4	28	0.306
≥ 60 years	10	39	
Tumor location			
Skull base	11	38	0.172
Non-skull base	3	29	
Tumor size			
< 5 cm	6	53	0.002*
≥ 5 cm	8	14	
Simpson grade			
I, II, III	2	50	< 0.001*
IV	12	17	
WHO grade			
I	2	62	< 0.001*
II, III	12	5	
Ki-67			
< 9%	6	62	< 0.001*
≥ 9%	8	5	
PgR			
Negative	8	14	0.008*
Positive	6	53	
VEGFR-1			
Negative	7	43	0.346
Positive	7	24	
VEGFR-2			
Negative	3	37	0.035*
Positive	11	30	
VEGFR-3			
Negative	6	20	0.288
Positive	8	47	
PDGFR-alpha			
Negative	10	59	0.099
Positive	4	8	
PDGFR-beta			
Negative	5	16	0.547
Positive	9	51	
c-Kit			
Negative	4	25	0.408
Positive	10	42	

*Statistical significance

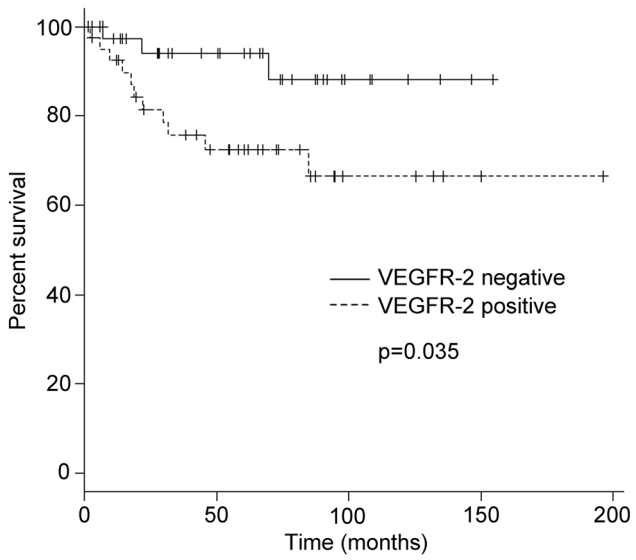

Fig. 2 Kaplan–Meier curves for progression-free survival in meningioma with and without the expression of VEGFR-2. VEGFR-2-positive meningioma was associated with significantly shorter progression-free survival than VEGFR-2-negative meningioma

Table 4 The multivariate analysis of risk factors for recurrence/regrowth

Variables	Hazard ratio	95% CI	*p* value
Male sex	0.4683	0.11–1.96	0.299
Skull base	6.9020	1.07–44.4	0.042*
Size ≥ 5 cm	1.6200	0.30–8.81	0.576
Simpson grade IV	5.2120	0.75–36.4	0.096
WHO grade II and III	96.530	5.12–1820	0.002*
Ki-67 ≥ 9%	1.0710	0.20–5.66	0.936
PgR positive	0.4505	0.07–3.06	0.415
VEGFR-2 positive	2.2500	0.39–13.0	0.364

*Statistical significance

In a 2 × 3 Fisher's test, the expression of VEGFR-2 was significantly associated with the WHO grade ($p = 0.012$). The p value of a 2 × 2 Fisher's test for the association between VEGFR-2 and WHO grade II/III was 0.007. The expression of VEGFR-2 was significantly high in WHO grade II/III meningiomas. VEGFR-2 seemed to be associated with progression via WHO grades.

Furthermore, the expression of VEGFR-2 was significantly associated with a high Ki-67 labeling index ($p = 0.013$) and the expression of VEGFR-1 ($p = 0.001$) in a 2 × 2 Fisher's test. Fisher's test revealed no other associations between VEGFR-2 and other clinical or pathological factors.

Discussion

Brain invasion was added as a criterion for atypical meningioma in the meningioma grading sections of the WHO 2016 Classification of Tumors of the Central Nervous System [1]. In the histological review of our series, one meningioma with brain invasion and recurrence was changed from WHO grade I to WHO grade II. Regarding the histological features that define atypical meningiomas, Barresi et al. reported that brain invasion and the co-presence of sheeting and a high mitotic index in 62 atypical meningiomas had the highest sensitivity (90.9%) and highest specificity (86.7%) [9]. In our analysis of all WHO grades of meningioma, each histological feature that defined atypical meningiomas was significantly associated with shorter progression-free survival, but there were no significant differences in 13 WHO grade II meningiomas. This might be because there were fewer cases of WHO grade II meningioma in this study.

VEGFR-2 was known as the main mediator of angiogenesis and the inhibition of VEGFR-2 activity blocks sarcoma cells in mice [4]; furthermore VEGFR-2 predicts decreased survival in patients with soft tissue sarcomas, such as undifferentiated pleomorphic sarcoma, leiomyosarcoma, synovial sarcoma, liposarcoma, and angiosarcoma [10]. In this study, angiomatous meningioma and other WHO grade I variants were not significantly associated with the expression of VEGFR-2. Regarding the angiogenesis of meningioma, the upregulation of VEGF in meningiomas has been reported, suggesting its role as a pro-angiogenetic factor responsible for peritumor edema; however, the correlation between the expression of VEGF and WHO grade is controversial [11].

