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Research Article

Association Between Size Of Residual Non-Functioning Pituitary Adenoma and Regrowth after Surgery

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Abstract

Objective: A residual non-functioning pituitary adenoma (NFPA) after surgical removal is a well-known predictive risk factor for the regrowth of tumors, but there is no guide for the size of the residual tumor to predict. This study utilized the size of the residual tumor to predict the regrowth of non-functioning pituitary adenoma after surgical removal and investigated other predictors for tumor regrowth.

Methods: The retrospective study included 123 newly diagnosed NFPA cases that had been operated on at Maharaj Nakorn Chiang Mai Hospital from January 2009 to December 2020. The size of the residual tumor was monitored through CT scans or 1.5 Tesla MRI interpreted by a neurosurgeon and neuroradiologists. Multivariate analysis was employed to identify predictors of tumor regrowth, and the Kaplan-Meir method was used to determine regrowth-free survival.

Results: This study comprised 123 patients newly diagnosed with NFPA after surgical removal. Comparisons were made between a regrowth/recurrence tumor group (22 patients) and a no-progression group (101 patients). Univariate analysis indicated that residual tumor size, especially tumors larger than 1 cm (HR 4.00, 95%CI 1.16-13.83, p = 0.03), was the most significant factor. In multivariate analysis, adjusted for radiotherapy, hormonal deficit, age, and gender, it was revealed that regrowth or recurrence of the tumor depends on the size, especially more than 1 cm (HR 6.52, 95%CI 1.37-31.07, p = 0.02).

Conclusion: Residual non-functioning pituitary adenoma after surgical removal could predict progression in the future, particularly for sizes larger than 1 cm. Neurosurgeons must pay attention to patients in this group.

Keywords: pituitary adenoma, non-functioning pituitary adenoma, residual non-functioning pituitary adenoma

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บทคัดย่อ

ความสัมพันธ์ระหว่างขนาดของเนื้องอกต่อมใต้สมองชนิดที่ไม่ผลิตฮอร์โมนที่เหลือหลังผ่าตัดและการกลับมาโตของเนื้องอก

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ที่มาและวัตถุประสงค์: เนื้องอกต่อมใต้สมองชนิดที่ไม่ผลิตฮอร์โมน (Non-functioning Pituitary Adenoma (NFPA)) ที่เหลือหลังผ่าตัดเป็นปัจจัยสำคัญสำหรับการกลับมาโตของเนื้องอก แต่ในปัจจุบันยังไม่มีแผนปฏิบัติที่ชัดเจน ว่าขนาดเนื้องอกเหลือหลังผ่าตัดเท่าไรถึงจะมีผลกับการกลับมาโตของเนื้องอกในอนาคต การศึกษานี้ ศึกษาเกี่ยวกับ ขนาดของเนื้องอกที่เหลือหลังผ่าตัดจะสามารถทำนายการกลับมาโตของเนื้องอกในอนาคต และ ศึกษาปัจจัยต่าง ๆที่สัมพันธ์กับการโตของเนื้องอก

วิธีการศึกษา: เป็นการศึกษาแบบ retrospective ในผู้ป่วยที่ได้รับการวินิจฉัยเป็นเนื้องอกต่อมใต้สมองชนิดที่ไม่ผลิตฮอร์โมน 123 คน ที่ได้รับการผ่าตัดในโรงพยาบาลมหาราชนครเชียงใหม่ ตั้งแต่ เดือนมกราคม ปี พ.ศ. 2552 - เดือนธันวาคม พ.ศ. 2563 และได้รับการติดตามขนาดของเนื้องอก โดย CT scan หรือ 1.5 Tesla MRI และได้รับการแปลผลโดยประสาทศัลยแพทย์และประสาทรังสีแพทย์ การศึกษาได้แปลผลเพื่อหาปัจจัยสำคัญในการกลับมาโตของ เนื้องอกหลังผ่าตัด โดย multivariate analysis และ Kaplan Meir Method เพื่อหาอัตราการไม่กลับมาเป็นซ้ำของเนื้องอกหลังผ่าตัด

