Title

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Journal

Pituitary, 13(3)

ISSN

1386-341X

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Publication Date

2010-09-01

DOI

10.1007/s11102-010-0221-z

Peer reviewed

Pituitary (2010) 13:223–229
DOI 10.1007/s11102-010-0221-z

Long term outcome following repeat transsphenoidal surgery for recurrent endocrine-inactive pituitary adenomas

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Published online: 9 March 2010

Abstract It is widely accepted that the standard first-line treatment for most endocrine inactive pituitary macroadenomas (EIA) is surgery, usually via a transsphenoidal approach. What is less clear is what approach to take when these tumors recur, especially when this recurrence involves areas which are difficult to surgically remove tumor from, such as the suprasellar region or cavernous sinuses. We present long term follow-up for a series of 81 patients who underwent repeat surgery for recurrent non-secreting pituitary adenomas. We analyzed data collected from all adult patients undergoing their second microsurgical transsphenoidal resection of a histologically proven endocrine-inactive pituitary adenoma at the University of California at San Francisco between January 1970 and March 2001. Data for these patients were collected by review of medical records, mail, and/or telephone interviews. Visual function, anterior pituitary function, and tumor control rates were analyzed for the series. Records were available for a total of 81 recurrent EIA patients. The median time between their initial and repeat operations was 4.1 years. The mean tumor size was 2.2 ± 0.2 cm. A total of 35/81 patients had greater than 5 years of follow-up. A total of 24/81 patients had greater than 10 years of follow-up. Over one half of these patients presented with visual disturbance, and we found that 39% of these patients experienced improved vision with a second surgery. More importantly, no one with normal vision suffered any appreciable decline in vision. Approximately, 35% of patients with pre-operative anterior pituitary dysfunction recovered function after surgery in our series; and no patient's function worsened. A total of 4/52 (8%) patients with greater than 2 years of post-op follow-up experienced a clinically meaningful tumor recurrence requiring additional treatment. Our data suggest that when performed by experienced transsphenoidal surgeons, durable tumor control can be obtained in these frequently locally aggressive tumors with acceptable rates of post-operative morbidity.

Keywords Adenomas · Recurrent · Outcome · Transsphenoidal

Introduction

While many pituitary adenomas are hormonally active and cause systemic symptoms by secreting hormones in an uncontrolled fashion, a large fraction of pituitary adenomas cause morbidity through local mass effect compressing the neighboring normal adenohypophysis and the optic apparatus [4, 14]. It is widely accepted that the standard first-line treatment for most endocrine inactive pituitary macroadenomas (EIA) is transsphenoidal surgery [2, 4, 7, 10, 14]. Modern transsphenoidal surgery generally can achieve excellent tumor control rates, with a minimal amount of discomfort and morbidity [2, 7, 10, 11, 18].

What is less clear is what approach to take when these tumors recur, especially when this recurrence involves areas which are difficult to surgically remove tumor from, such as the suprasellar region or cavernous sinuses [16].

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Given that in most cases these recurrent tumors are usually not hormonally active, there is less of a clear indication for repeat attempts at curative or cytoreductive surgery. In many institutions, recurrent tumors are treated with repeat surgical resection, however, the evolution of less invasive treatments, such as radiosurgery and conformal radiotherapy [9, 12], raises the possibility of avoiding a repeat operation, especially in cases where surgical cure is difficult or unlikely. These options become more appealing in light of the difficulties of repeat transsphenoidal surgery [8]: the bony landmarks useful in maintaining a midline trajectory are frequently distorted and destroyed from the previous surgery, and there is frequently exuberant mucosal overgrowth and scar tissue in the surgical field, making orientation more difficult [17, 8]. Further, given that these tumors are not hormonally active, one could make the argument that many patients with recurrent tumors should not be treated at all, especially if the tumor is not surgically curable.

