Management of Recurrent Pituitary Adenoma by Endoscopic Endonasal Transsphenoidal Approach: Surgical Technique and Challenges

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Abstract

OBJECTIVE: Complete removal of a pituitary adenoma is a challenging endeavor. Recurrent or residual pituitary adenoma is a frequent occurrence following microscopic, endoscopic, or craniotomy procedures. The objective of this investigation is to assess the effectiveness of the endoscopic endonasal transsphenoidal technique in removing recurrent and persistent pituitary adenomas.

Methods: We conducted a prospective analysis of twenty cases who had endoscopic endonasal surgery for recurring or residual pituitary adenomas between 2016 and 2020, following previous microscopic or endoscopic transphenoidal operations.

Results: we achieved gross total resection in 6 patients (30%) and 14 (70%) subtotal resection. 2 of them were operated microscopically in the previous surgery. All those six patients have the adenoma limitted to the sellar and suprasellar space. Extension to the parasellar space is one of limiting the total excision. Mortality occurred in one patient who was complicated by intraoperative csf leak and subarachnoid hge and brain stem and cerebellar infarction.

Conclusions: excision of recurrent pituitary adenoma by endoscopic endonasal transsphenoidal approach is a safe, effective & advantageous method in treating recurrent pituitary adenoma. Factors that limit total resection are: parasellarextention, prolonged dopamine antagonists' therapy and tumor size. The presence of suprasellar extension didn't limit the extent of resection and might provide an advantage over microscopic speculum-based techniques.

Key words: Recurrent, pituitary adenoma, endonasal, transphenoidal, sellar, suprasellar and parasellar.

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Introduction:

Pituitary adenoma is one of the commonest brain tumours representing about 10%. Although these adenomas are benign lesions; they may grow and extend to the suprasellar and parasellar spaces making complete excision is difficult [1]. Pituitary adenomas can manifest as hormonally active tumors that secrete hormones independently or, more frequently, as nonfunctioning growths that cause symptoms due to their size. The most frequently observed symptoms at the time of diagnosis are headaches, visual disturbances caused by the tumor extending to the optic chiasm, and impairments of cranial nerves (CN III, IV, V1, V2, VI) due to lateral expansion into the cavernous sinus. [2]. Resection of pituitary adenoma through transsphenoidal route is one of the most frequently conducted operations for intracranial tumors [3]. Cushing in 1930s after publishing a series of 400 patients abandoned the procedure in favor of transcranial approach due to high rate of complication following transsphenoidal approach. After invention of microscope and endoscope there is great advancement in managing pituitary adenoma. Large series have documented satisfactory gross tumor resection (GTR) rates of approximately 80%, hormone resolution rates of approximately eighty to eighty five percent, and reduced visual symptoms in conjunction with a low rate of morbidity (<2% CSF leakage, 0.24% death). Nevertheless, there is a lack of information in the literature about the therapy of residual or recurring adenoma [4]. Following the transsphenoidal surgery either microscopic or endoscopic there is excellent outcome as regard clinical improvement & endocrinological remission. There is also minimal rate of mortality & morbidity

following transsphenoidal surgery. Unluckily, a significant percentage of both nonfunctioning & hormone-secreting pituitary adenomas have a recurrence after a successful transsphenoidal operation. Moreover, it is common for a remaining tumor to be present after the operation. [5]. The recurrence rate of pituitary adenoma is high worldwide ranging from 7% to 33% depending on the type of adenoma being high in nonfunctioning adenoma and prolactinomas. Proceeding in managing those recurrent cases is difficult because some lesions are firm in consistency and attachment to important structures (optic nerve and carotid artery). Managing the recurrent or residual tumors can be done in many ways, observation, radiotherapy, medical therapy, stereotactic radiosurgery, or repeated surgery. None of these ways is superior to the other and differ from patient to patient and sometimes many ways could be the option in treating one patient. Revision endoscopic surgery is a difficult procedure because of obliteration of the anatomical landmarks, adhesions and effect of previous radiotherapy and medical therapy [6]. Compression of the visual system, patients fearing radiation risks, big tumors are the indications for revision endoscopic operation. The effectiveness of the endoscopic endonasal technique for treating pituitary tumors was documented in scientific literature, demonstrating results and rates of complications that are comparable to or better than those of larger microsurgical studies. [7]. The advantage of endoscope over microscope is the better visualization (utilizing 0 degree and angled scopes), preservation of sinus function, short hospital stay and less morbidity [8]. In this research, we explore the outcomes of the endoscopic transsphenoidal approach in the management of recurrent pituitary adenomas.

