Postoperative LINAC-Based Stereotactic Radiotherapy for Grade I Intracranial Meningioma in Subtype Classification

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Objective: *To evaluate outcomes of postoperative radiotherapy (RT) for residual WHO grade I meningioma based on subtype classification and relevant factors that may influence the outcomes.*
Material and Method: *Medical records from 252 patients, with known histology of intracranial meningioma, who underwent stereotactic RT in Ramathibodi Hospital between 1998 and 2008, were reviewed. One hundred and two out of 252 patients were included. The data were categorized into 2 groups: common subtype (meningothelial and transitional subtypes) and uncommon subtype (fibroblastic, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic subtypes). Analysis of tumor control rate, tumor shrinkage rate and risk factors of treatment failure were conducted.*
Results: *The median of follow-up period was 46 months (interquartile range (IQR): 53). The five-year tumor-control rates of overall, common and uncommon subtypes were 89.9%, 92.9% and 81.5%, respectively, which showed no significant difference between the two groups, p = 0.108. The five years tumor shrinkage rates of overall, common, and uncommon subtypes were 42.5%, 42.3% and 42.7%, respectively, there was no significant difference, p = 0.934. In univariate analysis, gender (male), total minimal dose and fraction demonstrated statistically significant impact on treatment failure. However, only a total minimal dose had any significant effect in multivariate analysis.*
Conclusion: *Radiotherapy is highly effective in controlling postoperative residual meningioma. This study may be useful to evaluate patients' prognosis and possibility of recurrence based on histology subtypes. In addition, total minimal dosage was the sole risk factor of treatment failure found in the present study.*

Keywords: *Meningioma, Radiotherapy, Postoperative, Intracranial, WHO grade I, Subtype*

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Meningioma is one of the common brain tumors. It originates from arachnoid cap cells. Most of them are WHO grade I which have nine histological subtypes(1-3). Although surgical excision is the treatment of choice, RT can be helpful in controlling the residual tumor.

The benefits of RT for subtotal resection of benign meningioma have been confirmed in several studies)(3,4). Notably in Serdar Soyuer et al demonstrated the five-year Progression Free Survival (PFS) rate of 91% in an adjuvant RT group. On the contrary, the group without adjuvant RT showed a rate of 38% (p = 0.0005)(3). Other studies confirmed that RT has become one of the best options to control the residual tumor, especially in the inoperable or high risk area for reoperation(4).

Although a lot of publications mentioned the efficacy of RT for grade I meningioma, there was no evidence of studies regarding the association between histological subtypes and RT outcome. Thus, this study aimed to determine the results of postoperative RT outcome of categorized subtypes in grade I meningioma.

Material and Method

Two hundreds and fifty-two patients with intracranial meningioma who underwent stereotactic RT in Ramathibodi Hospital between 1998 and 2008 were reviewed. All patients underwent stereotactic RT using the X-Knife (Varian Clinac 600SR, Varian medical systems, Palo Alto, CA, USA). The CT-based with MRI

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fusion images were used to plan and locate the target areas. Moreover, the MRI scan result was periodically obtained in order to follow-up in all cases. The exclusion criteria were using RT as a primary treatment, grade II or III meningioma, loss to follow-up cases (follow-up less than 1 year) and unclassified subtype.

The changes in size, which were increase, decrease and stable, of residual tumor were reported by neuroradiologists. The treatment failure was defined as tumor size increased after RT with or without symptoms. The tumor under control was defined as no increase in tumor size. The tumor shrinkage was defined as decrease of tumor size after RT.

To analyze factors which correlated to the rate of treatment failure, the following parameters were analyzed: histology (common subtype compared with uncommon subtype), age (<50 years compared with ≥50 years), sex (male compared with female), fraction (hypofraction compared with conventional fraction), duration from surgery to RT, tumor volume and total minimal dose. Those factors were analyzed by Receiver Operating Characteristic (ROC) analysis.