Our ability to determine the best treatment for these patients is most limited by the lack of long term follow-up data for patients undergoing repeat surgery at time of recurrence [2]. Much more has been written about the management of residual or recurrent hormonally active pituitary adenomas where the appropriate management approach is largely dictated by laboratory data [1, 5, 6, 8]. The lack of definitive data regarding the risk and efficacy profiles of various approaches for treating recurrent EIA's is especially problematic given that these tumors are generally slow growing, and evaluation of the true efficacy of any treatment must take into account the possibility of very late second recurrences [2]. We present long term follow-up for a series of 81 patients who underwent repeat surgery for recurrent non-secreting pituitary adenomas. Our aim was to delineate the safety and efficacy profile so that it can be compared to other treatment modalities.

Methods

Patient population

We analyzed data collected from 81 adult patients undergoing their second microsurgical transsphenoidal resection of a histologically proven endocrine-inactive pituitary adenoma at the University of California at San Francisco by two surgeons (C.W. and S.K.) between January 1970 and March 2001. All patients had undergone a previous technically adequate transsphenoidal resection at least 2 years prior to the operation in question (meaning the operations were not performed in the early post-operative period for technical mistakes leaving large residual tumors [13], but rather represented true recurrences). No patient in this series had previously undergone radiation therapy prior to the second surgery. Early repeat operations for technical failures, and patients with clinical or radiographic evidence of pituitary apoplexy were excluded from this analysis.

Data collection and analysis

Data for these patients were collected retrospectively at a number of time points between 1994 and 2004 by review of medical records, mail, and/or telephone interviews. Hospital and clinic records were reviewed to extract data pertaining to patient age, dates of surgery, pre-operative symptoms, pre and post-operative endocrine and visual field tests, intra-operative findings, post-operative complications, radiation therapy, and clinical evidence of recurrence. Pre and post-operative T1 weighted post-gadolinium MRI images were evaluated to determine tumor size, tumor characteristics, such as suprasellar and cavernous sinus invasion, and the extent of tumor resection.

Visual function was assessed in all patients using formal visual acuity testing and formal perimeter field testing. The timing of this analysis post-operatively was variable, but was general performed at least 3 months post-operatively if the patient was not complaining of visual decline. Improvement in visual function was defined as >30% reduction in visual field deficit and/or meaningful improvement in visual acuity on post-operative examination. Worsening in visual function was defined as any new visual field cut, or any significant decline in visual acuity post-operatively. Visual function was defined as "unchanged" if no change or minor change occurred on both tests.

Anterior pituitary function was tested in all patients pre- and post-operatively. We decided to focus our analysis on Gonadal, Thyroid, Hypothalamic–pituitary–adrenal (HPA) axis function. Pre-operative anterior pituitary dysfunction was defined as endocrinologic evidence of secondary endocrine dysfunction (hypothyroidism with low TSH, hypocortisolemia with low ACTH, or secondary gonadal failure), or the need for hormone replacement therapy. Because no patients without pre-operative anterior pituitary dysfunction in this cohort developed it post-op, analysis was limited to patients with pre-operative dysfunction. Post-operative improvement in anterior pituitary function was defined as the normalization of one or more previously abnormal anterior pituitary functions off replacement therapies at last follow-up, without new dysfunction of another hormone system. Post-operative worsening in anterior pituitary function was defined as a newly abnormal anterior pituitary function, or new need for long term hormone replacement. Patients were not considered to have worsening if they transiently required hormone replacement for several months following surgery (i.e. short term

cortisol replacement), but eventually had normal function off replacement therapy at last follow-up.

Post-operative tumor recurrence/progression was defined as unequivocal radiographic evidence of new tumor or clinically significant tumor growth in a known residual nest of tumor.

Statistical analysis

All between group comparisons of binary variables were performed using Fisher's exact test. Survival analysis of tumor recurrence was performed using the Kaplan–Meier method with between group survival comparisons being made using the Log-rank test. All continuous variables are presented as mean ± SE.

Results

Patient characteristics

Records were available for a total of 81 recurrent EIA patients. The median time between the initial and repeat operations was 4.1 years. The median age was 50.4 years (range 20–92 years). The mean tumor size was 2.2 ± 0.2 cm. The median length of follow-up was 3.62 years (range 6 months to 21 years) (Table 1). A total of 35/81 patients had greater than 5 years of follow-up. A total of 24/81 patients had greater than 10 years of follow-up.