ผลการศึกษา: การศึกษาได้ทำการแบ่งกลุ่มผู้ป่วยเป็น 2 กลุ่ม ระหว่าง กลุ่มที่มีการกลับมาโตซ้ำของเนื้องอก (22 คน) และ กลุ่มที่ไม่มีการกลับมาโตซ้ำ (101 คน) , การแปลผลแบบ univariate analysis พบว่า ขนาดของเนื้องอกที่เหลือหลังผ่าตัดเป็นปัจจัยสำคัญและโดยเฉพาะอย่างยิ่งเนื้องอกที่มีขนาดมากกว่า 1 เซนติเมตร (HR 4.00 95%CI 1.16-13.83 p = 0.03) และ multivariate analysis หลังจากได้ adjust โดย การได้รับการฉายรังสี,การมีภาวะฮอร์โมนบกพร่อง, อายุ และเพศ พบว่า การกลับมาเป็นซ้ำของเนื้องอกขึ้นอยู่กับขนาดของเนื้องอกโดยเฉพาะอย่างยิ่งขนาดมากกว่า 1 เซนติเมตร (HR 6.52 95%CI 1.37-31.07 p = 0.02)

สรุป: เนื้องอกต่อมใต้สมองชนิดที่ไม่ผลิตฮอร์โมนที่เหลือหลังการผ่าตัด สามารถทำนายการโตกลับมาของเนื้องอกได้ในอนาคต โดยฉพาะอย่างยิ่งขนาดที่มากกว่า 1 เซนติเมตร ประสาทศัลยแพทย์ควรดูแลผู้ป่วยในกลุ่มนี้อย่างใกล้ชิด

คำสำคัญ: เนื้องอกต่อมใต้สมอง , เนื้องอกต่อมใต้สมองชนิดที่ไม่ผลิตฮอร์โมน , เนื้องอกต่อมใต้สมองชนิดที่ไม่ผลิตฮอร์โมนที่เหลือหลังการผ่าตัด

Introduction

Non-functioning pituitary adenoma (NFPA) is the most common subtype of pituitary adenoma, typically causing compressive symptoms such as visual field deficits and headaches. Transsphenoidal surgery is the treatment of choice, intending to achieve gross total resection to alleviate symptoms. However, there is a high rate of recurrence associated with incomplete resection.

Gross total resection faces limitations, including tumor consistency and adherence to structures like the internal carotid artery and cavernous sinus,

leading to the development of postoperative residual tumors. Approximately 12-58% of patients with residual tumors experience regrowth[1]. The management of regrowth includes options such as re-surgery, radiotherapy, or closed follow-up[2], posing challenges for neurosurgeons. Revision surgery is complicated due to anatomy distortion by scar tissue, and there are limitations for reconstruction to prevent cerebrospinal fluid leakage. Radiotherapy serves as an adjuvant treatment for residual tumors, significantly reducing the risk of tumor regrowth, with 80-97% long-term tumor control[3].

Studies predicting the recurrence or regrowth of tumors are limited, primarily due to the benign and slow-growing nature of these tumors, requiring extended follow-up periods. Several studies indicate that residual tumor is a predictor of non-functioning pituitary adenoma behavior post-surgery. For instance, Maletkovic et al demonstrated a higher risk of tumor growth in patients with postoperative residual tumors. Other predictors include invasion of the cavernous sinus, absence of immediate postoperative radiotherapy[4,10], and immunohistochemical features involving gonadotrophins and other hormones[5], or pathologic features such as Ki-67 labeling index and extensive p53 immunoreactivity[6-8,12-15]. Few studies relate residual tumor size after surgery to tumor regrowth, with a lack of consensus on the size predicting tumor growth.

The main objective of this study was to determine the residual tumor size after surgery that can predict tumor regrowth. Additionally, the study aimed to identify other predictors that can predict regrowth or recurrence of tumors. The study was conducted at Maharaj Nakorn Chiang Mai Hospital from January 2009 to December 2020.

Material and Methods

Study design

We conducted a retrospective review of all newly diagnosed cases of non-functioning pituitary adenoma (NFPA) that underwent surgery between January 2009 and December 2020 at Maharaj Nakorn Chiang Mai Hospital. The inclusion criteria were newly diagnosed NFPA cases. We excluded patients who lacked post-operative imaging within 6 months, did not have comparative imaging at least 1 time after surgery within 5 years, or had undergone previous surgery. All NFPA patients underwent surgical removal by neurosurgeons at Maharaj Nakorn Chiang Mai Hospital, employing either a transsphenoidal or transcranial approach.