Patients and methods

The research was performed between 2016 and 2020 on 20 patients who had endoscopic endonasal operation for residual (75%) or recurrent (25%) pituitary adenomas following previous endoscopic or microscopic transphenoidal surgery. All cases had endocrinological evaluation before & after surgery. MRI of the sella with IV gadolinium are requested for all patients. CT of the paranasal sinuses also requested to delineate the sellar floor anatomy and precise understanding of the previous route utilized in the previous surgery. Neuronavigation was used in selected patients. Follow up CT brain was done to all patients at the night of surgery and MRI Sella was done three months following operation to evaluate the extent of resection.

Technique of the procedure

A head rest is placed on the supine patient under general anesthesia. The neck has a slight extended. If not previously performed in a prior procedure, we employed the posterior septostomy and binostril method. We have scopes with 0 and 30 degrees. When necessary, we prepare the thigh to harvest fascia lata. If neuronavigation is prepaired, three pins fixation is employed. To enhance the visualization of the sphenoid sinus & detect any previous bone defect in the sellar floor resulting from previous microscopic operations, the inferior and middle turbinate can be laterally moved to extend the corridor. Additionally, if needed, the previous sphenoidotomy can be further enlarged. In most cases as previous endoscopic operation has been performed, there is typically a significant connection among the nasal & sphenoidal cavities. If there are lesions that have a significant component above the sella turcica the tuberculum sellae and the planum sphenoidale can be surgically removed using the same principles as the extended transplanum technique. Regarding the reconstruction, it is important to note that the presence of nasal mucosal adhesions caused by the absence of septal bone can make the raising of a nasoseptal mucosal flap difficult when needed. In such cases, it is easier to harvest free mucosal flaps from the middle turbinates. The excision of the tumor is carried out in the same manner as the initial endoscopic surgery. [9, 10, 11].

Results

According to demographic data, age of patients was ranged from 30 to 60 year with mean 45.95± 7.84and 7 (35%) of patients were males while 13 (65%) of patients were females, period of symptoms was varied from 1 to 14 months with mean 5.75±3.4. we have 5 patients (25%) with recurrence and 15 patients (75%) with regrowth. Among recurrent cases we have 3 cases ACTH secreting adenoma and 1 case GH adenoma and 1 case prolactinoma. Among the regrowth cases we have 6 cases prolactinoma, 4 cases nonfunctioning adenoma, 3 cases ACTH adenoma, 1 case GH adenoma and 1 case of plurihormonal secreting GH and Prolactin. We 6 patients with visual loss preoperative; 4 of them showe improvement of their vision post operatively and 2 patients did not improve. The table (1) shows the distribution of patients charachterstics.

The Interval among 1st & 2nd operation varied from 2 to 72 months with mean 20.8± 17.78. According to MRI, all patients had intrasellar and Suprasellar extension of adenoma and 7 (35%) had

Parasellarextension of adenoma. 14 (70%) of patients had Subtotal resection and 6 (30%) had Total resection. We could totally excise the adenoma in 3 cases of prolactinoma and 2 cases of ACTH and one case GH secreting adenoma. According to Complications, 3 (15%) had Transient DI, 2 (10%) had CSF leakage, 1 (5%) had pneumocephalus, 1 case had Subarachnoid Hge and brain stem infarction who eventually die in ICU and we have 3 patients (15%) had Sinusitis as shown in table (2).

Table (1): Distribution of patient characteristics in the studied group.

	Studied Group N=20
Visual loss	6 (30%)
Manifestation of increased ICP	3 (15%)
Hormonal Production	16 (80%)
Non Functioning Adenomas	4 (20%)
Prolactinoma	7 (35%)
ACTH secreting Adenoma	6 (30%)
GH Adenoma	2 (10%)
Plurihormonal Adenoma	1 (5%)
previous radiosurgery	1 (5%)
previous surgery	
Microscopic	4 (20%)
Endoscopic	15 (75%)
Transcranial	1 (5%)
Result of the previous surgery	
subtotal Excision	14 (70%)
Total Removal	6 (30%)

ICP: increased intracranial pressure, ACTH: Adrenocorticotropic hormone, GH: Growth hormone.