The most common presenting symptom for these patients was visual dysfunction (49 of 81 patients, 60%). A total of 36% (29/81 patients) of patients had anterior hypopituitarism, and 33% (27/81 patients) presented with headache. A total of 19 patients (23%) had asymptomatic radiographic recurrence (Table 1).

A total of 51/81 of these tumors demonstrated suprasellar extension, 15/81 had cavernous sinus invasion, and 9/81 had an infrasellar/intrasphenoidal component. A total of 9 tumors had some intrasellar cystic component. A total of 19/81 tumors were purely intrasellar.

Table 1 Pre-operative clinical characteristics for the 81 patients in this series

Patient demographics		
Age	50.4 years	20–92 years
Follow-up	3.62 years	6mo–21 years
Size	2.2 ± 0.2 cm	
	# of Patients	(%)
Deficit		
Visual field deficits	49/81	60
Hypopituitarism	29/81	36
Headache	27/81	33
Incidental finding	19/81	24
Imaging characteristics		
Suprasellar extension	51/81	63
Infrasellar/intrasphenoidal extension	9/81	11
Cavernous sinus invasion	15/81	19
Intratumoral cyst	9/81	11
Purely intrasellar	19/81	23

Factors influencing the frequency of clinical and radiographic gross total resection

The treating surgeon felt a gross total resection (GTR) had been achieved in 32/81 cases, with the other 49 cases receiving subtotal resections (STR). We found that the surgeon's intra-operative impression of extent of resection did not correlate well with post-operative imaging findings, with discordant findings being found in 39% of the 60 cases for which adequate post-operative imaging was available for review. A total of 39/60 of these patients had no evidence of residual disease on post-operative imaging, while 21/60 patients demonstrated residual tumor. Surgeons were significantly more likely to underestimate the extent of resection (i.e. to feel that tumor was left behind when it was not visible on the scan) compared to imaging findings than to overestimate them ($P < 0.001$) (Table 2a).

A statistical trend towards more frequent subtotal resections occurred in patients with infrasellar/intrasphenoidal tumor extension ($P = 0.09$). While suprasellar extension and cavernous sinus invasion were more frequently observed in patients receiving subjective subtotal

Table 2 (A) Rates of discordance between intraoperative impression and imaging assessment of extent of resection. Note that discordance for GTR patients means that the post-operative MRI demonstrated residual disease. For STR patients, this means no residual disease was seen on post-operative MRI. (B) Rates of gross total resection for patients with and without various types of extrasellar tumor resection

	GTR	STR
(A)		
Discordance	4	20
Concordance	19	18
(B)		
Imaging characteristics		
Suprasellar extension	20	31
Infrasellar/intrasphenoidal extension	1	8
Cavernous sinus invasion	4	11
Intratumoral cyst	3	6
Purely intrasellar	9	10

Note that no significant difference exists between groups for any category (*-*GTR* Gross total resection, *STR* Subtotal resection)

total resections, neither of increased the statistical likelihood of subtotal resections compared to purely intrasellar tumors (Table 2b).

Patients with cavernous sinus extension demonstrated a statistical trend towards increased rates of having radiographic residual disease seen on post-operative scans compared to patients with purely intrasellar tumors ($P = 0.07$). Suprasellar extension, infrasellar/intrasphenoidal extension, and intratumoral cysts demonstrated no significant increase in rates of radiographic residual compared to purely intrasellar tumors.

Visual outcomes following repeat transsphenoidal resection

Post-operatively, 95% of all patients had the same or improved visual function compared to pre-op. All four patients with worsened vision, had initial visual dysfunction pre-op, thus no patient with normal pre-op vision suffered visual decline post-operatively. Further, none of these patients went onto have known visual loss during the follow-up period. When analysis was limited to the 49 patients with pre-operative visual compromise, we found that the rate of meaningful partial or complete visual recovery was 39%. A total of 4/49 patients had worse vision post-op. Sub-set analysis found that extent of resection did not have any effect on visual outcomes in these patients (Table 3).

Endocrine outcomes following repeat transsphenoidal resection

As stated in the methods, no patient without hypopituitarism pre-op developed it post-op. Further, no patient had worse endocrine function post-op than they had pre-op. Of patients with pre-existing endocrine dysfunction, 10/29 patients (35%) experienced improvement in anterior pituitary function compared to pre-op, while 19/29 maintained the same endocrine function.

