Growth of Pituitary Macroadenomas Postpartial Resection: Implications for Adjuvant Radiotherapy

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Abstract

Objective To determine the volumetric growth in macroadenomas (MAs) patients with residual postoperative disease and to identify subpopulations with rapid postoperative growth rate that may benefit from early salvage radiotherapy (RT).

Methods Patients who had undergone a partial resection for MAs and did not receive immediate postoperative RT were eligible. Residual tissue was contoured on serial magnetic resonance imaging and planimetric and volumetric changes in size were measured. Growth rates were established by a single observer using serial volumetric measurements. Data were analyzed to find a relationship among growth rate, adjuvant treatment, and patient and tumor characteristics.

Results Thirty-one patients met the eligibility criteria. Nine patients (29%) required adjuvant treatment because of tumor growth. Volumetric growth was identified 95% of the time compared with 64% planimetrically. Planimetric growth could not be established in 10% of patients showing volumetric changes. Median growth rate was 0.4464 mL/y. Growth rate positively correlated with size of residual postoperative volume ($p < 0.001$). Receiving salvage treatment positively correlated with growth rate ($p = 0.001$), particularly at a rate above 2.19 mL/y ($p = 0.0064$). Five patients (16%) had a growth rate above this level, all of which required salvage treatment. Patients with postoperative residual volume > 3.95 mL were most likely to experience rapid growth rate and require salvage treatment ($p = 0.007$).

Conclusion Volumetric measurement was found to be superior to planimetric measurement in detecting changes in patients with residual tumors. Patients with postoperative residual volume > 3.95 mL should be considered for early treatment with RT.

Keywords

- pituitary
- macroadenoma
- radiotherapy
- surgery
- volumetric growth

Introduction

Pituitary adenomas are benign tumors of the pituitary, classified by their cell of origin and their size, with macroadenomas (MAs) measuring at least 1 cm in size. Approximately 30 to 35% of pituitary adenomas are clinically

nonfunctioning. These nonfunctioning macroadenomas (NFMAs) comprise ~15% of pituitary tumors.¹ Transsphenoidal surgery remains the primary treatment for NFMAs. However, NFMAs can be quite large at the time of diagnosis making a complete tumor resection not always possible for various reasons.

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There are several studies in the literature reporting regrowth of partially surgically resected MAs. With surgery alone, studies have reported regrowth rates of up to 30% at 5 years and 50% at 10 years, depending on the amount of residual tissue postoperatively.²⁻⁵ Radiotherapy (RT) in the adjuvant setting is therefore an attractive option to prevent regrowth of residual tumor where complete resection has not been achieved. However, there are concerns relating to potential long-term side effects of RT to this area, including panhypopituitarism, damage to the optic chiasm, as well as stroke and neurocognitive side effects.⁶ A majority of NFMA are slowly growing and there are currently no reliable clinical, biochemical, radiological, or pathological parameters that predict the likelihood of tumor regrowth, making it challenging to predict which tumors will progress and become symptomatic. As such, there are currently no established guidelines for the use of early salvage RT in the setting of partially resected NFMA.

Previous studies have assessed NFMA growth by measuring the greatest dimension of the lesion using crude two-dimensional measurements. Due to limitations in diagnostic imaging software, it may be difficult to truly estimate the regrowth of NFMA based on measurement in two dimensions. The aim of this study was to accurately determine volumetric tumor growth and to review patient demographics to explore correlations between baseline and postoperative patient characteristics and tumor regrowth to further identify those patients who may benefit from early RT.

Methods

After obtaining Institutional Review Board approval to conduct this retrospective review, patients who had undergone resection of NFMA were identified, and their charts and imaging studies were carefully reviewed (given the retrospective nature of the review, a written signed consent from patient was not required). Extent of resection, tumor histology, patient demographic information, length of follow-up, and salvage therapy were all recorded. Patients who had undergone partial resection, did not receive immediate postoperative RT, and had a minimum of two follow-up magnetic resonance imaging (MRI) studies were eligible for the study.

For patients meeting the study eligibility criteria, the preoperative and postoperative images were analyzed and transferred to commercially available RT treatment planning software (MIMvista, Cleveland, Ohio, United States). Tumors were contoured on each imaging slice and volumes were determined. Planimetric measurements on the axial, coronal, and sagittal planes were also taken on the same images for each patient. To minimize interobserver variability, a single radiation oncologist (K.S.) contoured on all images. To minimize bias, the radiation oncologist was blinded to all patient information and temporal sequencing of scans by anonymizing all scans. Axial and coronal T1 gadolinium-enhanced MRI scans were used for all measurements except in one case where a gadolinium-enhanced scan was not available and T1 sequence alone was used. Follow-up MRIs were not necessarily done on the same plane each time. Slice thickness ranged from 1 mm on preoperative images to 5 mm on follow-up scans. Initial

follow-up images were obtained from 1 to 26 months postoperatively (median 8.9 months). Tumor growth and growth rate were assessed by increases in tumor volume and size on serial imaging. Failure was defined as any change in size or volume of the residual tumor.