We have 3 (15%) of patients had medical Therapy post operative to control the resisual part of the lesion, 3 (15%) had radiosurgery as postoperative additional therapy. According to final outcome 6 (30%) of patients had relapsed while 14 (70%) of patients were not relapsed. According to patient outcome, there was no significant association between outcome and age, sex, duration of Symptoms, visual loss, hormonal Production, prolactinoma, GH Adenoma, plurihormonal adenoma, previous radiosurgery, previous surgery, result of the previous surgery as shown in table (3).

Table (2): distribution of complications among the studied group.

	Studied Group N=20
Complications	
No complication	10 (50%)
Transient Diabetes insipidus (DI)	3 (15%)
CSF leakage	2 (10%)
pneumocephalus	1 (5%)
Sinusitis	3 (15%)
Subarachnoid Hge and brain stem infarction	1 (5%)

Table (3): regression analysis for patient outcome.

	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
Age	.009	.016	.147	.549	.598
Sex	.188	.281	.196	.669	.523
Duration of Symptoms	-.027	.037	-.195	-.739	.481
Visual loss	-.086	.551	-.086	-.156	.880
Hormonal Production	-.566	.667	-.494	-.850	.420
Prolactinoma	.468	.282	.487	1.656	.136
GH Adenoma	-.053	.839	-.035	-.063	.951
Plurihormonal Adenoma	.228	.597	.108	.382	.713
Previous radiosurgery	-.271	1.041	-.129	-.260	.802
Previous surgery	.597	.301	.622	1.984	.082
Result of the previous surgery	-.141	.319	-.133	-.440	.671

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant

Case Presentation

Female patient 35 years old presented with Amenorrhea-galactorrhea syndrome. She has history of excision of pituitary adenoma 2 years ago in another hospital. She has recurrent adenoma as shown in figure 1. We subtotally excise the lesion as shown in figure 2 three months postoperative.