Gross total resection did not lead to statistically improved endocrine outcomes at last follow-up, regardless of whether it was defined on clinical or radiographic grounds (Table 4).

Table 3 Post-operative visual outcomes at latest follow-up in the 49 patients who presented with pre-operative visual dysfunction

	GTR	STR	Overall	(%)
Improved	7	12	19	39
Same	10	16	26	53
Worse	2	2	4	8

Note that no significant difference exists between groups for any category (*-*GTR* Gross total resection, *STR* Subtotal resection)

Table 4 Post-operative endocrinologic outcomes at latest follow-up in the 29 patients who presented with pre-operative anterior pituitary dysfunction. Note that no significant difference exists between groups for any category. Table (A) compares impact of extent of resection based on subjective intraoperative impression while the data in Table (B) assess extent of resection using MRI imaging

Endocrine function	GTR	STR
Better	7	3
Same	9	10
Worse	0	0
Endocrine function	**GTR**	**Residual**
Better	3	4
Same	10	6
Worse	0	0

(*-*GTR* Gross total resection, *STR* Subtotal resection)

The effect of gross total resection on recurrence following repeat resection

A total of 52 patients had greater than 2 years of post-op follow-up. A total of 4/52 (8%) of these patients experienced a clinically meaningful tumor recurrence requiring additional treatment. These recurrences were discovered at 2.0, 5.1, 5.7, and 7.7 years following the repeat operation. A total of 3 of these 4 patients had suprasellar extension on their pre-operative scan. None of these patients had cavernous sinus invasion. The overall 2, 5, and 10 years recurrence rates were 1/52 (1.9%), 3/35 (8.6%), and 4/24 (17%), respectively. When analysis was limited to only patients followed by MRI, 2, 5, and 10 years recurrence rates were 1/43 (2.3%), 3/27 (11%), and 4/20 (20%), respectively.

Two of four patients with recurrence had intra-operative findings consistent with gross total resection, while 2/4 received a subtotal resection. Figure 1a, b demonstrate that there was no difference in tumor control rates between patients receiving gross total resection and subtotal resection, even when analysis was limited to patients followed with MRI alone.

The rationale for XRT was largely based on the treating clinician's preference. In the 2, 5, and 10 years tumor control cohorts described above, early post-operative XRT was administered to 23/52 (43%), 8/35 (23%), and 8/24 (33%) patients, respectively. Kaplan–Meier analysis (Fig. 1c) comparing surgery to surgery + XRT demonstrated no difference in tumor control rates between the groups. We also performed subgroup analyses limited to only patients who received subtotal resections, and to those who were followed with MRI imaging, and in both cases found no difference between the groups with regard to tumor control rates.