Variables analyzed for potential prediction of postoperative tumor growth and the need for adjuvant treatment included age, gender, preoperative volume, postoperative volume, preoperative and postoperative planimetric size, and growth rate. Receiver operating characteristics analysis was used to identify optimal cutoff points and chi-squared test (χ^2) was used to compare sets of categorical data. SPSS (version 22, IBM Corporation, Armonk, New York, United States) and MATLAB (release 2014a, MathWorks, Natick, Massachusetts, United States) were used for all statistical analysis.

Results

Between 1995 and 2010, 64 patients who had undergone surgery at our institution for a pituitary MA were identified. Twenty-one patients were excluded on the basis of having histology other than NFMA, four patients were excluded due to insufficient follow-up imaging, and three patients received immediate postoperative RT or underwent immediate reresection. Thirty-six patients with NFMA were identified. Only two of these patients had undergone complete resection and were excluded. Of the remaining 34 patients who met the study eligibility criteria, 3 patients were excluded from the final analysis, as tumor and postoperative changes could not be differentiated on imaging. Initial follow-up imaging reports were checked to confirm the presence of residual disease in all patients.

► **Table 1** shows the demographic information of the study population. A total of 81 postoperative MRIs were analyzed and tumor volumes were contoured. Volumetric growth was detected in 95% of all cases. Median time to detectable volumetric growth was 25 months (range: 4–84). Planimetric growth could only be confirmed on 64% of images analyzed and was missed on the remainder. This was later confirmed on the imaging reports once the data were unblinded. ► **Fig. 1**

Table 1 Patient characteristics

Parameter		Number of patients (%)
Median age	55 (range: 33–77)	
Gender		
Male		19 (61)
Female		12 (39)
Median follow-up time	4.4 y (range: 1.5–7.3)	
Median residual volume	1.65 mL (range: 0.19–19.79)	
Median growth rate	0.4464 mL/y (range: 0.0108–21.9)	
Retreatment		9 (29)

Fig. 1 Postoperative magnetic resonance images (left: immediate postoperative; right: 8 months postsurgery) showing example of pituitary macroadenoma growth, detected by volumetric but not by planimetric measurement.

shows serial MRIs from a patient in which no planimetric change was detected on consecutive MRIs while there was a volumetric change from 0.793 to 0.893 cm³. Median overall time to detectable planimetric growth was 29.5 months (range: 1–84). Nine patients (29%) required subsequent salvage treatment with RT (two patients) or resection (seven patients). Growth rate positively correlated with residual postoperative volume ($p < 0.001$). No relationship could be established with age, gender, or preoperative or postoperative planimetric size. Receiving salvage treatment positively correlated with growth rate ($p = 0.001$), particularly at a rate above 2.19 mL/y ($p = 0.0064$). Five patients (16%) had a growth rate above this level, all of which required salvage treatment. The median growth rate in all patients requiring retreatment was 3.08 mL/y (range: 0.39–21.9), compared with 0.27 mL/y (range: 0.01–1.3) in patients not requiring subsequent treatment. Patients with postoperative residual volume > 3.95 mL were most likely to experience rapid growth rate and require salvage treatment ($p = 0.007$). A total of eight patients (26%) had residual volume > 3.95 mL, of which five required adjuvant treatment. The median residual volume in patients requiring retreatment was 4.7 mL (range: 0.69–19.79), compared with 1.27 mL (range: 0.19–19.79) in those not requiring subsequent resection or RT. Median time to salvage treatment was 32 months (range: 17–79).

Discussion

By measuring sequential tumor volume on serial imaging, we were able to establish a growth rate for these tumors and show that changes not detected planimetrically could be detected by volumetric measurements, suggesting that it is the superior way to detect subtle changes in NFMA volume. Previous studies have used planimetric measurements, which may have underestimated NFMA growth. As Vakilian et al pointed out in their work on acoustic neuromas, volume is an important metric since small changes in diameter translate to large changes in the volume.⁷

