Post-operative Radiotherapy Did Not Improve the Treatment Outcomes of Intracranial Hemangiopericytoma

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Abstract

Background

The purpose of this study is to analyze the impact of post-operative radiotherapy on the results in patients with intracranial hemangiopericytoma (HPC).

Materials and methods

We retrospectively reviewed 66 intracranial HPC patients between 1999 and 2019 including 29 with surgery followed by radiotherapy (11 with intensity-modulated radiotherapy (IMRT) and 18 with stereotactic radiosurgery (SRS)) and 37 with surgery alone. Chi-squared test was used to compare the clinical characteristic between the groups. The Kaplan-Meier method was used to analyze overall survival (OS) and recurrence-free survival (RFS). Multivariate Cox proportional hazards models were used to examine prognostic factors of survival.

Results

The crude local control rates were 58.6% in the surgery plus post-operative radiotherapy group (PORT) and 67.6% in the surgery alone group ($p = 0.453$). In the subgroup analysis of the PORT patients, local controls were 72.7% in the IMRT group and 50% in the SRS group ($p = 0.228$). The median OS in the PORT and surgery groups were 122 months and 98 months, respectively ($p = 0.169$). The median RFS was 96 months in the PORT group and 72 months in the surgery alone group ($p = 0.714$). The median OS and RFS of the SRS group were not significantly better than those in the IMRT group ($p = 0.256, 0.960$). The median RFS were 112 and 72 months for pathology grade II and III patients, respectively ($p = 0.001$).

Conclusion

PORT did not improve the local control rates nor the survivals. The local control rates after IMRT and SRS were similar even though the IMRT technique had a much higher biological dose compared with the SRS technique. PORT is not indicated for intracranial HPC patients with a complete resection margin.

Introduction

In 1942, Stout AP and Margaret RM described a new type of vascular tumor showing the characteristic formation of endothelial tubes and sprouts surrounded by a sheath of rounded and sometimes elongated cells. They believed that these cells were derived from the capillary pericytes and suggested that the tumors be called hemangiopericytoma (HPC) (1). From then on until 1954, a total of thirty eight cases were reported. In 1954, Begg and Garret reported the first patient of primary cranial meningeal HPC. The tumor histologically resembled both the soft tissue HPC previously described by Stout and Murray and

the aggressive variant of angioblastic meningioma reported by Cushing and Eisenhardt (2–3). Compared to extracranial HPC, intracranial HPC is less frequent and remains a rare entity representing 0.4% of all primary central nervous system tumors (4); meningioma is approximately 50 to 60 times more common than intracranial HPC (5–7). It was reported that 1.6–2.5% of tumors presumed to be meningiomas by neuroimaging were intracranial HPC (8–9). The histological origin of central nervous system HPC has been controversial for a long time, and it is now widely accepted that this tumor arises from the meningeal capillary pericytes. The current WHO classification includes HPC in the group of meningeal mesenchymal non-meningothelial tumors with uncertain malignant potential or borderline malignancy (10–12).

In a study of 191 HPC patients, the authors reported that at first local recurrence, patients who underwent repeated surgery survived longer than those patients who did not (median survival time, 53.0 months vs. 35.7 months; $P = 0.028$) (13). In another report, postoperative radiotherapy (PORT) was shown to reduce local recurrence from 88% with surgery alone to 12.5% with PORT (14). Kim et al. demonstrated that routine PORT with 50 to 60 Gy regardless of the resection margin and histology significantly improved the median time to local recurrence from 19.5 months in those without PORT to 80.5 months in patients with PORT ($p = 0.0003$) (15). Some studies have suggested that complete surgical removal followed by PORT to the tumor bed is the best treatment policy for intracranial HPCs (8, 16–17). Others concluded that postoperative external beam radiotherapy (EBRT) to the tumor bed appears to delay recurrence (8, 16).

Although adjuvant radiotherapy after surgery has been frequently used in the treatment of HPC, there are no reports comparing conventionally fractionated EBRT and stereotactic radiosurgery (SRS) in HPC. The purpose of this study is to analyze the impact of different PORT techniques (conventionally fractionated EBRT versus SRS) on 66 patients with intracranial HPC.