The collected data included patient demographic information, follow-up time (in months), main symptoms (such as visual problems, headaches, incidental findings, or hormonal issues), tumor profile (such as the presence of cysts/hemorrhage), Knosp classification, preoperative tumor diameter, extension, residual tumor after surgical removal, hormonal deficits, Ki-67 labeling index in the surgical specimens using the MIB-1 monoclonal antibody, and postoperative radiotherapy.

Residual tumor

We defined a residual tumor term if a tumor is present in post-operative imaging. In this study, we used computed tomography (CT) scan with contrast or 1.5 Tesla magnetic resonance imaging (MRI) with gadolinium contrast interpreted by a neurosurgeon and neurological radiologists within 6 months after surgical removal. In some images, it was difficult to interpret residual tumor or no residual tumor, we then defined this group as an equivocal (ambiguous) group

and assigned it to the no residual tumor group

In the previous research[9], there has been no published study regarding the size of residual tumors after surgery that significantly influences the regrowth of the tumor. Therefore, this study serves as a pilot study to explore the statistical significance of this correlation.

Definition of tumor diameter

In this study, all imaging utilized CT scans with contrast or 1.5 Tesla MRI scans with gadolinium contrast (using T1 weighted image with gadolinium contrast) at Maharaj Nakorn Chiang Mai Hospital, interpreted by both a neurosurgeon and neuroradiologists. Tumor diameter was defined by measuring the maximal diameter of the tumor (in any plane) in centimeters.

Regrowth and recurrence of tumors

We defined the "regrowth tumor" group when there was evidence of tumor progression in the imaging compared to the first post-operative residual tumor imaging. Image comparison was conducted within 5 years after surgical removal. The "recurrence tumor" group was characterized by the absence of residual tumor in the first post-operative imaging, followed by the detection of a tumor in the subsequent comparison imaging.

Ki-67 labeling index analysis

All pathological diagnoses confirmed non-functioning pituitary adenoma, and MIB-1 antibody was utilized to identify Ki-67. The labeling index was subsequently calculated as the percentage of immunopositive nuclei by a neuropathologist.

Postoperative radiotherapy

The decision regarding whether a specific patient should undergo postoperative radiotherapy was left to the discretion of the neurosurgeon.

Statistical analysis

For categorical data, we utilized chi-squared and Fisher exact tests for comparisons. Mann-Whitney U test and student's t-test were employed for continuous data. Multivariate analysis was conducted to identify predictors of regrowth or recurrent tumors. Kaplan-Meier method was employed to determine residual tumor with regrowth or recurrent-free survival. A probability value of $p < 0.05$ was considered statistically significant.

Results

Patients Characteristics

This study includes a total of 123 patients meeting the inclusion criteria for this study, all of whom were newly diagnosed with non-functioning pituitary adenoma undergoing surgical removal (Table 1).

Demographic data were compared between the regrowth/recurrence tumor group (22 patients) and the no progression group (101 patients). Data (Table 1) demonstrates age, gender, main symptoms, tumor profile (presence of cyst/hemorrhage, Knosp classification, pre-operative maximal diameter, extension tumor, hormonal deficit at least 1 axis, Ki-67 Li > 1, and postoperative radiotherapy) did not differ between the two groups. Time follow-up (months) was higher in the regrowth and recurrence tumor group than in the no progression group, 41.9

Table 1 Demographic Data for the no Progression Group (N=101) and the regrowth/recurrence Tumor Group (N=22) based on evidence of tumor progression in comparison to the initial post-operative imaging.