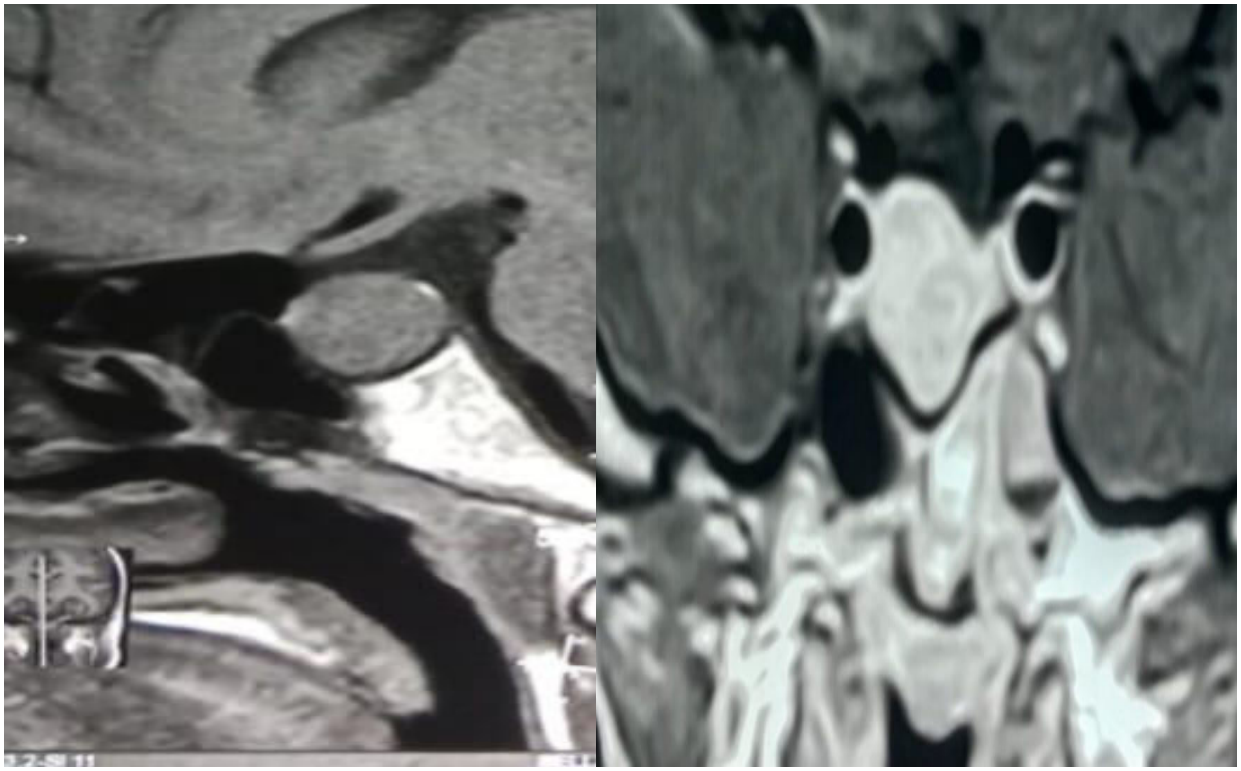

Figure 1: MRI T1 sagittal and coronal views post contrast enhancment preoperative recurrent pituitary macroadenoma reveals sellar and suprasellar extension with post contrast heterogenous enhancment.

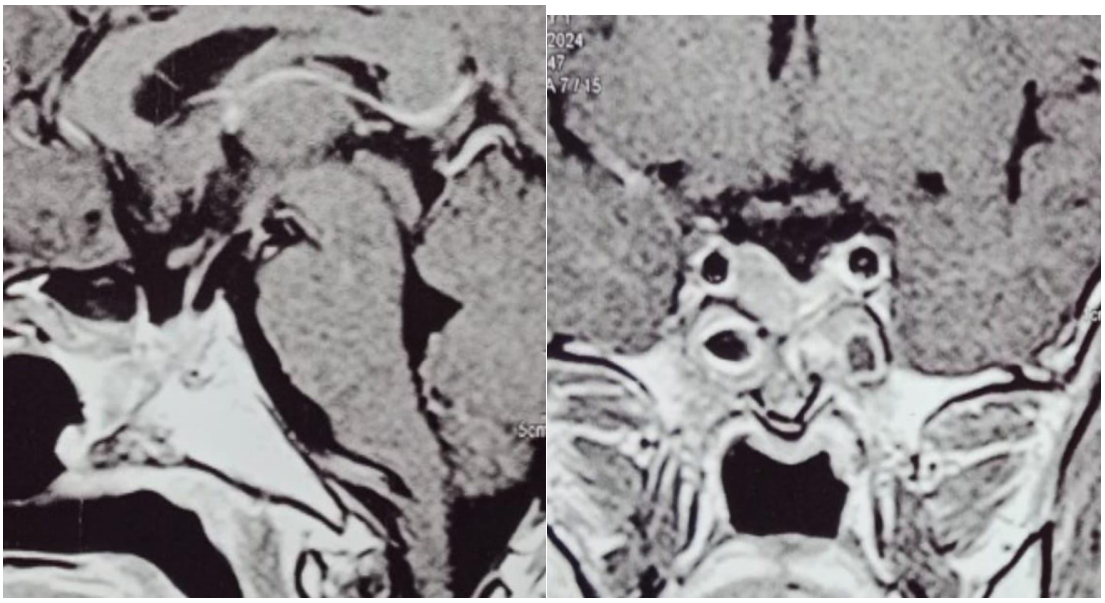

Figure 2: MRI T1 sagittal and coronal views postoperative demonstrates subtotal excision of recurrent macroadenoma.

Discussion

We achieved a NTR or GTR rate of thirty percent in cases with residual or recurring pituitary tumors utilizing an endoscopic endonasal technique. There was a ten percent incidence of major postoperative problems. According to the nonfunctioning adenoma, Endocrine Society guidelines, & prolactinomas are the most common cases amongst people who have undergone subtotal resection. The guidelines suggest that prolonged therapy with dopamine agonists should be the first choice for treating prolactinoma (Melmed et al., 2011). Nevertheless, although DA (Dekkers et al., 2010) has a significant therapeutic impact, surgical methods are favored for various reasons: 1) Possible adverse effects of prolonged dopamine agonist therapy, 2) Inability to tolerate dopamine agonists, 3) cases who do not respond to dopamine agonists. Roughly 33% of cases who received DA treatment had adverse effects, including symptoms including vomiting, nausea, headache, & dizziness. A recent analysis revealed the increased vulnerability to heart valve dysfunction in cases undergoing prolonged treatment with cabergoline. Moreover, other investigations (Kharlip et al., 2009) have demonstrated the recurrence of hyperprolactinemia.

