

Extracapsular Tumor Resection May Improve Long-Term Biochemical Remission Rates Compared to Piecemeal Intracapsular Resection in Cushing's Disease Patients

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Abstract

Objective

The pseudocapsule-based extracapsular resection (ER) technique was first described by Dr. Edward Oldfield in 2006 as a surgical method to improve gross total resections in patients with functioning pituitary adenomas where any residual could cause significant morbidity. Additionally, identification of the pseudocapsule has aided in finding microadenomas intraoperatively not visualized on imaging. The technique is more challenging than traditional intracapsular (IR) piecemeal resection and in the hands of unexperienced surgeons may increase the likelihood of generating a CSF leak. We aim to study in our large institutional series, whether achievement of ER significantly reduces residual tumor and tumor recurrence in Cushing's disease patients.

Methods

An institutional review board–approved retrospective review was performed identifying all patients with diagnosed Cushing's disease who underwent an endoscopic trans-nasal transsphenoidal tumor resection between December 12, 2007 and April 21, 2021 at our institution. Variables assessed included patient characteristics, pre- and intra-operative tumor characteristics, post-operative outcomes such as residual, recurrence, and biochemical remission.

Results

Ninety patients were identified based on our inclusion criteria. En-bloc ER was achieved in 21 patients. The average tumor size was 8.4 mm for ER cases and 8.5 mm for the remaining ones. The overall intraoperative CSF leak rate for our series was 26%, which was not significantly affected by whether a pseudo-capsular dissection was done. Of the thirteen cases where no clear tumor was visualized intraoperatively, only the 7 with complete postoperative immediate biochemical remission were considered true Cushing's Disease patients and included. Radiographic GTR was achieved at higher rates in the ER group relative to those without complete ER (100% vs. 89%). Postoperative biochemical remission was achieved in 95% and 93% of the ER and IR groups, respectively. At the latest follow-up, of the patients without radiographic residual and initial biochemical cure, recurrence rates were 5%, 16% and 22% in the complete-, partial- and no- ER groups, respectively.

Conclusion

Early remission rates were similar whether ER was possible or not, without any increase in CSF leak rates or other complications when ER was employed. Tumor consistency and level of adherence affected the likelihood of complete ER. There was a trend towards more long-lasting biochemical remission rate with use of the ER technique.

Introduction

Advances in pituitary surgery techniques aim to improve tumor removal, reduce recurrence, and enhance hormonal remission^{1–5}. There is a shift toward endoscopic transnasal transsphenoidal surgery (eTNTS) for microadenomas, which provides better safety, outcomes, and shorter hospital stays than the traditional microsurgical approach⁶. eTNTS also decreases nasal symptoms, operating time, and blood loss⁶. Before pseudocapsule-based extracapsular resection (ER), remission rates were similar between the microsurgical and eTNTS approaches^{7–14}.

The ER technique, first described in 1930, involves identifying a pseudocapsule around soft adenoma tissue, developing the extracapsular plane, and keeping that capsule intact during tumor removal for gross total resection (GTR). Intracapsular resection (IR) involves piecemeal debulking until all visible tissue is removed. In 2006, Dr. Edward Oldfield refined the technique, showing improved GTR in patients with functioning pituitary adenomas (PA)^{15–17}.

In Cushing's disease (CD) patients, achieving a GTR is difficult and recurrence remains high. Even with experienced teams using an eTNTS intracapsular approach, 5-year recurrence is 25–35%, as ACTH-secreting PAs are often small and hard to detect via imaging^{18–20}. In 2009, Jagannathan et al. showed ER was linked to high remission rates and low complication rates in CD patients¹. Identifying the pseudocapsule has helped locate microadenomas intraoperatively, often missed on imaging, a common issue in CD patients¹⁷.

Residual tumor tissue can cause significant morbidity in patients. Untreated Cushing's disease had a median survival of 4.6 years (Harvey Cushing, 1932) and a 50% five-year survival (Plotz et al.)^{21,22}. Patients with persistent disease face high mortality; a Swedish study found a 16-fold higher risk of death, mainly due to hypertension-related cardiovascular issues and immune deficiency^{23–28}. Optimizing surgical techniques to improve cure rates is crucial given the disease's morbidity.

The ER technique is underused and more challenging than intracapsular resection. In inexperienced hands, it may increase CSF leaks or pituitary injury^{9,14,29}. We aim to study whether en bloc ER reduces residual tumor, recurrence, and improves remission in Cushing's disease patients compared to IR, through a retrospective analysis of our cohort with documented corticotroph tumor resection.

Methods

Study Design and Population

We retrospectively reviewed electronic medical records of all patients diagnosed with Cushing's disease who underwent an eTNTS for tumor resection between February 2008 and April 2021 at the Ronald Reagan UCLA Medical Center in Los Angeles, CA. Inclusion criteria were: 1) diagnosis of Cushing's disease based on a combination of clinical findings and strict biochemical laboratory data; 2) underwent eTNTS; and either 3) immunohistochemical pathologic confirmation of corticotroph adenoma. In cases of microadenomas where pathological specimen was not sent or was too small for analysis, a more stringent determination of biochemical remission (post-operative cortisol < 2 ug/dl) postoperatively was required to confirm removal of the tumor. Patients with radiographically invasive tumors (cavernous sinus invasion, extradural extension into the sphenoid sinus, subarachnoid) were excluded from the analysis. All ages were included.

One hundred and two patients were identified and 90 were included in the study based on the above inclusion criteria. Of 15 patients who did not have a confirmatory pathological diagnosis of a corticotroph PA, seven were included in this study as evidenced by the significant drop in cortisol levels post-operatively. This study was approved by the University of California, Los Angeles' (UCLA) institutional review board. The requirement to obtain informed consent was waived for this observational study based on its retrospective design and anonymized data.

Demographic information (age, gender, BMI), laboratory values, radiographic (e.g. tumor size), preoperative, intraoperative and postoperative clinical data were extracted from the electronic medical records.

Pre-Operative Cushing's Disease Evaluation and Diagnosis

All patients were evaluated pre-operatively by a neuro-endocrinologist (APH). The decision to proceed with eTNTS surgery was based on there being a high degree of certainty of the clinical diagnosis of Cushing's disease based on the Endocrine Society Guidelines³⁰. Though clinical features of CD are not always present at diagnosis, all patients in this cohort exhibited multiple clinical findings suggestive of hypercortisolism. Exogenous cortisol intake was ruled-out in all cases. The biochemical criteria used to establish ACTH-dependent hypercortisolism included two or more of the following:

- Two 24-hour urinary free cortisol (24h UFC) tests at least 1.3 times the upper limit of normal. The 24h UFC test was preferred, with most patients included in the study meeting this criteria.
- Two late-night salivary cortisol (LNSC) tests > 0.112 nmol/L

- An abnormal low dose dexamethasone suppression test (DST) defined as failure to suppress cortisol to < 1.8 mcg/dl. The DST was considered in only a small minority of patients who typically had had the test performed by the referring physician.