	No (N=101)	Yes (N=22)	*p*-value
Age	53.4 (42.0-60.4)	49.9 (42.7-58.3)	0.45
Gender			
Male	47 (46.5%)	9 (40.9%)	0.81
Female	54 (53.5%)	13 (59.1%)	
Time follow-up (months)	41.9 (27.4-67.8)	70.1 (58.5-100.4)	< 0.001
Main Symptom			
Visual problem	69 (69%)	15 (68.2%)	0.69
Headache	16 (16%)	5 (22.7%)	
Incidental	11 (11%)	1 (4.5%)	
Hormonal	4 (4%)	1 (4.5%)	
Presence of Cyst			
Yes	71 (70.3%)	14 (63.6%)	0.61
No	30 (29.7%)	8 (36.4%)	
Presence of Hemorrhage			
Yes	77 (76.2%)	19 (86.4%)	0.40
No	24 (23.8%)	3 (13.6%)	
Knosp Classification			
Grade 0	45 (44.6%)	5 (22.7%)	0.10
Grade I	18 (17.8%)	4 (18.2%)	
Grade II	15 (14.9%)	2 (9.1%)	
Grade III	10 (9.9%)	4 (18.2%)	
Grade IV	13 (12.9%)	7 (31.8%)	
Preoperative Maximal Diameter (cm)	2.8 (2.3-3.5)	3.2 (2.5-3.6)	0.22
Extension			
Suprasellar	64 (63.4%)	12 (54.5%)	0.72
Parasellar	32 (31.7%)	9 (40.9%)	
Residual Tumor			
No	45 (44.6%)	3 (13.6%)	0.008
Yes	56 (55.4%	19 (86.4%)	
Hormonal deficit at least 1 axis			
No	41 (42%)	7 (39%)	0.82
Yes	57 (58%)	11 (61%)	
Ki-67 Li > 1			
No	31 (78%)	7 (88%)	1.00
Yes	9 (23%)	11(13%)	
Radiotherapy			
No	91 (90.1%)	21 (95.5%)	0.69
Yes	10 (9.9%)	1 (4.5%)	

(27.4–67.8) vs 70.1 (58.5–100.4) ($p < 0.001$).

The first post-operative imaging showed residual tumor in 75 patients (61%) and no residual tumor in 48 patients (39%). Residual tumor after surgical removal was higher in the regrowth and recurrence tumor group ($p = 0.08$).

Ki-67 Li has several missing values; we only have 58 pathological specimens from 123 patients in this study due to storage problems in our hospital, with only 18 specimens suspected of old storage issues.

Outcome predictor of regrowth, recurrence of tumor

In the univariate analysis (Table 2), residual tumor size emerged as the most critical outcome predictor, particularly for residual tumor sizes exceeding 1 cm (HR 4.00, 95% CI 1.16–13.83, $p = 0.03$), and sizes less than 1 cm, respectively (HR 3.03, 95% CI 0.68–13.57, $p = 0.15$).

Table 2 Univariate analysis , involves defining multiple factors that can predict tumor progression.

Outcome predictor	HR	95% CI	*p*-value
Age	1.00	0.96–1.04	0.94
Gender	1.20	0.51–2.81	0.68
Preoperative tumor diameter > 4 cm	1.74	0.59–5.16	0.32
Extension			
Suprasellar	1.21	0.16–9.46	0.85
Parasellar	1.70	0.21–13.58	0.62
Knosp Classification			
Grade I	1.93	0.52–7.21	0.33
Grade II	1.06	0.20–5.45	0.95
Grade III	2.73	0.73–10.19	0.13
Grade IV	4.60	1.45–14.57	0.01
Hormone deficit at least 1 axis	1.05	0.41–2.72	0.91
Residual tumor size			
Residual < 1 cm	3.03	0.68–13.57	0.15
Residual 1 cm or more	4.00	1.16–13.83	0.03
Radiotherapy	0.38	0.05–2.80	0.34

Knosp Classification was identified as a predictive factor for tumor progression based on grading, with grade IV carrying the highest risk of tumor progression (HR 4.60, 95% CI 1.45–14.57, $P = 0.01$). Other factors did not achieve statistical significance in univariate analysis, such as age (HR 1.00, 95% CI 0.96–1.04, $P = 0.94$), gender (HR 1.20, 95% CI 0.51–2.81, $P = 0.68$), preoperative tumor diameter > 4 cm (giant NFPA) (HR 1.74, 95% CI 0.59–5.16, $p = 0.32$), suprasellar extension (HR 1.21, 95% CI 0.16–9.46, $p = 0.85$), parasellar extension (HR 1.70, 95% CI 0.21–13.58, $p = 0.62$), hormonal deficit at least 1 axis (HR 1.05, 95% CI 0.41–2.72, $P = 0.91$).