One the one hand, pituitary operation has shown remission rates of more than eighty percent in the long term for cases with microprolactinomas. Based on this study, it is stated that prolactin (PRL) concentrations return to their normal state and gonadal dysfunctions are restored following undergoing total surgical removal. Moreover, the advancement of pituitary operations has significantly enhanced the clinical results over the past twenty years. The incidence of surgical complications in patients with prolactinomas is rare and has been documented to be under one percent in specialized medical facilities that focus on pituitary disorders. The microscopic transsphenoidal approach (TSA) for prolactinomas is specifically recommended for certain cases, including cases who don't respond to medical treatment, those who can't take dopamine agonists , and those having neurological impairments for example sudden vision loss or cranial nerve paralysis caused by tumor hemorrhage or apoplexy. However, it is worth noting that over seventy percent of our cases successfully attained remission following surgical resection, which is consistent with the findings reported in published research. Consistent with prior research, our study revealed that the rate of remission was greater among cases with microprolactinomas compared to those with macroprolactinomas (Akin et al., 2016). Furthermore, there was a negative correlation between tumor size and the likelihood of achieving remission following operation. Nevertheless, the size of the tumor didn't demonstrate a significant correlation with remission after adjusting for parasellar invasion. In line with our results, Raverot et al. (2010) found that the invasiveness of prolactinomas, rather than their size, was indicative of the outcomes following surgery for prolactinomas. nevertheless some researchers discovered that both the size and invasiveness of prolactinomas are independent factors that can

predict the outcomes of prolactinoma treatment. Our research indicates that the invasiveness of prolactinoma, as evaluated using radiological methods, is a reliable indication of the tumor's level of aggressiveness. None of the cases with Knosp grades 3–4, indicating cavernous sinus invasion (Han et al., 2018), obtained remission following operation.

Our study found that cases who achieved early biochemical remission had significantly decreased prior to treatment serum prolactin levels compared to cases who didn't achieve remission. Prior studies have found no correlation between before surgery prolactin levels and long-term results. On the other hand, the levels of prolactin in the blood serum that were examined just after the removal of prolactinoma were found to be crucial in determining whether remission would occur. It was observed that those who had remission had much lower prolactin concentrations on the first day following the operation. Furthermore, another investigation found that elevated levels of prolactin after operation were related to an increased risk of surgical failure (Song et al., 2017). In addition, Amar et al. (2002) demonstrated that almost all cases with prolactinomas with prolactin levels below ten nanograms per milliliter, tested one day following operations, achieved remission. This included one hundred percent of cases with microprolactinomas and ninety-three percent of cases with macroprolactinomas. These findings are probably surgical removals, which are related to poorer results. Furthermore, people with Cushing's illness who have low levels of cortisol immediately after surgery are more likely to have successful tumors excision, as indicated by a study conducted by Witek et al. in 2013.

The primary complication observed in Transsphenoidal Adenomectomz is cerebrospinal fluid leakage, occurring in two to twenty of cases. A life-threatening hemorrhage is rare, affecting fewer than one percent of cases. The occurrence of panhypopituitarism, a condition characterized by decreased pituitary hormone production, varies and is estimated to be roughly 1-14%. The outcomes of our study revealed no instances of life-threatening problems, with just three patients experiencing panhypopituitarism that necessitated treatment. Therefore, it may be prudent to carefully evaluate the use of surgical intervention, specifically TSA, as the initial treatment for prolactinomas, since it is likely to be a safe and effective method (Dallapiazza and Jane, 2015).