In our study VEGFR-1/2 and PDGFR-β were expressed in the cytoplasm and membrane, which was consistent with Hilton's study [12]. The new finding in our analysis was that the VEGFR-2 expression was found to be significantly associated with the WHO grade by Fisher's test and the expression of VEGFR-2 was significantly associated with progression-free survival in the log-rank univariate analysis. This discrepancy might be due to the difference in the numbers of patients and/or the races of patients between Hilton's and ours. Our data based on 81 meningiomas including 17 WHO grade II/III in Japanese patients, but Hilton's study had 30 meningiomas including 10 WHO grade II /III in UK [12].

There was a significant association between the expression of VEGFR-2 and progression-free survival in the log-rank univariate analysis in our data, although Kaley reported that VEGFR-2 positivity predicted better progression-free survival than VEGFR-2 negativity in patients with meningioma in Phase II trials of sunitinib

for recurrent and progressive WHO grade II/III meningioma [13]. It might be that VEGFR-2 positive meningiomas have a worse prognosis without VEGFR-2 inhibitor treatment, but a better prognosis with VEGFR-2 inhibitor treatment. In our analysis, all two recurrent WHO grade I meningiomas were VEGFR-2 positive; one was located in the skull base, the other located in the convexity; both were resected (Simpson grade IV and II, respectively). The latter tumor recurred 19.5 months after the first surgery (shown in Fig. 1j, k, l). With regard to the VEGFR-2 expression in WHO I meningiomas alone, 2 of 29 VEGFR-2-positive tumors had recurrence; no recurrence was detected in 35 VEGFR-2-negative tumors. Accordingly, it might be necessary for patients with VEGFR-2 positive WHO grade I tumors to be followed up closely, even after gross total resection.

In conclusion, VEGFR-2-positive cranial meningiomas showed significantly higher recurrence and regrowth rates in a univariate analysis and a significant correlation between the expression of VEGFR-2 and the WHO grades was identified by Fisher's test in the present study. Thus, inhibitors of VEGFR-2 and downstream molecules in its signaling pathway might be good candidate agents for the molecular therapy for the treatment of recurrent meningioma. Further studies are needed to establish better molecular therapies for meningiomas.

Acknowledgements The authors thank A. Nakayama for her technical assistance. This work was supported by Grant for Promoted Research from Kanazawa Medical University (S2018-8).

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

Informed consent For this type of study formal consent is not required.

References

1. Perry A, Louis DN, Budka H, von Deimling A, Sahm F, Rushing EJ, Mawrin C, Claus EB, Loeffler J, Sadetzki S (2016) Meningiomas. WHO Classif. tumours Cent. Nerv. Syst. Revis, 4th edn, pp 232–245
2. Kim D, Niemierko A, Hwang WL et al (2018) Histopathological prognostic factors of recurrence following definitive therapy for atypical and malignant meningiomas. J Neurosurg 128:1123–1132. https://doi.org/10.3171/2016.11.JNS16913
3. Ehresman JS, Garzon-Muvdi T, Rogers D et al (2018) The Relevance of Simpson grade resections in modern neurosurgical treatment of World Health Organization Grade I, II, and III meningiomas. World Neurosurg 109:e588–e593. https://doi.org/10.1016/j.wneu.2017.10.028
4. Karaman S, Leppänen V-M, Alitalo K (2018) Vascular endothelial growth factor signaling in development and disease. Development 145:dev151019. https://doi.org/10.1242/dev.151019
5. Tuchen M, Wilisch-Neumann A, Daniel EA et al (2017) Receptor tyrosine kinase inhibition by regorafenib/sorafenib inhibits growth and invasion of meningioma cells. Eur J Cancer 73:9–21. https://doi.org/10.1016/j.ejca.2016.12.004
6. Gupta S, Bi WL, Dunn IF (2018) Medical management of meningioma in the era of precision medicine. Neurosurg Focus 44:E3. https://doi.org/10.3171/2018.1.FOCUS17754
7. Allred DC, Harvey JM, Berardo M, Clark GM (1998) Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 11:155–168
8. Kaneda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48:452–458. https://doi.org/10.1038/bmt.2012.244
9. Barresi V, Lionti S, Caliri S, Caffo M (2018) Histopathological features to define atypical meningioma: what does really matter for prognosis? Brain Tumor Pathol 35:168–180. https://doi.org/10.1007/s10014-018-0318-z
10. Kampmann E, Altendorf-Hofmann A, Gibis S et al (2015) VEGFR2 predicts decreased patients survival in soft tissue sarcomas. Pathol Res Pract 211:726–730. https://doi.org/10.1016/j.prp.2015.04.015
11. Barresi V (2011) Angiogenesis in meningiomas. Brain Tumor Pathol 28:99–106. https://doi.org/10.1007/s10014-010-0012-2
12. Hilton DA, Shivane A, Kirk L et al (2016) Activation of multiple growth factor signalling pathways is frequent in meningiomas. Neuropathology 36:250–261. https://doi.org/10.1111/neup.12266
13. Kaley TJ, Wen P, Schiff D et al (2015) Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. Neuro Oncol 17:116–121. https://doi.org/10.1093/neuonc/nou148