RT can be an important part of the control of MAs. In the adjuvant setting, control rates as high as 95% at 10 years and 91% at 20 years have been reported.⁶ The side effects of RT are well known and can include hypopituitarism, visual deficits, and stroke.⁶ Given the potential toxicity of the treatment, it is important to properly select patients in which the benefits of local control clearly outweigh the risk of toxicity. Toxicity with RT increases with the volume of tissue treated. Although the risk of developing RT-induced toxicity cannot be eliminated entirely, it can potentially be minimized by treating smaller volumes, making it important to identify those at greatest risk for recurrence; therefore, they can receive treatment earlier when the residual volume is small. However, there are no established guidelines in terms of when to use RT in the setting of partially resected MAs. In many series published reporting the control in patients who received salvage RT, the criteria for patient selection are not discussed.⁸ Current studies have shown that the degree of surgical resection, that is, residual tumor in the sella is the most important factor in predicting tumor recurrence.⁹ In this series, roughly one-third of the patients required retreatment either with RT or repeat surgery. We attempted to find variables that would be predictive of the potential need for salvage treatment. Variables analyzed included preoperative and postoperative planimetric size and volume, age, gender, and growth rate. No relationship could be established with any of the variables mentioned except growth rate ($p = 0.001$), that is, tumors showing a growth rate of at least 2.19 mL/y on serial imaging were the most likely to become problematic and require salvage treatment ($p = 0.0064$), be it repeat surgery or RT. Growth rate, for obvious reasons, is not a metric variable, which can be used immediately postoperatively to predict the future need for salvage treatment, as it requires serial imaging over a sufficient period of time. We therefore attempted to identify surrogate variables, which would be predictive of rapid growth rate. Variables analyzed included preoperative and postoperative planimetric size, tumor volume, age, and gender. Notwithstanding the fact that the number of patients studied in our review is relatively small preventing a

definitive conclusion, in multivariate analysis only postoperative volume greater than 3.95 mL was found to be a significant predictor of rapid growth rate ($p = 0.007$), defined as growth of at least 2.19 mL/y. Based on these results, we suggest using a residual tumor volume of 3.95 mL on postoperative imaging as a reasonable indication to proceed with RT or repeat surgery when the volume of disease is reasonably small potentially limiting the toxicity of treatment.

The optimal time to intervene on a postoperative residual pituitary MA remains controversial. From the radiation therapy standpoint, it is intuitive that offering treatment earlier, at a time the tumor volume is smaller, rather than later may lead to better disease control. In fact, the guidelines from the Congress of Neurological Surgeons, based on a review of 49 studies, do recommend (level II recommendation) either radiation therapy or radiosurgery for treatment of residual nonfunctioning pituitary adenomas.¹⁰ The authors carefully also reviewed the potential risk for radiation injury, including hypopituitarism (0–39%) and cranial nerve neuropathy (0–14%), indicating that a judiciously long-term follow-up is required for these patients. Recently, Pomeranec et al performed a matched-cohort comparison on the timing of stereotactic radiosurgery (earlier vs. later treatment) in patients with subtotaly resected adenomas.¹¹ The authors concluded that earlier treatment was associated with a lower risk of radiological progression compared with expectant management followed by late radiosurgery. Whether a threshold volume of 3.95 mL is the optimal volume remains to be confirmed, particularly considering that our analysis was done using a continuous variable in a relative small number of patients.

This study suffers from the inherent and expected flaws associated with retrospective reviews. The relatively small number of patients and its retrospective nature limits our study. Furthermore, treatment decision postsurgery was based on individual physician decision. In addition, follow-up images sequence and technique were not prospectively established which could certainly lead to uncertainty in planar and volumetric measurements. We also acknowledge that with 5 mm slices, it is entirely possible that patient position differences can account for changes in smaller pituitary adenomas. In addition, a single rater was used to determine measurements and it is conceivable that interobserver reliability could occur if two or more raters participated in the assessment. A further limitation was the occasional difficulty in assessing residual volume from postoperative changes, which can persist for quite some time following surgery. A larger, prospective study with specific and predefined imaging guidelines is necessary to validate the value of assessing residual volume and volumetric growth rate and may provide better estimates of residual volumes that can be used to guide adjuvant treatment decisions. Nevertheless, despite these shortcomings, the information reported here can be used as guidance for adjuvant therapy in those patients with residual tumor and a fast growth rate. Future studies should prospectively define criteria for follow-up imaging including planar orientation, consistent MRI field strength, and preferably, volumetric acquisition. It should also include multiple observers performing the contouring of the patient set as a measurement of interobserver reproducibility. It is also

worth noting that 5 mm slice thickness on MRI may be too large to detect subtle but important changes in the volume of NFMA.

Conclusion

Our study shows that a majority of incompletely resected NFMA undergo growth following surgery and that volumetric measurement is superior to planimetric measurement in detecting earlier changes. We have also confirmed that the volume of residual disease after surgery is the single most important predictor of recurrence and the potential need for further treatment. In the absence of other guidelines in the literature, we suggest that patients with postoperative residual volume > 3.95 mL should be considered for early adjuvant treatment with RT with potentially less toxicity due to smaller volume of residual disease.

Note

This study was presented as a poster in the annual meeting of the American Society for Radiation Oncology, San Francisco, CA, September 14–17, 2014.

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