Univariate analysis was conducted by using the Kaplan-Meier statistic with the log-rank test. Multivariate analysis was conducted by using a forward stepwise selection method. All analytical processes were computed by STATA software (version 12.0, College Station, TX: Stata Corp LP). The *p*-values less than 0.05 were considered statistically significant.

Results

Of the 252 patients, 150 were excluded because RT was used as a primary treatment (30 patients), grade II or III meningioma (22 patients), loss to follow-up cases (23 patients) and unclassified subtype (75 patients). Thus, one hundred and two patients were included (Fig. 1).

The patient's characteristics have been summarized in Table 1. Mean age at the time of SRT was 45.5 years (SD: 12). Eighty-three patients (81%) were female and nineteen patients (19%) were male. After RT, patients were followed-up for a median of 46 months (IQR: 53). Median planning tumor volume was 17.3 cc (IQR: 18.9). Hypofraction technique was used in 25 cases (24.5%) while 77 cases (75.5%) underwent conventional fraction technique. Median time from

Loss F/U = loss to follow-up cases; No subtype = the pathologist did not classify the subtype of tumor

Fig. 1 Number of patients.

Table 1. Overall demographic data

Characteristics	Data
Age (years)	Mean: 45.5 SD: 12
Gender	
Male	19 (19%)
Female	83 (81%)
Follow-up time (months)	Median: 46 (IQR: 53)
RT data	
Tumor volume (cc)	Median: 17.3 (IQR: 18.9)
Fraction	
Hypofraction	25 (24.5%)
Total minimal dose (Gy)	Mean: 24.31 SD: 3.07
Conventional	77 (75.5%)
Total minimal dose (Gy)	Mean: 38.14 SD: 5.53
Duration: surgery to RT (weeks)	Median: 38 (IQR: 46)

RT = radiotherapy; Gy = gray; SD = standard deviation; cc = cubic centimetres; IQR = interquartile range last surgery to RT was 38 weeks (IQR: 46). The tumor locations are enumerated in Table 2. The data were categorized into 2 groups: common subtype (meningothelial and transitional subtypes) and uncommon subtype (fibroblastic, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic subtypes). There was no significant difference in any characteristics between the two groups (Table 3).

Table 2. Tumor location

Location	No. (%)
Convexity	7 (6.9)
Cerebellopontine angle	8 (7.8)
Posterior fossa	1 (1)
Sphenoid wing	27 (26.4)
Cavernous	16 (15.7)
Tentorial	4 (3.9)
Parasagittal/falcine	5 (4.9)
Orbit	1 (1)
Sellar	8 (7.8)
Intraventricular	1 (1)
Tuberculum/planum	7 (6.9)
Olfactory groove	1 (1)
Multiple	6 (5.9)
Petrous/petroclival	9 (8.8)
Pineal region	1 (1)

Five years tumor control rate was 89.9 % in all 72 patients, 92.9% in common subtype and 81.5% in uncommon subtype (Fig. 2 and 3). This was not significantly different between the two groups, Hazard ratio = 2.57 ($p = 0.108$).

Overall tumor shrinkage rate at 5 years was 42.5 %. This figure was statistically equal between the two groups (common subtype = 42.3%, uncommon subtype = 42.7%) ($p = 0.934$) (Fig. 4 and 5). The median time to shrinkage was 14 months (IQR: 20) after RT in total data. Also, there was no significant difference between common and uncommon subtypes.

Using univariate analysis, gender (male), total minimal dose and fraction had significant influence on tumor control (Table 4). In multivariate analysis, total minimal dose was the only significant factor ($p = 0.041$).