An elevated serum ACTH is not required for diagnosis though it can support it if present.

With the establishment of ACTH-dependent hypercortisolism, all patients underwent a pituitary protocol 3T MRI study. If no definitive tumor was identified, the patient underwent one or more repeat pituitary protocol 3T MRI studies. In 3 patients, no definitive tumor could be identified despite multiple MRI studies, and so these patients underwent inferior petrosal sinus sampling to rule-out ectopic tumors.

Operative Technique and Indices

All surgeries were performed using a team approach endoscopic TNTS: a Head and Neck skull base rhinologist (MBW, JDS, JTL) and neurosurgeon with expertise in pituitary surgery (MB, WK). An ER was attempted in all cases in which 1) a tumor was identified on pre-operative MRI and 2) there was no imaging evidence of tumor invasiveness (e.g. cavernous sinus invasion, extradural extension into the sphenoid sinus, and/or transdiaphragmatic invasion).

A templated operative report was used in all cases. This template included drop-down menus of defined fields including extent of pseudocapsular dissection, tumor “firmness”, tumor “adherence”, and CSF leak grade. With regards to pseudocapsule dissection, choices included 1) complete en bloc, 2) complete following central debulking, 3) near complete, 4) partial, 5) not possible, 6) not attempted, and 7) no tumor identified. “Near complete” was subjectively defined as > 75% circumferential dissection of the pseudocapsule but with loss of this dissection plane at the final stage. The remainder of the tumor was removed using a traditional intra-capsular technique. For logical and statistical reasons, the two “complete” designations (1 and 2) were grouped as “extracapsular resection” (21 patients) and the others as “intracapsular resection” (72 patients), even though a significant proportion of the dissection had indeed been accomplished using the ER technique. Seven patients had no identifiable tumor mass intraoperatively.

Tumor firmness was subjectively categorized as soft, semifirm, firm, or cystic. Another subjective assessment was “adherence” properties which qualified how easily the pseudocapsule and/or tumor boundary separated from the surrounding normal gland, the diaphragma sellae, and/or the medial wall of the cavernous sinus. Intra-operative CSF leaks were graded according to the following scale [: grade 0 – no leak; grade 1 – subarachnoid (or weeping after Valsalva without an obvious diaphragmatic defect); grade 2- cisternal (or moderate); grade 3 – ventricular (large diaphragmatic/dural defect)³¹.

In-Hospital Post-Operative Biochemical Remission Criteria, Imaging Protocol, and Pathological Diagnosis

Serum cortisol levels were measured every 6 hours following surgery until a nadir was documented or 72 hours, whichever came first. The Endocrine Society defines biochemical remission as an immediately post-operative serum cortisol < 5 ug/dl. At our institution, we further stratify biochemical remission patients into two groups: 1) cortisol $\geq$ 2 and < 5 ug/dl and 2) a cortisol < 2 ug/dl. Arginine vasopressin deficiency syndrome (AVP-D), formerly referred to as diabetes insipidus (DI), was diagnosed in patients based on presence of polyuria (> 400cc/hr of urine for two consecutive hours) in presence of urine specific gravity of < 1.005 and a serum sodium level > 145.

In-hospital post-operative MRI studies were not routinely ordered. Instead, a pituitary protocol MRI was obtained if the cortisol did not drop below 2 ug/dl within 48 hours of surgery. If possible residual tumor was identified on this study, operative re-exploration was discussed with the patient. Five patients underwent repeat eTNTS surgery.

For patients for whom no definitive tumor was identified intra-operatively, the diagnosis of CD was still considered plausible if the immediate post-operative cortisol dropped to < 2 ug/dl, and therefore these patients were included in this study. All

pathological specimens underwent routine histological analysis as well as immunohistochemical staining for pituitary hormones including ACTH.

Follow-Up Data

Patients achieving biochemical remission, defined as an immediate post-operative serum cortisol <5ug/dl, during hospitalization were discharged on replacement hydrocortisone therapy, which was continued for a period between 9–12 months after which the dose was weaned and ultimately stopped once the patient had an 8–9 am serum cortisol > 8-10ug/dl. Thereafter, patients were monitored on a semi-annual basis. Recurrence was defined by a combination of recurrence of clinical features and biochemical assessment. This assessment was typically an LNSC > 0.112 nmol/L, but often confirmed by a supplementary test (e.g. increased 24-hour urinary free cortisol and/or an abnormal low dose DST). Recurrence was based on biochemical recurrence of hypercortisolism with or without radiographic tumor recurrence on MRI. Follow-up pituitary protocol MRI studies were arranged at 3 months and then typically yearly thereafter.

New onset pituitary insufficiency, conceivably related to the surgical procedure, was defined as below normal levels of any hormones in the hypothalamic-pituitary-adrenal axis.

Statistical Analyses

Continuous variables were described as mean ± standard deviation. Categorical variables were described as percentages. Univariable analyses were carried out, computing unadjusted odds ratios and using the chi-square or Fisher’s exact test for comparing categorical variables, and the unpaired t-test or Mann-Whitney-U test for continuous variables, as appropriate. The primary outcomes were comparing CSF leak rate, residual, recurrence, and biochemical remission between the ER and IR cohorts. We also investigated whether certain patient and tumor characteristics correlate with a higher likelihood of achieving ER. To determine the effect of patient and tumor characteristics on feasibility of ER as well as tumor residual and recurrence outcomes, multivariable regression and sensitivity analysis were performed. A probability value < 0.05 was considered statistically significant. Statistical analyses were performed using the Stata/IC software (v16.0; StataCorp LP, College Station, TX, USA).