Transsphenoidal operation is typically the preferred initial therapy for the majority of non-prolactin-secreting pituitary adenomas (PAs). Transsphenoidal operations has gained appeal since the invention of endoscopy, primarily because it enables superior vision of the supra- and parasellar areas, while also minimizing disruption to surrounding structures. Preliminary findings indicate favorable outcomes in terms of tumor removal rates and postoperative complications following endoscopic transsphenoidal surgery (ETS). Nevertheless, postoperative recurrences (PAs) have a high probability of occurring even after a thorough removal, particularly over an extended period. The documented overall recurrence rate following complete removal of the tumor is between seven percent and thirty-three percent, but cases where the tumor was not completely removed have higher rates of recurrence. Recurrence risk factors encompass labelling index, cavernous sinus invasiveness, and early age at diagnosis (Penn et al., 2018).

Radiation treatment and medication are safe therapy options for recurrent PAs. Nevertheless, in cases when the tumor is significantly large, located near the optic chiasm, or secreting hormones, repeat operation is often the preferable course of action. Performing additional procedures for recurrent or residual PAs (rrPAs) is technically difficult since there are no clear anatomical landmarks and scar tissue is present. Re-operative pituitary operations have a higher incidence of complications & a lower rate of achieving gross total resection (GTR) compared to first operations. Nevertheless, there have been limited investigations into the factors that influence gross total resection, or the risk factors associated with problems in re-operative pituitary operations. There have been a few investigations that directly compare the results of endoscopic transsphenoidal surgery for recurrent or residual pituitary adenomas (rrPAs) with those for non-recurrent or residual pituitary adenomas (non-rrPAs). The objective of this investigation was to provide an exhaustive account of a group of cases involving resection of rrPAs using ETS and to investigate parameters associated with GTR and leakage of cerebrospinal fluid during surgery. In addition, our objective was to assess the results and potential issues of ETS for recurrent respiratory papillomatosis & non-rrPAs.

Most tumors in cases undergoing re-operation were residual from the previous operation rather than a recurrence. To achieve the most extensive removal of rrPAs, it is crucial to assess the precise location & underlying cause of the remaining tumor. Residual malignancies were frequently observed in the parasellar& suprasellar regions following previous transsphenoidal operations in our study. On the other hand, persistent tumors were more frequently

observed in the sphenoidal sinus &parasellar region following the initial transcranial operation. Frequent observations reveal a common occurrence of insufficient opening of the sphenoid and sella. Thus, in the case of a repeat surgery, we select for a large sphenoidotomy and extensive visualization of the sellar floor. In addition, the tuberculum sellae as well as planum had been removed for tumors that significantly invaded the supra-diaphragmatic region. The mass infiltrated the lateral compartment of the cavernous sinus, resulting in the opening of the anterior wall of the sinus (Fernandez-Miranda et al., 2017).

The preoperative parameters that affect the ability to achieve gross total resection are not yet well-defined. According to Farrell et al. (2019), the degree of removal is said to be linked to the invasion of the cavernous sinus, the size of the tumor, and the type of initial operation (either microscopic or endoscopic transsphenoidal approach). Based on another investigation, Knosp-Steiner Grade three or four status was strongly related to a non-gross total resection . Nevertheless, the GTR did not vary based on the previous technique. Our investigation found that there was a correlation between increased tumor volume and reduced GTR rate, as shown by the Knosp grade. However, inside the logistic regression model, it was found that only the Knosp grade had the ability to independently predict the extent of gross total resection (GTR). Tumors that invade the lateral compartment of the cavernous sinus (Knosp grade 4) present significant challenges, even when using a trans-cavernous sinus approach. This difficulty can be attributed to the invasive nature of the tumor, as evidenced by its extension into the lateral compartment of the cavernous sinus, and the resulting anatomical complexity (Micko et al., 2019). In their 2017 study, Do et al. found that the rate of gross total resection was 51.7 percent in patients who had a reoperation for pituitary adenoma. Specifically, they observed GTR rates of 70.3 percent for patients with Knosp grade zero to two and 21.7 percent for those with Knosp grade three to four. The GTR rate in our cases was 87.5 percent for cases with Knosp grade zero to two and 47.4 percent for those with Knosp grade three to four. These rates were greater than those reported in prior research.

Conclusions: excision of recurrent pituitary adenoma by endoscopic endonasal transsphenoidal approach is a safe, effective and advantageous method in treating recurrent pituitary adenoma. Factors that limit total resection are: parasellarextention, prolonged dopamine antagonists' therapy and tumor size. Suprasellar extension was not a factor limiting extent of resection and may prove to be an advantage over microscopic speculum-based approaches.

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