Discussion

This study aimed to explore the difference in tumor control by radiation therapy of postoperative residual intracranial meningioma (WHO grade I) that was classified into subtypes. Currently, there was no available publication regarding this topic. One of the possible reasons could be limited sample data for analyzing and categorizing those subgroups because the numbers in each subtype were too small. Hence, we decided to categorize subtypes into common subtype and uncommon subtypes. The common subtype included meningothelial (40.2%) and

Table 3. Demographic data in subgroups

Characteristics	Data		*p*-value
	Common subtype	Uncommon subtype	
Patients	79 (77.5%)	23 (22.5%)	-
Age (years)	Mean: 45.1 SD: 11	Mean: 47.1 SD: 13	0.466
Gender			
Male	12 (15.2%)	7 (30.4%)	0.098
Female	67 (84.8%)	16 (69.6%)	
Follow-up time (months)	Median: 45 (IQR 57.1)	Median: 51 (IQR 39.37)	0.647
RT data			
Tumor volume (cc)	Median: 17.8 (IQR 24.8)	Median: 12.6 (IQR 9.7)	0.230
Fraction			
Hypofraction	22 (27.8%)	10 (43.5%)	0.155
Total minimal dose (Gy)	Mean: 24.27 SD: 3.04	Mean: 24.40 SD: 3.30	0.913
Conventional	57 (72.2%)	13 (56.5%)	
Total minimal dose (Gy)	Mean: 37.67 SD: 5.82	Mean: 40.18 SD: 3.48	0.141
Duration: surgery to RT (weeks)	Median: 40 (IQR: 41.3)	Median: 34 (IQR: 28)	0.475

RT = radiotherapy; Gy = gray; SD = standard deviation; cc = cubic centimetres; IQR = interquartile range

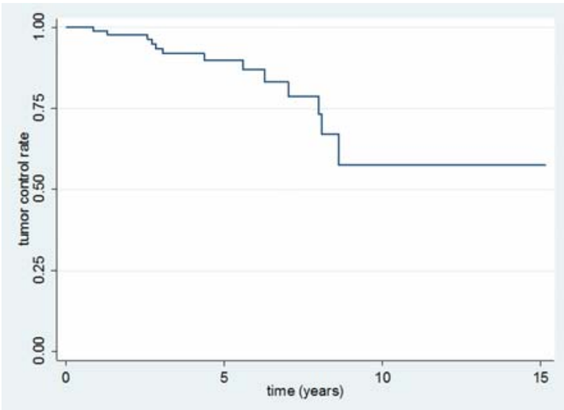
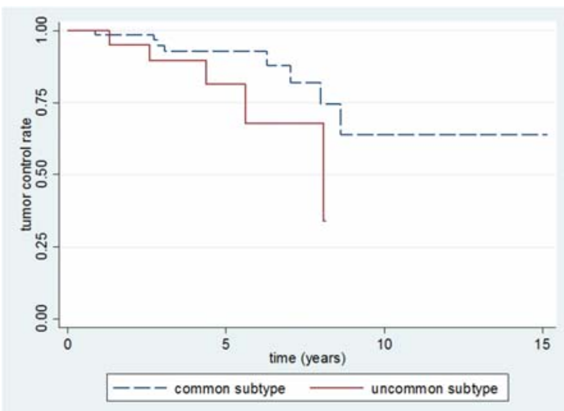
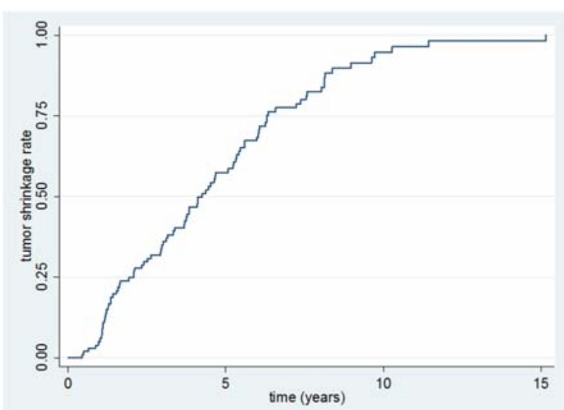


Fig. 2 Overall tumor control rate.