Compliance with Ethical Standards

This study was submitted and approved by institutional review board. All human participant research was performed in accordance with relevant guidelines and regulations set forth by the institution and the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Pre-operative Data (Table 1)

Table 1. Pre-operative patient and tumor characteristics, and presenting symptoms

Patient and Tumor Characteristics at Diagnosis		Extracapsular Resection n (%)	Intracapsular Resection n (%)
Sex	Male	0 (0)	11 (16)
	Female	21 (100)	58 (84)
Age (years) at Surgery	Mean ± SD (Range)	40.0±15.4 (16-68)	39.9±14.0 (12-71)
Mean Tumor Size (mm)	Mean ± SD (Range)	8.4±5.5 (3-20)	8.5±7.7 (2-45)
BMI	<18.5	0 (0)	2 (3)
	18.5-24.9	3 (14)	13 (19)
	25.0-29.9	6 (29)	12 (17)
	30.0-34.9	5 (24)	17 (25)
	35.0-39.9	3 (14)	15 (22)
	≥ 40.0	4 (19)	10 (14)
	Mean ± SD (Range)	32.7±8.4 (19.2-51.0)	32.3±8.4 (17.4-59.9)
Pre-operative ACTH level (pg/mL)	Mean ± SD (Range)	118.7±186.0 (10-912)	159.1±422.5 (6-2950)
Pre-operative AM serum cortisol level (µg/dL)	Mean ± SD (Range)	43.2±53.9 (5-247)	29.7±41.9 (1-271)

Symptoms	n (%)
Incidental	3 (3)
Weight gain (abdominal girth, moon face, buffalo hump)	85 (93)
Fatigue or weakness	35 (38)
Striae or skin pigmentation	35 (38)
Easy bruising	32 (35)
Depression, anxiety or mood changes	23 (25)
Hypertension	20 (22)
Amenorrhea or irregular menses	18 (20)
Hirsutism	17 (19)
Impaired glucose tolerance or diabetes	15 (16)
Headache	14 (15)
Acne	13 (14)
Hair loss or thinning	13 (14)
Blurry vision	11 (12)
Insomnia or obstructive sleep apnea	9 (10)
Palpitations, diaphoresis, or tremors	5 (5)
Decreased libido	4 (4)
Osteoporosis and/or multiple fractures	4 (4)
Frequent infections or inflammatory	3 (3)
Poor wound healing	2 (2)

The cohort demographics, clinical characteristics and tumor size at diagnosis are described in Table 1. The majority of the patients (88%) were female (Table 1). The mean age, tumor size, BMI, pre-operative ACTH and AM Cortisol levels were comparable between the ER and IR groups ($p>0.05$).

Intra-operative Findings (Table 2)

Table 2. Intra-operative Findings

Intra-operative Tumor Characteristics		En Bloc ER	IR	No Tumor Found
		n (%)	n (%)	n (%)
Tumor Adherence	No	10 (50)	26 (42)	-
	Yes	4 (15)	6 (10)	-
	Not described	7 (35)	30 (48)	-
	No			
Tumor Consistency	Soft	16 (75)	57 (92)	-
	Firm	5 (25)	4 (6)	-
	Not described	-	1 (2)	-
Cavernous Sinus Invasion or Suprasellar extension	No	17 (80)	51 (82)	-
	Yes	4 (20)	11 (18)	-
Knosp Grade	0	9 (40)	22 (35)	-
	1	9 (45)	25 (40)	-
	2	1 (5)	4 (6)	-
	3	2 (10)	3 (5)	-
	4	0 (0)	4 (6)	-
	Missing Data	-	4 (6)	-
Intra-operative CSF leak	No	17 (85)	45 (73)	5 (71)
	Yes : Grade 1	2 (5)	14 (23)	1 (14)
	Grade 2	2 (10)	2 (3)	1 (14)
	Grade 3	0	1 (2)	0

ER was accomplished successfully in 42% of cases (Figure 1). The consistency of the tumor significantly differed between the ER and IR groups ($\chi^2(1, N = 82) = 4.76, p < 0.05$) with a larger proportion of firm tumors in the former group. There was no significant difference in tumor adherence between the ER and IR cohorts.

The intraoperative CSF leak rate for the entire cohort was 26% (excluding immediate take-back operations for suspected residual tumor). The intra-operative CSF leak rate with ER was lower (15%) compared to 28% for the IR group, but this did not reach statistical significance.

Early Post-Operative Outcomes (Table 3)

Table 3. Post-operative Outcomes

Post-Operative Data		En Bloc ER	IR	No Tumor Found
Post-operative CSF leak, n (%)		1 (5)	1 (2)	0 (0)
Radiographic residual tumor, n (%)		0 (0)	7 (11)	NA
Cushing's Disease Recurrence, n (%)		2 (10)	9 (14)	0 (0)
Biochemical remission, n(%)		20 (95)	52 (84)*	7 (100)
Latest Follow Up (months)	Mean $\pm$ SD (Range)	39.6 $\pm$ 36.8 (0-122)	55.7 $\pm$ 50.6 (0-172)	66.1 $\pm$ 59.6 (0-133)
	Median	28	42	30

*Data was missing data for one patient in this cohort (2%), the remaining nine patients (14%) did not achieve biochemical remission

Based on our institutional definition of biochemical remission, all but one patient in the ER group, and 59 patients in the IR group, achieved immediate biochemical remission. Immediate-biochemical remission did not significantly differ between the ER and IR groups ($\chi^2(1, N = 90) = 1.42, p > 0.05$).

Five patients in the IR group underwent a take-back eTNTS surgery during the index hospitalization based on possible residual tumor on post-operative MRI in the context of failure to achieve biochemical remission (Figure 2). Tumor was found in two of the five cases but ER was not possible. None of these five achieved biochemical remission.

Of the 13 patients with no tumor identified on preoperative imaging or intraoperatively (Tables 1 and 3, Figure 2), 9 had complete biochemical remission (postoperative cortisol nadir $< 5 \mu\text{g/dl}$) postoperatively from exploration with partial gland tissue removal, 7 of which had a postoperative cortisol nadir $< 2 \mu\text{g/dl}$ and were considered true CD patients.

There were two (2.4%) post-operative CSF leaks, one in each cohort; both required operative repair. The incidence of post-operative CSF leaks was not significant between cohorts ($p > .05$). The ER group had no readmissions and two cases (9%) of postoperative hyponatremia. In contrast, the IR group had 14 readmissions (20%), 10 cases (14%) of hyponatremia, 2 cases (3%) of epistaxis, and 1 case of sinusitis (1%).

The ER group had one case (5%) of temporary arginine vasopressin deficiency syndrome (AVP-D), whereas the IR group had 9 cases (11%) of temporary and one case (1%) of permanent AVP-D, plus 3 cases (4%) of new pituitary insufficiency.

Follow-Up Data

Overall mean length of follow up for our series was 52.8 months (median of 33 months, ranging from 0 to 172 months) and was similar between the cohorts. Three patients were lost to follow-up after the surgery, and 4 patients after the first post-operative visit. Figure 2 represents a flowchart detailing the postoperative findings and follow-up treatment based on the extent of ER. Table 3 describes our series postoperative data including postoperative CSF leak, tumor residual, recurrence, biochemical remission, and length of latest endocrine follow up.