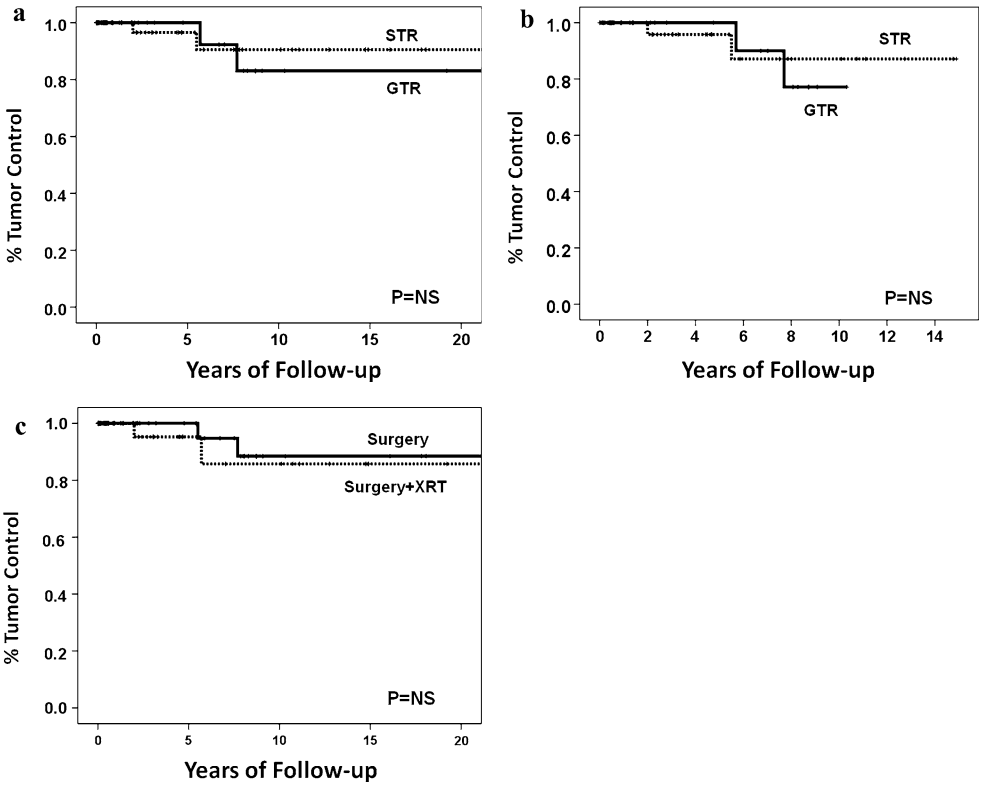

Fig. 1 Kaplan–Meier analyses comparing tumor control rates in patients undergoing **a** GTR vs. STR, **b** GTR vs. STR limited to recurrences monitored during MRI era, **c** surgery versus surgery + XRT (*-GTR = Gross total resection, STR = Subtotal resection)

The effect of external beam radiotherapy following repeat transsphenoidal resection

A total of 35/81 patients in this cohort underwent external beam radiation therapy following their repeat surgery. A total of five of these patients had received subjective gross total resection, and 15 patients had no evidence of disease on their post-operative MRI. Treatment protocols were largely consistent (38–50 Gy. over 25 fractions in all patients). Patient outcomes are summarized in Table 5.

Visual outcomes were marginally improved in patients receiving radiation therapy though this difference was not significantly different. Of note, 3 of 4 patients whose vision worsened post-op did not receive radiation therapy.

Endocrine outcomes did not differ significantly between patients receiving radiotherapy and those that did not. Of note, no patient receiving radiation had worse post-operative endocrine function than their pre-op function.

Morbidity and mortality following repeat transsphenoidal resection

A total of 18/81 (22%) patients experienced at least one non-endocrine, non-visual complication related to their surgery. These are summarized in Table 6. There was one

Table 5 Post-operative visual and endocrinologic outcomes at latest follow-up in the 35 patients who received post-operative external beam radiation therapy

Visual function	XRT	None
Better	12	12
Same	22	31
Worse	1	3
Endocrine function	**XRT**	**None**
Better	3	8
Same	7	9
Worse	0	0

Note that no significant difference exists between groups for any category

Table 6 Rates of post-operative non-visual, non-endocrinologic complications for patients in this series

Complication	# of Patients	Rate (%)
Overall	18	22
DI	4	4.9
Permanent DI	1	1.2
Hyponatremia	3	3.7
Sinusitis	5	6.2
Spinal headache	5	6.2
Meningitis	2	2.5
Post-operative hematoma	2	2.5
Death	1	1.2

death within the early post-operative period from medical complications stemming from a post-operative hematoma requiring repeat evacuation. Permanent posterior pituitary dysfunction was rare, as permanent diabetes insipidus occurred in 1/81 patients. Only 2/81 patients experienced meningitis due to CSF leak post-operatively, and 5/81 patients had clinically significant post-op sinusitis. There were no other episodes of transient CSF rhinorrhea. No new cranial neuropathy was noted in any patient post-op.

Discussion

In this study, we present long term data from a large cohort of patients undergoing repeat transsphenoidal surgery for recurrent non-secreting pituitary macroadenomas. Our data suggest that when performed by experienced transsphenoidal surgeons, durable tumor control can be obtained in these frequently locally aggressive tumors with acceptable rates of post-operative morbidity. While it is tempting to refer these patients to radiosurgery in an attempt to save them a second operation [12], it should be noted that these tumors can change their hormonal and biologic phenotype at the time of recurrence [15]. Given the good results we have seen with repeat surgery, we feel monotherapy with radiosurgery should be undertaken only in select cases when after endocrinologic work-up, it is certain that the tumor has not become a hormone secreting tumor.