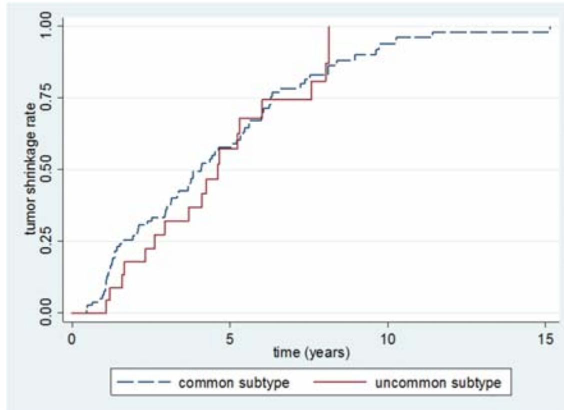
5 years tumor control rate in common subtype = 92.9% and uncommon subtype = 81.5%, Hazard ratio = 2.57, *p*-value = 0.108.

Fig. 3 Tumor control rate in subgroups.



Overall 5 years tumor shrinkage rate = 42.5%

Fig. 4 Overall tumor shrinkage rate.



5 years tumor shrinkage rate common subtype = 42.3% uncommon subtype = 42.7%, *p*-value = 0.934.

Fig. 5 Tumor shrinkage rate in subgroup.

transitional (37.3%). The uncommon subtype included fibroblastic (4.9%), psammomatous (2.9%), angiomatous (8.8%), microcystic (0.9%), secretory (1.9%), lymphoplasmacyte-rich (8.8%) and metaplastic (0.9%).

Though not statistically significant, the result from univariate analysis showed a trend indicating higher treatment failure rate in uncommon subtype (*p*-value = 0.096). If sufficient sample data were collected, the result might have potentially demonstrated significant difference between the two groups.

Most of residual tumors in this study were quite large (median 17.3 mlinterquartile range: 18.9) compared with other studies, for instance, the median tumor volume was 12.3 ml (range: 2.5-86.1) in Shunsuke Onodera et al(6), and 4.1 ml (range: 0.8-20) in Davidson et al(7). One possible explanation is that Thai patients generally seek medical attention later than other reported countries' patients. However, the five-years tumor control rate from our study (89.9%) was in the comparable range of several previous studies, for example, the five-years tumor control rate was 76% in Connell Philip P et al(8), 78% in Toshinori Hasegawa et al(14), 91% in Serdar Soyuer et al(3) and 93% in Yoshiyasu Iwai et al(9). Also in Asian countries, the five-years tumor control rate were similar, for example, the five-years tumor control rate was 93% in Iwai Y et al (Japan)(10), 94% in Hasegawa T et al (Japan)(11), 93.75% in Kumar R et al (India)(12) and 90.2% in Han JH et al (Korea)(13).

There have been attempts to identify risk

Table 4. Risk factors of treatment failure univariate

Variable	
Subtype	p = 0.096, log-rank; p = 0.108, Cox
Gender (male)	p = 0.007, log-rank; p = 0.013, Cox
Age (<50 years)	p = 0.199, log-rank; p = 0.229, Cox
Duration: surgery to RT	p = 0.527, log-rank; p = 0.530, Cox
Tumor volume	p = 0.129, log-rank; p = 0.140, Cox
Total minimal dose	p = 0.033, log-rank; p = 0.043, Cox
Hypofraction vs. conventional fraction	p = 0.003, log-rank; p = 0.007, Cox

RT = radiotherapy

factors of tumor regrowth after RT. Some studies have shown that male gender and age (less than 50 years old) affect the tumor control rate[14-16]. However, the results from our study could identify that only "total minimal dose" was the only significant factor for the risk of tumor regrowth.

In addition, there were two techniques of X-knife RT employed in our study, the conventional fraction and the hypofractionated techniques. There was no difference between these two techniques.

There were some limitations in this study. The data of 75 patients (29.8%) were excluded because the subtypes were unclassified and also 75 patients (29.8%) were excluded because of others reasons (use of RT as a primary treatment, loss to follow-up and the pathology was higher grade). This large number of cases might have statistically influenced the result of analysis in this study.

Conclusion

RT had excellent outcomes in controlling the residual grade I meningioma. It is very useful for high risk reoperation patients. About half of these tumors were shrunk over a period of time; hence the patients' symptom ms could be relieved by RT. The "total minimal dose" is the only risk factor of treatment failure. About subtype, the uncommon subtype has a tendency to recur more easily.

What is already known on this topic?