There were 34 patients in whom tumor was found but ER was either not attempted or not possible. Twenty-seven patients (79%) achieved early biochemical remission; six of those (22%) went on to have recurrence in later follow up. In contrast, en bloc ER was done in 21 patients of whom 20 (95%) achieved early biochemical remission. One of those patients (5%) went on to have later recurrence. In sum, based on the latest follow-up, of the patients without radiographic residual and initial biochemical cure, recurrence rates were 5%, 16% and 22% in the complete-, partial- and no- ER groups, respectively. While these recurrence rates were not statistically different between the groups, a trend is evident, and suggests that this study may have been underpowered to detect the true difference.

Discussion

The Pituitary Pseudocapsule and its Use in Adenoma Resection

Undergoing pituitary surgery for Cushing's disease does not guarantee remission, and often these patients require further treatment. According to the literature, up to 25-35% of Cushing's disease patients do not achieve endocrine remission after sellar surgical exploration³²⁻³⁷. Certain factors can, however, increase the likelihood of remission, such as obtaining an extracapsular, also known as pseudocapsular, resection when possible. Traditionally, PA resection was performed from within the encapsulated tumor with occasional subsequent stripping of portions of the pseudocapsule, greatly increasing the likelihood of residual tumor cells. There are technically three layers around a pituitary tumor: the innermost pseudocapsule, the pituitary capsule and the dural envelope³⁸. The pseudocapsule, initially described by Costello in the 1930s, is a condensed layer of the anterior pituitary tissue that encircles the tumor and can be a useful guide to an en bloc surgical resection separating normal pituitary gland from tumor^{1,38,39}. Histologically, it is multiple layers of reticulin with thickness directly proportional to the size of the adenoma^{17,39}. Therefore, very small adenomas can be challenging to find intraoperatively without a well-formed identifiable pseudocapsule¹⁷. Since adenomas grow slowly, compressing the surrounding glandular tissue and eventually forming an identifiable pseudocapsule, it can be used successfully and facilitate resection of PAs <2-3 mm in diameter¹. Identifying the pseudocapsule can aid in resection of adenomas not found on preoperative imaging, and is indispensable to obtaining a complete histological and endocrinological resection^{17,40}. The technique has been shown to be feasible and successful in both endoscopic and microscopic approaches⁴¹.

Likelihood of Extracapsular Resection Based on Tumor Characteristics

ER may not always be feasible, especially when there is cavernous sinus invasion, a negative predictor of remission and more likely to lead to recurrence. Other situations where no ER can be performed is with cystic tumors or when no tumor is found on preoperative imaging or intra-operatively. The best outcomes with this technique have been described in the literature for noninvasive microadenomas contained within the pituitary gland^{15,42}. According to our series, non-invasive, firmer and non-adherent tumors were more likely to be associated with an en bloc ER, though this difference was only significant for tumor consistency. The type of functioning adenoma appears to give an advantage as well, with ER being more frequently achieved in prolactin-secreting adenomas, followed by growth hormone or TSH-secreting tumors, and lastly ACTH-secreting adenomas (up to 40% of the time)^{43,44}.

Of note, Kinoshi et al. reported a larger number of intraoperative CSF leaks with ER, not consistent with our series where the CSF leak rate in the ER cohort was less than the piecemeal intracapsular resection group⁴⁵. Though Taylor et al. had higher intra-operative CSF leak rates than our series, the ER cohort had a lower incidence (22%) than the IR cohort (38%)⁴¹.

Early Biochemical Remission

In our series, early biochemical remission was achieved in 95%, 89% and 79% of patients in the complete-, partial- and no- ER groups, respectively. Kim et al. report 100% endocrinological remission after en bloc ER, though their series includes all types of functioning adenomas⁴³. More broadly, reported rates of biochemical remission specific to the Cushing's disease population are significantly higher after ER ranging from 90.0 to 100%, including both endoscopic TNS and sublabial microscopic approaches^{1,15,41,44,46}. Moreover, Monteith et al demonstrated that ER led to a significantly more rapid drop in post-operative cortisol levels, with a nadir at an average of 19.4 hours, compared to 29.5 hours without en bloc ER¹⁵. They found no difference in time to postoperative cortisol nadir between the noninvasive tumors removed piecemeal and those invading the cavernous sinus or incompletely resected¹⁵.

Patients who did not have any identifiable tumor intraoperatively still attained a relatively high remission rate (70%) in our series as a result of a partial or complete hypophysectomy. Lastly, ER does not only have high remission rates, but they are also sustained. Monteith et al. reported 98% remission at 10 years follow up¹⁵.

In a series of acromegaly patients, the overall rate of remission after endoscopic TNS surgery was reported as 75% with a very strong correlation between ER and endocrine remission⁴⁷. Another series found a 90% remission rate after ER of growth hormone-secreting adenomas, compared to 61% after intracapsular resection⁴⁰.

Tumor Residual and Recurrence after Extracapsular Resection

Consistent with our series, GTRs were more likely after ER across various series, including both functioning and non-functioning adenomas^{41,43,46}. According to Taylor et al., looking at all noninvasive adenoma types confined to the sella, only 9% of patients after ER had residual tumor, compared to 41% who underwent a piecemeal intracapsular resection⁴¹. The same trend of decreased residual tumor was seen for partial ER versus IR in extrasellar tumors and those invading the cavernous sinus⁴¹. The clinical importance and impact of GTR varies, however, between functioning and non-functioning adenomas.

Early postoperative biochemical remission does not preclude later recurrence, though the probability is much lower, especially when postoperative serum cortisol is <2 µg/dl.^{42,15} In fact, despite higher early biochemical remission rates after resection of Cushing microadenomas relative to macroadenomas, recurrences increase rapidly the longer the follow up with rates as high as 48% in this microadenoma population at 5-10 years of follow up, irrespective of resection technique^{1,15,42,46,48-51}.

Though there has been more of a consensus in the literature regarding the definition of biochemical remission in Cushing's disease, defining biochemical recurrence is much more controversial with no consistent recommendations on combination of tests required to follow these patients, timing of the tests, and the administration of peri-operative corticosteroids or cortisol-lowering medications. We typically wean patients off peri-operative glucocorticoids around 9-12 months postoperatively.