Materials And Methods

Patients

This is a retrospective, observational study. The study protocol was approved by the hospital review board of the five participant hospitals. The medical charts and electronic databases of the hospitals were searched to identify patients diagnosed with primary intracranial HPC who had surgery as the first therapy between 1999 and 2019. Three patients who underwent initial surgery at other hospitals and were later treated for recurrent diseases at one of the five hospitals were also included. All of the patients had pathological confirmation of HPC. Information about their demographic data, pathology, surgery, PORT dose and technique, tumor control, survival status, and treatment-related side effects, were recorded. The pathology slides, when available, were reviewed by one of the authors to confirm the diagnosis.

One of the five participant hospitals used SRS routinely for their intracranial HPC patients. Patients from the other five hospitals were treated with conventionally fractionated intensity-modulated radiotherapy (IMRT) using linear accelerators. The patients were divided into the surgery plus PORT group and the

surgery alone group; patients in the surgery plus PORT group were further separated into the IMRT group and the SRS group for subgroup analysis. All of the patients were evaluated clinically and radiologically with magnetic resonance imaging (MRI) scans with and without contrast. Follow-up MRI images were compared to the preoperative images by one of the authors and the tumor dimensions, if present, were measured in the axial, sagittal, and coronal planes.

Statistical methods

The primary endpoint is local tumor control, and secondary endpoints include overall and recurrence-free survivals. All of the statistical analyses were performed by using SPSS v.19. (SPSS Inc., Chicago, IL, USA). Mann-Whitney U-tests (two-tailed) were used to analyze the differences in continuous variables. Fisher's exact test (two-tailed) was used to analyze the differences in categorical variables. Chi-squared test was conducted to compare the differences of clinical characteristics between groups. Kaplan-Meier method was used to analyze local control, overall survival (OS) and recurrence-free survival (RFS). The outcomes were compared between those who receive and did not receive PORT and also between the IMRT and the SRS groups. Univariate and multivariate Cox proportional hazards models were used to search for potential prognostic variables including age (≥ 50 years), gender, tumor location, tumor resection, pathology grade and radiation therapy.

Results

Patients and Radiotherapy Techniques

A total of 66 patients diagnosed with intracranial HPC were collected (Table 1). There were 35 males and 31 females with 83.3% having supratentorial lesions. Gross tumor resection (GTR) was conducted in 61 (92.4%) and subtotal tumor resection (STR) in 5 (7.6%) patients. Grade II HPCs were diagnosed in 35 (53%) patients, and grade III HPCs (anaplastic HPC) were diagnosed in 31 (47%) patients. Twenty-nine (43.9%) patients had surgery followed by radiotherapy while thirty-seven (56.1%) had surgery alone. The differences in patient characteristics between the two groups with and without PORT were not statistically significant (Table 1). The median follow-up time after operation in all patients was 50.5 months (range, 2-153); it was 57 and 47 months in the surgery plus PORT and the surgery alone groups, respectively.

Table 1
Characteristics of 66 patients with intracranial hemangiopericytoma by the treatment types.

	All patients N (%)	S + PORT (29 patients) N (%)	S (37 patients) N (%)	P value
Age in years				0.892
≥ 50	29(43.9%)	13(44.8%)	16(43.2%)	
< 50	37(56.1%)	16(55.2%)	21(56.8%)	
Gender				0.493
Male	35(53%)	14(48.3%)	21(56.8%)	
Female	31(47%)	15(51.7%)	16(43.2%)	
Tumor location				0.579
Supratentorial	55(83.3%)	25(86.2%)	30(81.1%)	
Infratentorial	11(16.7%)	4(13.8%)	7(18.9%)	
Pathology grade				0.493
Grade II	35(53%)	14(48.3%)	21(56.8%)	
Grade III	31(47%)	15(51.7%)	16(43.2%)	
Extent of resection				0.452
GTR	61(92.4%)	26(89.7%)	35(94.6%)	
STR	5(7.6%)	3(10.3%)	2(5.4%)	
Recurrence				0.453
Yes	24(36.4%)	12(41.4%)	12(12.4%)	
No	42(63.6%)	17(58.6%)	25(67.6%)	
PORT, post-operative radiotherapy; S, surgery; GTR, gross total resection; STR, subtotal resection.				