Radiotherapy in residual meningioma was effective way to control the tumor. The good results of this treatment were reported. But there was no study that analyzed the tumor in a subtype classification.

What this study adds?

This study reported the results of radiotherapy in grade I residual meningioma by classifying subtypes. As above, the uncommon subtype has a tendency to recur easily.

Potential conflicts of interest

None.

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การฉายแสงหลังการผ่าตัดเนื้องอกสมอง Meningioma ระดับที่ 1 โดยแบ่งเป็นชนิดย่อย

พีรพงศ์ เหลืองอาภาพงศ์, มัณฑนา ธนะไชย, เอก หังสสูต

วัตถุประสงค์: *เพื่อศึกษาผลของการฉายแสงหลังการผ่าตัดเนื้องอกสมอง Meningioma ระดับที่ 1 โดยแบ่งเป็นชนิดย่อย และปัจจัยที่มีผลต่อผลการรักษา*

วัสดุและวิธีการ: *จากข้อมูลผู้ป่วยเนื้องอกสมอง Meningioma ทั้งหมด 252 คน ซึ่งได้รับการฉายแสงในโรงพยาบาลรามาธิบดีระหว่างปี พ.ศ. 2541 ถึง พ.ศ. 2551 ผู้ป่วย 102 คน ได้ถูกนำมาศึกษาโดยแบ่งออกเป็น 2 กลุ่มตามชนิดย่อยของเนื้องอกสมอง Meningioma ระดับที่ 1 กลุ่มที่ 1 ชนิดที่พบบ่อย (Meningothelial and Transitional subtypes) และกลุ่มที่ 2 ชนิดที่พบไม่บ่อย (Fibroblastic, Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich and Metaplastic subtypes) โดยผู้นิพนธ์ได้ศึกษาในด้านอัตราการควบคุมเนื้องอก อัตราการหดตัวของเนื้องอก และปัจจัยที่มีผลต่อผลการรักษา*

ผลการศึกษา: *ค่ามัธยฐานของระยะเวลาการติดตามผู้ป่วยเท่ากับ 46 เดือน (12-182 เดือน) โดยพบว่าผู้ป่วยทั้งหมดมีอัตราการควบคุมโรคที่ 5 ปี เท่ากับร้อยละ 89.9 ในกลุ่มที่ 1 เท่ากับร้อยละ 92.9 และในกลุ่มที่ 2 เท่ากับร้อยละ 81.5 ซึ่งไม่มีความแตกต่างกันทางสถิติ ($p = 0.108$) อัตราการหดตัวของเนื้องอกที่ 5 ปีของผู้ป่วยทั้งหมดกลุ่มที่ 1 และกลุ่มที่ 2 เท่ากับร้อยละ 42.5 42.3 และ 42.7 ตามลำดับ ซึ่งไม่มีความแตกต่างกันทางสถิติเช่นกัน ($p = 0.934$) การวิเคราะห์โดยวิธีตัวแปรเดียว (univariate analysis) พบว่าเพศชายปริมาณรังสีรวมที่น้อยที่สุด (total minimal dose) และการแบ่งการฉายรังสี มีผลต่อผลการรักษาแต่เมื่อนำมาคำนวนโดยวิธีหลายตัวแปร (multivariate analysis) พบว่าปริมาณรังสีรวมที่น้อยที่สุดเป็นปัจจัยที่มีผลต่อผลการรักษาเพียงปัจจัยเดียว*

สรุป: *การฉายรังสีเป็นวิธีควบคุมเนื้องอก meningioma ตามหลังการผ่าตัดที่มีประสิทธิภาพ การศึกษานี้อาจช่วยวิเคราะห์การพยากรณ์โรคและโอกาสการกลับมาเป็นซ้ำของเนื้องอก meningioma ที่ผ่าตัดไม่หมดโดยแบ่งเป็นชนิดย่อย อย่างไรก็ตามปริมาณรังสีรวมที่น้อยที่สุดเป็นปัจจัยที่มีผลต่อผลการรักษาเพียงปัจจัยเดียวในการศึกษา*