With such high rates of recurrence in Cushing's disease patients, it is imperative to attempt ER when possible in order to best decrease the chances of recurrence^{15,42}. Our data showed a trend towards improved long-term biochemical control in patients treated with ER (5% recurrence with en bloc ER vs. 22% with IR), though our study was underpowered to detect a statistical difference. The trend observed is supported by other literature reporting significantly lower recurrence rates following en bloc ER^{1,15,41,43,44,46}. Kim et al. found little to no recurrence in all functioning adenomas resected via the en bloc pseudocapsular technique⁴³. Recurrence rates ranged from 0.8 to 2.56% after ER of corticotrophic tumors specifically^{1,44,46}. Lee et al. demonstrated tumor infiltration into the pseudocapsule, explaining the higher likelihood of recurrence without en bloc ER⁴⁴.

Postoperative Complications

One of the potential risks with ER is removal of small portions of the adjacent normal pituitary gland which could lead to various levels of endocrinopathy¹. This has not been the case according to various institutional series. The majority of case series published, including both functional and non-functional adenomas, report no statistically significant difference in post-operative pituitary insufficiency or endocrinopathies such as AVP-D, between adenomas resected via the extracapsular technique versus intracapsular piecemeal resection^{40,41,43,45,46}. Some have even found the incidence of new endocrine deficits to be fewer after ER, though not significantly⁴¹. According to Jagannathan et al., the incidence of post-operative AVP-D after ER of corticotroph adenomas via sublabial approach was 0.06% and hyponatremia 11.5%¹. Qu et al. reported transient AVP-D in 26.9% of ER patients, and 25% in the IR group, without any permanent AVP-D⁴⁶. Furthermore, according to Kinoshita et al. and Lee et al., the anterior pituitary function after surgery equally improved in both surgical groups^{41,44,45}.

Similarly, there were no reported significant differences in post-operative CSF leaks after ER, compared to partial or no ER^{41,45,46}. Reported post-operative CSF leak rates after ER in the literature range from 4.2 to 7.7% compared to 2.7% to 3.1% without ER, comparable to our series (5% and 2% respectively)⁴³.

Study limitations

These findings should be interpreted with caution, given the study's retrospective design and missing data from patients lost to follow-up. The short follow-up period for some patients limits recurrence interpretation. The recurrence rate for microadenomas not undergoing ER increases with time. Although our study includes 90 patients, the ER subgroup is small, requiring a larger study to confirm results and establish statistical significance. A confounding factor is that tumors unsuitable for the pseudocapsular technique often had cavernous sinus and skull base invasion, which may independently raise CSF leak risk. Comparing matched groups based on tumor invasion and size is needed to accurately assess intraoperative leak rates. Additionally, a learning curve for the neurosurgeon using this ER technique may have influenced outcomes.

Generalizability

Both subgroups are not significantly different when stratifying by demographics (age, BMI) and tumor size. This removes possible confounding variables and improves generalizability of our data. Nonetheless, the present study requires more patients in order to make meaningful conclusions regarding the feasibility, benefits and risks of ER that can influence clinical practice.

Conclusion

Given the morbidity associated with poorly controlled Cushing's disease, techniques to increase rates of early and sustained post-operative biochemical remission are imperative. Using the pseudocapsule to guide surgical resection of these tumors, when feasible, likely increases the likelihood of complete resection and biochemical remission with uncommon and minor complications. Our series demonstrates that adenoma characteristics affect the ability to carry out an ER; namely ER was found to be more likely achieved for non-invasive, non-cystic, non-adherent and firm tumors. While early remission rates were similar between ER and IR patients, long term recurrence rates showed a trend strongly favoring ER. While our study was likely underpowered to achieve statistical significance for this difference, it joins a body of evidence highlighting the utility of the ER technique in improving long-term disease control in Cushing disease, without a compromise in terms of post-operative complications (including CSF leak and other endocrinopathies).

Abbreviations

CD
Cushing's disease
eTNTS
endoscopic transnasal transsphenoidal surgery
GTR
gross total tumor resection
PA
pituitary adenoma
CSF
cerebral spinal fluid
ACTH
Adrenocorticotrophic Hormone
ER
Pseudocapsule-based Extracapsular Resection
IR
Intracapsular Resection

Declarations

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None.

Conflict of Interest

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS:

Sophie Peeters - study concept and design; drafting of the manuscript; acquisition of data; analysis and interpretation of data; and critical revision of the manuscript.

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Krystal Karunungan - acquisition of data.

Alex Valenzuela - acquisition of data.

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References

1. Jagannathan J, Smith R, DeVroom HL et al (2009) Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease. *J Neurosurg* 111(3):531–539. 10.3171/2008.8.JNS08339
2. Jane JA, Catalino MP, Laws ER et al (2000) Surgical Treatment of Pituitary Adenomas. In: Feingold KR, Anawalt B, Boyce A, eds. *Endotext*. MDText.com, Inc.; Accessed March 25, 2021. <http://www.ncbi.nlm.nih.gov/books/NBK278983/>
3. Kim W, Clelland C, Yang I, Pouratian N (2012) Comprehensive review of stereotactic radiosurgery for medically and surgically refractory pituitary adenomas. *Surg Neurol Int* 3(Suppl 2):S79–89. 10.4103/2152-7806.95419
4. Russ S, Shafiq I (2021) Pituitary Adenoma. In: *StatPearls*. StatPearls Publishing; Accessed March 25, 2021. <http://www.ncbi.nlm.nih.gov/books/NBK554451/>
5. Theodros D, Patel M, Ruzevick J, Lim M, Bettegowda C (2015) Pituitary adenomas: historical perspective, surgical management and future directions. *CNS Oncol* 4(6):411–429. 10.2217/cns.15.21