Of the twenty-nine patients with PORT after operation, 11 received IMRT and 18 had SRS (12 had gamma knife SRS and 6 had linac-based SRS) (Table 2). The clinical characteristics were not significantly different between the surgery and PORT groups; they were also similar between the PORT-IMRT and the PORT-SRS groups including the extent of tumor resection and the tumor grade. Eleven patients received fractionated IMRT with a median fraction number of 30 and a median prescription dose of 60 Gy (range 50–60 Gy). IMRT was delivered with 6 MV photons from linear accelerators (Varian Trilogy and Clinac IX; Elekta Synergy). Clinical target volume (CTV) was defined as the tumor cavity and/or the residual mass plus a 5–10 mm margin. An additional 3–5 mm was added to the CTV for planning target volume. Eighteen patients underwent gamma knife SRS with a single dose of 14–16 Gy at the margin of tumor

(12 had gamma knife SRS and 6 had X ray SRS) (Gamma Knife, Elekta, Perfection; Varian Clinac 23ES). At the time of the study cutoff day, 24 of the 29 patients in the PORT group and 25 of 37 patients in the surgery alone group were alive.

Table 2
Characteristics of 29 patients with intracranial hemangiopericytoma receiving post-operative radiotherapy divided by radiotherapy technique

	All patients N (%)	IMRT (11 patients) N (%)	SRS (18 patients) N (%)	<i>P</i> value
Age in years				0.074
≥ 50	13(44.8%)	7(63.6%)	6(33.3%)	
< 50	16(55.2%)	4(36.4%)	12(66.7%)	
Gender				0.316
Male	14(48.3%)	4(36.4%)	8(55.6%)	
Female	15(51.7%)	7(63.6%)	8(44.4%)	
Tumor location				1.000
Supratentorial	25(84.2%)	10(90.9%)	15(83.3%)	
Infratentorial	4(15.8%)	1(9.1%)	3(16.7%)	
Pathology grade				0.316
Grade II	14(48.3%)	4(36.4%)	10(55.6%)	
Grade III	15(51.7%)	7(63.6%)	8(44.4%)	
Extent of resection				0.862
GTR	26(89.7%)	10(90.9%)	16(88.9%)	
STR	3(10.3%)	1(9.1%)	2(11.1%)	
Recurrence				0.228
Yes	12(41.4%)	3(27.4%)	9(50%)	
No	17(58.6%)	8(72.7%)	9(50%)	
RT, radiotherapy; IMRT, intensity-modulated radiotherapy; SRS, stereotactic radiosurgery; GTR, gross total resection; STR, subtotal resection. * P values are statistically significant.				

Histological Findings

All of the 66 patients' pathological examinations with Hematoxylin & Eosin (H&E) staining showed an extensively vascularized and cellular tumor. These tumors showed compact and uniform cells with a

large number of small vascular cavities and compact reticular fibers. Immunohistochemical (IHC) staining showed a strong positivity for CD34. The percentage of ki67 positivity was lower in grade II HPC compared with grade III tumors; the median percentage of positive staining for Ki67 was 2% (range 1% – 5%) in grade II HPC and 12% in grade III HPC (range 10% – 16%). There were more prominent nuclear fission and cell morphology heterogeneity in the higher grade HPC. IHC was negative for PR, S-100 and EM (Fig. 1–1).

Imaging Findings

All of the patients had MRI examination before and after operation. After craniotomy, MRI was repeated at 3-6-month intervals in the first 3 years with and without contrast. The pre-contrast MRI showed a hypointense lesion on T1 weighted images (WI) and a heterogeneously hyperintense lesion on T2WI. A flow void signal was present in most tumor images, and cystic tumor necrosis and the dural tail sign were also very common. Contrast-enhanced MRI often showed markedly and heterogeneously enhanced lesions. Figures (1–2) showed one of the HPC patient' MRI images before and after operation.

Local Control and Survival

The crude local control rates were 58.6% in the surgery plus PORT group and 67.6% in the surgery alone group ($p = 0.714$) (Fig. 2C). In the subgroup analysis of the PORT patients, they were 72.7% (8/11) in the IMRT group and 50% (9/18) in the SRS group ($p = 0.960$) (Fig. 2E).

The median RFS in the pathology grade II and III were 112 and 72 months, respectively ($p = 0.001$). Salvage surgery with or without PORT was conducted for most patients with local recurrence (Fig. 2A). The 5-year RFS rates in the surgery plus PORT group and surgery alone group were 56.4% and 74.6%, respectively.

The median OS in the surgery plus PORT and surgery alone groups were 122 months and 98 months, respectively ($p = 0.169$) (Fig. 2B). The median OS in the SRS and IMRT groups were 127 months and 73 months ($p = 0.256$) (Fig. 2D). The 5-year OS rates in the PORT and surgery alone groups were 75% and 90.9%, respectively.