Probably the most interesting finding of our analysis is the relatively low rate of clinically important tumor recurrence/progression (8% at 5 years following the second operation), even though a large number of these patients (35%) had at least some residual tumor left on imaging. A number of these patients with residual disease have been followed well past 10 years, and in a few cases 20 years, without evidence of tumor growth requiring treatment. Also, interesting was the observation that none of the 24 patients in this cohort who made it to 10 years of follow-up without clinically significant tumor growth/regrowth, went onto have a subsequent recurrence. While the number of recurrences in this group was too low to make any definitive conclusions regarding recurrences rates, radiographic gross total resection did not seem to have a protective effect, or at least subtotal resection did not seem to predispose to certain recurrence in this group.

Over one half of these patients presented with visual disturbance, and in this cohort we found that 39% of these patients experienced improved vision with a second surgery. More importantly, no one with normal vision (in whom the indication for surgery is less certain), suffered any appreciable decline in vision. Interestingly, leaving a small amount of residual did not appear to make a difference in long term outcome, as these tumors infrequently recur, and when they do, they seldom make vision worse. While 8% of patients with pre-op visual compromise had post-operative visual worsening, these cases were evenly divided between subtotal and gross total resection, suggesting that the visual decline was not necessarily due to overaggressive attempts to obtain a gross total resection.

Approximately, 35% of patients with pre-operative anterior pituitary dysfunction recovered function after surgery in our series, and no patient's function worsened. This is important to note, as at repeat transsphenoidal surgery due to scar tissue it can be more difficult to discern clear planes between tumor and normal gland than at the initial surgery, and as such, it wouldn't be unreasonable to hypothesize that repeat surgery would have a higher rate of hypopituitarism. This does not seem to be the case whether a gross total or subtotal resection is performed, or even if the patient receives external beam radiotherapy. Why this rate seems to be lower than published rates for initial operation is not entirely clear, but perhaps a pseudocapsule of scar tissue around the gland protects the normal tissue at repeat surgery.

While these data and that reported by others demonstrate repeat transsphenoidal surgery can generally be performed with good results and a low amount of major morbidity [1], the single mortality in this series highlights the potential serious risk of repeat surgery, as typical landmarks and tissue planes helpful in the initial surgery, are not present at repeat surgery, increasing the risk of intrasellar and intracranial bleeding and the attendant complications resulting from these problems. Our complication rates for repeat surgery are slightly higher than those observed for very experienced transsphenoidal surgeons performing initial surgery [3]. The surgeon and patient must be aware of these risks when weighing the benefits and risks of a repeat entry into the sella.

Rational therapy for recurrent EIA's involves assessment and application of the cost-risk–benefit balance between treatment, continued observation, and radiation therapy. At time of recurrence, the histologic diagnosis of these tumors has been established, and the primary management goal of these tumors is the prevention of endocrine and visual morbidity related to tumor growth. Given the lack of hormonal hypersecretion for these tumors, the cost-risk–benefit balance largely centers around the issue of tumor control, and necessity of treatment for obtaining tumor control. While our data suggest that repeat surgery is a reasonable and safe option for achieving tumor control, it is certainly not the least invasive or least costly method for achieving this goal. While it is possible that recurrence of tumor implies a persistently growing tumor phenotype, more data regarding the natural history of untreated recurrent EIA's are needed to determine what fraction, if any, of these tumors plateau in growth, and what fraction

continue to regrow. A better understanding of the natural history of recurrent EIA's is necessary to determine the relative feasibility of observation of recurrent EIA's, and to determine the indications for repeat transsphenoidal surgery.

In short, we provide long term follow-up data demonstrating that repeat transsphenoidal surgery is a reasonable and effective therapy for large recurrences of endocrine inactive pituitary macroadenomas, which can be performed with good visual and endocrine outcomes, and a low rate of 3rd recurrence, even when followed out over a decade.

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