6. Yadav Y, Sachdev S, Parihar V, Namdev H, Bhatele P (2012) Endoscopic endonasal trans-sphenoid surgery of pituitary adenoma. *J Neurosci Rural Pract* 3(3):328–337. 10.4103/0976-3147.102615
7. Cho DY, Liao WR (2002) Comparison of endonasal endoscopic surgery and sublabial microsurgery for prolactinomas. *Surg Neurol* 58(6):371–375. 10.1016/S0090-3019(02)00892-3
8. Dehdashti AR, Ganna A, Karabatsou K, Gentili F, PURE ENDOSCOPIC ENDONASAL APPROACH FOR PITUITARY, ADENOMAS: EARLY SURGICAL RESULTS IN 200 PATIENTS AND COMPARISON WITH PREVIOUS MICROSURGICAL SERIES (2008) *Neurosurgery* 62(5):1006–1017. 10.1227/01.NEU.0000297072.75304.89
9. D'Haens J, Van Rompaey K, Stadnik T, Haentjens P, Poppe K, Velkeniers B (2009) Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas: a retrospective comparison with traditional transsphenoidal microsurgery in the same institution. *Surg Neurol* 72(4):336–340. 10.1016/j.surneu.2009.04.012
10. J G, M S, Jr TO. [Transnasal endoscopic surgery of the sellar region: study of the first 100 cases]. *Arq Neuropsiquiatr*. (2003) ;61(3B):836–841. 10.1590/s0004-282x2003000500024
11. Jho HD (2001) Endoscopic transsphenoidal surgery. *J Neurooncol* 54(2):187–195. 10.1023/A:1012969719503
12. Netea-Maier RT, van Lindert EJ, den Heijer M et al (2006) Transsphenoidal pituitary surgery via the endoscopic technique: results in 35 consecutive patients with Cushing's disease. *Eur J Endocrinol* 154(5):675–684. 10.1530/eje.1.02133
13. O'Malley BW, Grady MS, Gabel BC et al (2008) Comparison of endoscopic and microscopic removal of pituitary adenomas: single-surgeon experience and the learning curve. *Neurosurg Focus* 25(6):E10. 10.3171/FOC.2008.25.12.E10
14. Sarkar S, Rajaratnam S, Chacko G, Mani S, Hesargatta AS, Chacko AG (2016) Pure endoscopic transsphenoidal surgery for functional pituitary adenomas: outcomes with Cushing's disease. *Acta Neurochir (Wien)* 158(1):77–86 discussion 86. 10.1007/s00701-015-2638-7
15. Monteith SJ, Starke RM, Jane JA, Oldfield EH (2012) Use of the histological pseudocapsule in surgery for Cushing disease: rapid postoperative cortisol decline predicting complete tumor resection. *J Neurosurg* 116(4):721–727. 10.3171/2011.12.JNS11886
16. Oldfield EH (2011) Surgical management of Cushing's disease: a personal perspective. *Clin Neurosurg* 58:13–26. 10.1227/neu.0b013e3182269d3f
17. Oldfield EH, Vortmeyer AO (2006) Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg* 104(1):7–19. 10.3171/jns.2006.104.1.7
18. Ciric I, Zhao JC, Du H et al (2012) Transsphenoidal surgery for Cushing disease: experience with 136 patients. *Neurosurgery* 70(1):70–80 discussion 80–81. 10.1227/NEU.0b013e31822dda2c
19. Li QX, Wang WH, Wang XX (2019) Various Strategies of Transsphenoidal Pseudocapsule-Based Extracapsular Resection in Noninvasive Functional Pituitary Adenomas and their Effectiveness and Safety. *Neurol India* 67(6):1448–1455. 10.4103/0028-3886.273628
20. Nishioka H, Yamada S (2019) Cushing's Disease. *J Clin Med* 8(11). 10.3390/jcm8111951
21. Cushing H (1932) The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Obes Res*. 1994;2(5):486–508. 10.1002/j.1550-8528.1994.tb00097.x
22. Plotz CM, Knowlton AI, Ragan C (1952) The natural history of Cushing's syndrome. *Am J Med* 13(5):597–614. 10.1016/0002-9343(52)90027-2
23. Ragnarsson O, Olsson DS, Papakokkinou E et al (2019) Overall and Disease-Specific Mortality in Patients With Cushing Disease: A Swedish Nationwide Study. *J Clin Endocrinol Metab* 104(6):2375–2384. 10.1210/jc.2018-02524
24. Baykan M, Erem C, Gedikli O et al (2008) Assessment of left ventricular diastolic function and Tei index by tissue Doppler imaging in patients with Cushing's Syndrome. *Echocardiogr Mt Kisco N* 25(2):182–190. 10.1111/j.1540-8175.2007.00572.x
25. Newell-Price J, Bertagna X, Grossman AB, Nieman LK (2006) Cushing's syndrome. *Lancet Lond Engl* 367(9522):1605–1617. 10.1016/S0140-6736(06)68699-6

26. Ross EJ, Linch DC (1982) Cushing's syndrome—killing disease: discriminatory value of signs and symptoms aiding early diagnosis. *Lancet Lond Engl* 2(8299):646–649. 10.1016/s0140-6736(82)92749-0
27. Sherlock M, Ayuk J, Tomlinson JW et al (2010) Mortality in patients with pituitary disease. *Endocr Rev* 31(3):301–342. 10.1210/er.2009-0033
28. Würzburger MI, Prelević GM, Brkić SD, Vucković S, Pendić B (1986) Cushing's syndrome—transitory immune deficiency state? *Postgrad Med J* 62(729):657–659. 10.1136/pgmj.62.729.657
29. Dallapiazza RF, Jane JA (2015) Outcomes of endoscopic transsphenoidal pituitary surgery. *Endocrinol Metab Clin North Am* 44(1):105–115. 10.1016/j.ecl.2014.10.010
30. Nieman LK, Biller BMK, Findling JW et al (2008) The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 93(5):1526–1540. 10.1210/jc.2008-0125
31. Conger A, Zhao F, Wang X et al (2018) Evolution of the graded repair of CSF leaks and skull base defects in endonasal endoscopic tumor surgery: trends in repair failure and meningitis rates in 509 patients. *J Neurosurg* 130(3):861–875. 10.3171/2017.11.JNS172141
32. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Müller OA, Fahlbusch R (2008) Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. *J Neurosurg* 108(1):9–18. 10.3171/JNS/2008/108/01/0009
33. Mampalam TJ, Tyrrell JB, Wilson CB (1988) Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. *Ann Intern Med* 109(6):487–493. 10.7326/0003-4819-109-6-487
34. Nieman LK (2002) Medical therapy of Cushing's disease. *Pituitary* 5(2):77–82. 10.1023/a:1022308429992
35. Ram Z, Nieman LK, Cutler GB, Chrousos GP, Doppman JL, Oldfield EH (1994) Early repeat surgery for persistent Cushing's disease. *J Neurosurg* 80(1):37–45. 10.3171/jns.1994.80.1.0037
36. Sheehan JM, Lopes MB, Sheehan JP, Ellegala D, Webb KM, Laws ER (2000) Results of transsphenoidal surgery for Cushing's disease in patients with no histologically confirmed tumor. *Neurosurgery*. ;47(1):33–36; discussion 37–39. 10.1097/00006123-200007000-00008
37. Thapar K, Laws E Jr (2001) Pituitary tumors. *Brain Tumor*. Churchill Livingstone, pp 803–854
38. Qu X, Xu G, Qu Y, Song T (2011) The pseudocapsule surrounding a pituitary adenoma and its clinical significance. *J Neurooncol* 101(2):171–178. 10.1007/s11060-010-0247-0
39. Costello RT (1936) Subclinical Adenoma of the Pituitary Gland. *Am J Pathol* 12(2):205–2161
40. Kawamata T, Kubo O, Hori T (2005) Surgical removal of growth hormone-secreting pituitary adenomas with intensive microsurgical pseudocapsule resection results in complete remission of acromegaly. *Neurosurg Rev* 28(3):201–208. 10.1007/s10143-005-0384-7
41. Taylor DG, Jane JA, Oldfield EH (2017) Resection of pituitary macroadenomas via the pseudocapsule along the posterior tumor margin: a cohort study and technical note. *J Neurosurg* 128(2):422–428. 10.3171/2017.7.JNS171658
42. Patil CG, Prevedello DM, Lad SP et al (2008) Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *J Clin Endocrinol Metab* 93(2):358–362. 10.1210/jc.2007-2013
43. Kim EH, Ku CR, Lee EJ, Kim SH (2015) Extracapsular en bloc resection in pituitary adenoma surgery. *Pituitary* 18(3):397–404. 10.1007/s11102-014-0587-4
44. Lee EJ, Ahn JY, Noh T, Kim SH, Kim TS, Kim SH (2009) Tumor tissue identification in the pseudocapsule of pituitary adenoma: should the pseudocapsule be removed for total resection of pituitary adenoma? *Neurosurgery*. ;64(3 Suppl):ons62-69; discussion ons69-70. 10.1227/01.NEU.0000330406.73157.49
45. Kinoshita Y, Tominaga A, Usui S et al (2016) The Surgical Side Effects of Pseudocapsular Resection in Nonfunctioning Pituitary Adenomas. *World Neurosurg* 93:430–435e1. 10.1016/j.wneu.2016.07.036
46. Qu X, Yang J, Sun JD et al (2011) Transsphenoidal pseudocapsule-based extracapsular resection for pituitary adenomas. *Acta Neurochir (Wien)* 153(4):799–806. 10.1007/s00701-011-0961-1