Prognostic Factors of OS and RFS

Age ≥ 50 years is the only prognostic factor for OS by both the univariate ($p = 0.020$) and multivariate ($p = 0.029$) Cox regression analyses (Table 3). The median OS time is 84 months in the older group (age ≥ 50 years) and 122 months in the younger group (age < 50 years) ($p = 0.018$). The median RFS time is 72 months in the older group (age ≥ 50 years) and 96 months in the younger group (age < 50 years) ($p = 0.100$).

Table 3

Univariate and Multivariate Analysis of Factors Associated with Overall Survival in Patients of Intracranial Hemangiopericytoma

Univariate Analysis			Multivariate Analysis	
	OS		OS	
Variable	P	95%CI	p	95%CI
Age	0.020*	0.116–0.834	0.029*	0.103–0.883
Gender	0.346	0.235–1.661	0.573	0.406–5.096
Location	0.184	0.000–5.044	0.963	0.000
Resection (GTR)	0.338	0.000–28.840	0.971	0.000
Recurrence	0.324	0.212–1.670	0.348	0.136–2.022
Pathology grade	0.352	0.586–4.485	0.898	0.335–3.478
Radiation (Yes)	0.178	0.721–5.869	0.133	0.114–1.333
OS, Overall survival; CI, confidence interval; GTR, gross total resection; * P values are statistically significant.				

The median RFS in the pathology grade II and III were 112 and 72, respectively ($p = 0.001$). Pathology grade is the only prognostic factor for RFS by both the univariate ($p = 0.003$) and multivariate ($p = 0.005$) Cox regression analyses (Table 4).

Table 4

Univariate and Multivariate Analysis of Factors Associated with Recurrence-free Survival in Patients of Intracranial Hemangiopericytoma

Univariate Analysis			Multivariate Analysis	
	RFS		RFS	
Variable	P	95%CI	p	95%CI
Age	0.107	0.208–1.166	0.083	0.173–1.114
Gender	0.231	0.248–1.400	0.302	0.229–1.580
Location	0.787	0.293–2.538	0.518	0.175–2.409
Resection (GTR)	0.103	0.832–7.404	0.238	0.591–8.314
Pathology grade	0.003*	1.639–10.663	0.005*	1.495–9.813
Radiation (Yes)	0.716	0.375–1.961	0.781	0.463–2.783
RFS, Recurrence free survival; CI, confidence interval; GTR, gross total resection; * P values < 0.5				

Discussion

Intracranial HPC is a rare disease, and it is also rare in the literature for any single study having a large case number and a satisfactory length of follow-up. In our present report on 66 patients, some of our findings concur with the previously published results in the literature, but some do not. Impact of the extent of tumor resection have been examined by several papers, and complete tumor resection was shown to play a pivotal role for both local control and survival (6, 13, 18–22). In our study, however, GTR did not affect the treatment results. This may be explained by that 90% of our patients had GTR and thus making it difficult to detect a difference statistically when compared with the small number of patients with residual tumor.

Most studies investigating the effect of PORT in intracranial HPC were based on single center analysis with a limited patient number, and the results were often contradictory. Meta-analyses and studies based on accumulated database have been conducted to overcome the problems of small case series, but their results were also inconsistent (23–25). Although the role of PORT in the GTR patients is not clear, the general consensus is that PORT is beneficial for patients undergoing STR. Some studies found that PORT following STR improves both RFS and OS compared with STR alone (7, 24–27), and the others reported that PORT following GTR may also prolong OS (23, 25, 27, 28) or improve local control (29, 30). Contrary to the above, some authors have reported that PORT after GTR has no impact on survival (5, 24, 31) or that PORT should not be used except for patients with recurrences (32, 33). In our study, we have found that PORT after surgery has no significant impact on the overall and disease-free survivals. This is in line with the results from Lee et al who underwent an analysis of practice pattern in the US for intracranial HPC and the PORT effect on its survival. They obtained data of 588 cases from the cancer registry, of which 323 (54.9%) received postoperative radiation. The 5-year overall survival for those receiving PORT 77.1%, not significantly different from the 83.8% for those who did not ($p = 0.14$). Postoperative radiation was not prognostic for survival on multivariable analysis (34).