We observed that postoperative radiotherapy appeared as a protective factor, although this result

did not reach statistical significance (HR 0.38, 95% CI 0.05–2.80, p = 0.34).

In the multivariate analysis (Table 3), after adjusting for radiotherapy, hormonal deficit, age, and gender, the outcome predictor for regrowth or recurrence of the tumor was found to depend on its size, especially for residual tumor sizes exceeding 1 centimeter (HR 6.52, 95% CI 1.37–31.07, p = 0.02).

Table 3 Multivariate analysis of residual non-functioning pituitary adenoma

Outcome predictor	HR	95% CI	*p*-value
Residual < 1 cm	5.29	0.94–29.90	0.06
Residual 1 cm or more	6.52	1.37–31.07	0.02

Discussion

Residual non-functioning pituitary adenoma after surgical removal is a well-known predictor of regrowth or recurrent tumors, yet there is a lack of Class I evidence to guide the management of patients with residual pituitary adenoma.[9]

Previous studies[4-5,11] have consistently identified residual tumors as the most crucial predictive factor for relapse after surgery, resulting in tumor growth-free survival rates inferior to those of the tumor-free group. Other predictive factors for the regrowth/recurrence of non-functioning pituitary adenoma (NFPA) include a high Ki-67 index[6-8], pre-operative maximal diameter, and cavernous sinus invasion. Postoperative radiotherapy has proven to be the most effective protective adjuvant therapy against tumor growth.[3] Ki-67 Labeling Index (Li) serves as a clinically useful prognostic parameter, indicating the probability of progression in postoperative residual tumors.[14-15] However, its definitive value in daily practice remains controversial, with conflicting literature on its significance in correlating with recurrent or regrowth tumors.

This study emphasizes the significance of residual tumors, particularly when their size exceeds 1 centimeter. The natural history of NFPA, characterized by its benign and slow-growing nature, necessitates prolonged follow-up for a comprehensive understanding.[1] Kaplan Meier survival estimates (Graph 1) indicate a decreasing regrowth-free rate over time for tumors with residual components compared to the recurrence-free rate in the no residual tumor group. The findings underscore the importance of guiding management strategies, especially for tumors larger than 1 cm, where the risk of regrowth/recurrence increases.

The challenging management of postoperative pituitary adenoma patients lacks clear guidelines and a defined size cut-off for residual tumor management.[9] This study suggests an accessible approach for physicians to follow up on patients using the size of residual tumor diameter. Large residual tumors may warrant close monitoring or aggressive treatments such as re-surgery or radiotherapy.

Other predictive factors align with previous studies, including high-grade Knosp classification, parasellar extension, and preoperative tumor diameter exceeding 4 centimeters. Notably, radiotherapy emerges as a crucial protective factor, especially for patients with residual tumors posing challenges for re-surgery (Graph 2). Neurosurgeon decisions should consider the individualized risk-benefit profile of each patient.

Limitations

This study lacked a definite protocol for postoperative patient follow-up, resulting in individualized management by multiple physicians and an absence of a standardized timeline for follow-up. This limita-

tion, stemming from delayed postoperative imaging, could be addressed through prospective studies.

Postoperative imaging, including 1.5 Tesla MRI with gadolinium contrast and CT brain with contrast encompassing the pituitary gland, posed challenges in defining and monitoring residual tumors. Particularly during the initial postoperative imaging, distinguishing unequivocally between residual tumor and no residual tumor was challenging. Another research challenge involves measuring tumor size, with potential compromises in accuracy by neurosurgeons. To enhance precision in future research, incorporating standard software for tumor volume calculations is recommended.

Significant differences in patient follow-up between the groups are noted. The group without regrowth tumors has an average follow-up duration of 41.9 months, while the group with regrowth tumors has a considerably higher average follow-up duration of 70.1 months (p-value < 0.001). These results highlight a potential risk of misinterpretation in the comparative analysis due to the inherent limitations of retrospective studies, where variables cannot be controlled. Patients without regrowth tumors might have sought further care at local hospitals, leading to a significantly shorter follow-up duration in this group.

Conclusion

Residual non-functioning pituitary adenoma post-surgery that could predict progression in the future, consists of residual tumor size greater than 1 centimeter. Neurosurgeons must pay particular attention to patients in this group.

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