47. Anik I, Cabuk B, Gokbel A et al (2017) Endoscopic Transsphenoidal Approach for Acromegaly with Remission Rates in 401 Patients: 2010 Consensus Criteria. World Neurosurg 108:278–290. 10.1016/j.wneu.2017.08.182
48. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B (2005) Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf) 63(5):549–559. 10.1111/j.1365-2265.2005.02380.x
49. Chee GH, Mathias DB, James RA, Kendall-Taylor P (2001) Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome? Clin Endocrinol (Oxf) 54(5):617–626. 10.1046/j.1365-2265.2001.01261.x
50. Invitti C, Pecori Giralaldi F, de Martin M, Cavagnini F (1999) Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. J Clin Endocrinol Metab 84(2):440–448. 10.1210/jcem.84.2.5465
51. Yap LB, Turner HE, Adams CBT, Wass J, a. H (2002) Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit. Clin Endocrinol (Oxf) 56(1):25–31. 10.1046/j.0300-0664.2001.01444.x

Figures

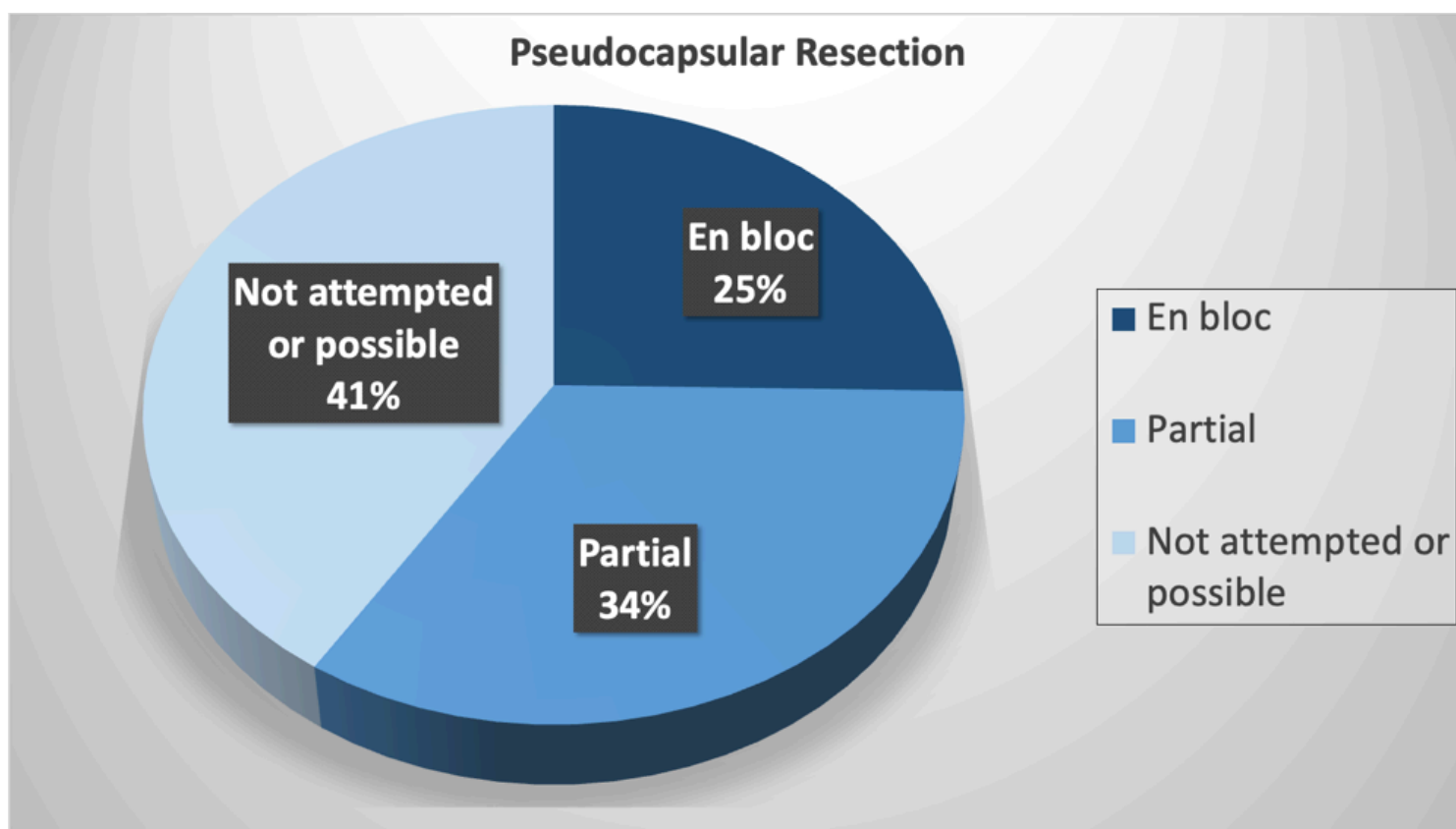


Figure 1

Feasibility of Pseudocapsular Resection (excludes patients with no obvious tumor found intra-operatively)