SRS has been used for the patients with residual or recurrent intracranial HPCs (17, 32, 35–39). It was reported that postoperative SRS resulted in a better local tumor control in intracranial HPC patients (17). In our subgroup analysis, patients with SRS had a similar OS to the patients with IMRT. The biologically effective dose (BED) of the SRS and IMRT groups for HPC with an α/β ratio of 10 Gy was about 33.6–41.6 Gy₁₀ and 72 Gy₁₀, respectively. The biological effectiveness of the IMRT technique was much higher than the SRS method, yet resulting in no higher local control. The reason is not clear, but considering that SRS may be able to minimize the radiation to the adjacent tissues due to the high-precision delivery of radiation to HPC with a steep radiation dose gradient, it is a reasonable PORT option for HPC patients (32, 40). There is no consensus on the optimal radiation dose for single-fraction SRS for intracranial HPC. Some centers have reported an improved local control at higher tumor margin doses, ranging from 14 to 17 Gy (41, 42), but other studies using tumor margin doses exceeding 20 Gy did not show an improved local control (43, 44).

From our analysis, PORT does not seem to improve local control, RFS and overall survival. It should not be given to intracranial HPC patients without a positive margin. The weakness of this study includes the retrospective nature and a small sample size. To examine the exact impact of PORT on local control and survival and the different effects between IMRT and SRS as a PORT option requires a multi-center randomized trial with a larger sample size.

Data sharing statement:

All of the data are presented in this article except the MRI and pathological images which are available on request.

Declarations

Sources of support:

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Conflict of Interest statement:

The authors have no conflicts of interest

Data sharing statement:

All of the data are presented in this article except the MRI and pathological images which are available on request.

Compliance with Ethical Standards:

Funding:

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Conflict of interest:

All the authors declare no conflict of interest.

Ethical approval:

The study protocol was approved by the hospital review boards of the participant hospitals with a waiver of informed consent of the individual patients. The study was conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments of comparable ethical standards.

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Figures

Figure 1

Figure (1-1). A, B and C: Microphotographs of the pathologic images of a grade II intracranial hemangiopericytoma patient (magnification x200). A, Hematoxylin & Eosin staining demonstrated an extensively vascularized and cellular tumor; B, Immunohistochemical staining showed a strong positivity for CD34; C, immunohistochemical staining showed a 5% positivity for Ki67; D, E and F: Microphotographs of the histologic images of a grade III intracranial hemangiopericytoma patient

(magnification x200). D, Hematoxylin & Eosin staining demonstrated an extensively vascularized and cellular tumor; E, Immunohistochemical staining showed a strong positivity for CD34; F, Immunohistochemical staining showed a 10% positivity for Ki67. Compared with grade II HPC, the grade III tumor showed a higher percentage of ki67 positivity and more prominent nuclear fission and cell morphology heterogeneity. Figure (1-2). Magnetic resonance imaging (MRI) of a grade II intracranial hemangiopericytoma patient without recurrence after gross total resection. (A-C): Preoperative T1-weighted MRI scans with contrast: (A) axial, (B) coronal and (C) sagittal images, showing an enhanced lesion at the right temporal lobe with central necrosis. (D-F) Postoperative T1-weighted MRI scans with contrast: (D) axial, (E), coronal, and (F), sagittal images, showing a complete tumor removal. The patient was recurrence-free twenty-two months after surgery. His histologic images were shown in figure 1-1.

A

Figure 2

(A) A diagram showing the initial patient treatments, local recurrence and salvage therapy after local recurrence. Twenty-nine (43.9%) patients had surgery followed by post-operative radiotherapy (PORT) while thirty-seven (56.1%) had surgery alone. Of the 29 patients with PORT after operation, 11 received intensity-modulated radiotherapy and 18 had stereotactic radiosurgery (SRS) (12 had gamma knife SRS and 6 had linac-based SRS). There were 12 local recurrences out of the 29 patients with surgery plus

PORT, and 11 of the 37 surgery alone patients. (B) Kaplan-Meier estimates of the overall survival (OS) curves of intracranial hemangiopericytoma patients. There were no differences between the patients with and without PORT ($p = 0.169$). (C) Kaplan-Meier estimates of the recurrence-free survival (RFS) curves in intracranial hemangiopericytoma patients. Postoperative radiotherapy did not increase the RFS ($p=0.714$). (D) Kaplan-Meier estimates of the OS curves in intracranial hemangiopericytoma patients with PORT. The OS of the two groups were similar ($p = 0.256$). (E) Kaplan-Meier estimates of the RFS curves in intracranial hemangiopericytoma patients with PORT. The RFS of the two groups were similar ($p = 0.960$).

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