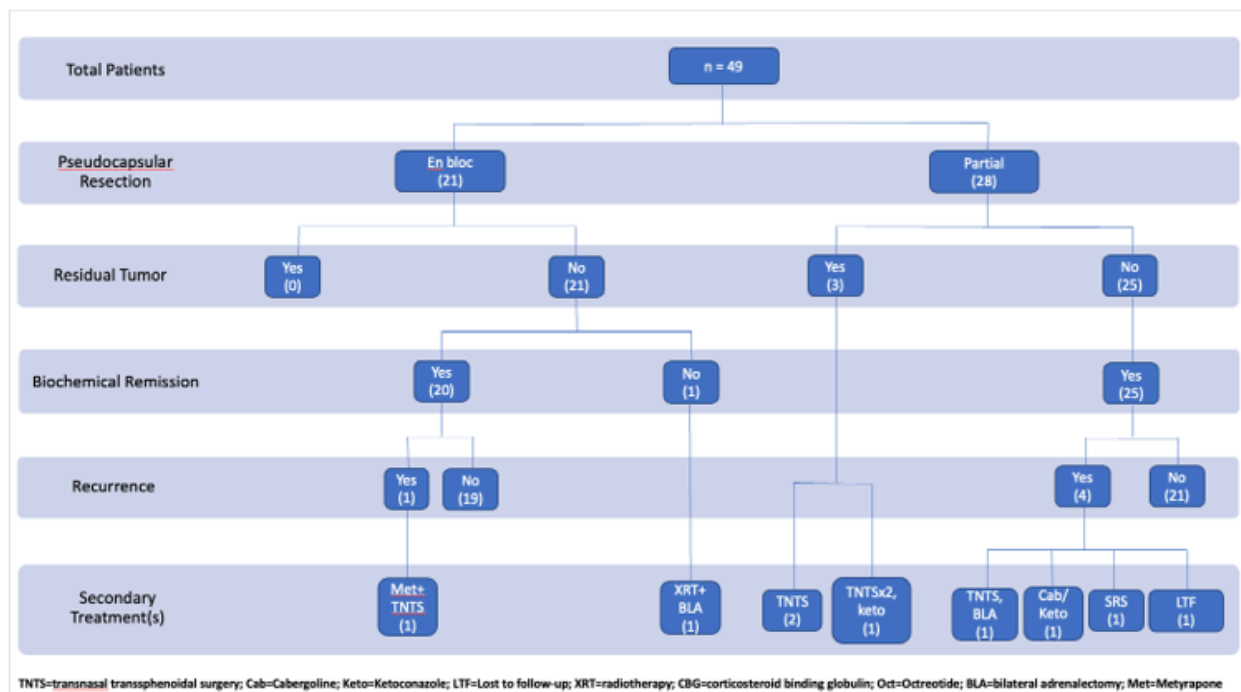


Fig. 2A

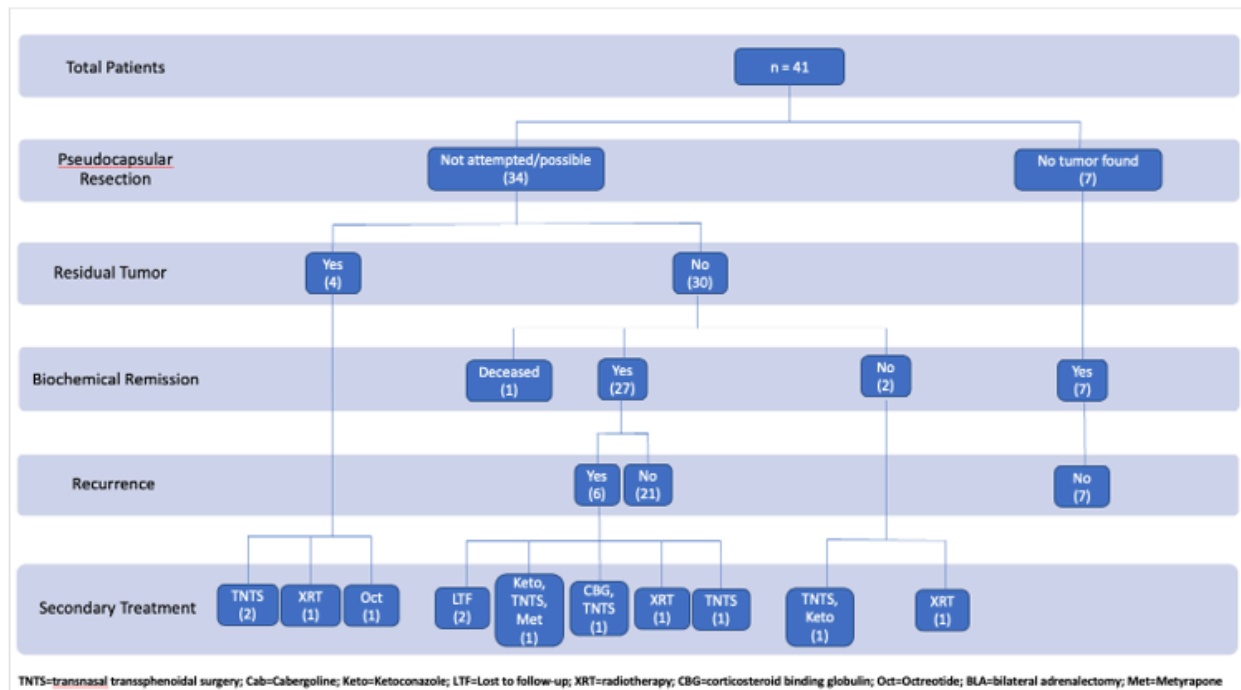


Fig. 2B

Figure 2

Flowcharts of Postoperative Radiographic Findings and Follow-Up Treatment Based on Extent of Pseudocapsular Resection (A- En bloc and partial pseudocapsular resection, B- pseudocapsular resection not attempted or possible and no tumor found).