Endonasal Endoscopic Surgery for Macroadenomas: New Understanding of Pseudocapsules

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Abstract

Purpose

Extracapsular resection of pituitary microadenomas has been widely reported, but only a few studies have carried out further investigations in macroadenomas, especially using the endonasal endoscopic approach. The authors of this study combined not only the interoperative characteristics of pituitary adenomas and pseudocapsules but also the surgical technique, outcomes and complications in macroadenomas to investigate the pseudocapsule.

Methods

In total, 143 consecutive patients with pituitary adenomas (maximum diameter 15 - 40 mm) who underwent endoscopic endonasal-transsphenoidal surgery between January 1, 2017, and August 1, 2019, were included in the study.

Results

Among 143 patients, 48 patients had an intact pseudocapsule, 56 patients possessed an incomplete pseudocapsule and the remaining 38 patients had no pseudocapsule. A white and thick pseudocapsule was more frequent (p=0.016) in fibrous adenomas, but tumor fibrosis (p=0.004) and adenoma apoplexy (p<0.001) were the factors that predicted the pseudocapsular integrity and hindered en bloc extracapsular resection according to a logistic regression analysis. In addition, the adenoma size (p=0.185) did not influence pseudocapsular integrity. Partial capsulectomy for macroadenomas did not show a significant advantage over piecemeal resection in gross total tumor resection (GTR) or biochemical remission (p=0.731 and p=0.685, respectively), but GTR in whole capsular resection was 100%. Additionally, this resection method had a higher risk of intraoperative cerebrospinal fluid leakage (p=0.010) and a lower incidence of new hormone deficit (p=0.043) than piecemeal resection.

Conclusions

The pseudocapsule widely exists in pituitary macroadenomas and extracapsular resection can improve GTR and hormone remission rate and reduce the occurrence of postoperative pituitary dysfunction in short-time.

Highlights

1. A large proportion of pituitary macroadenomas possess a pseudocapsule.
2. The size of macroadenomas does not affect the integrity of the capsule.
3. Adenoma apoplexy and fibrosis are predictors that the pseudocapsular en bloc resection whether can be performed.
4. Extraspseudocapsular resection has a lower rate of hypopituitarism but a higher incidence of intraoperative cerebrospinal fluid

**Introduction**

Although the histologic pseudocapsule around pituitary adenomas was noted by Costello in 1936[1], this delicate structure did not attract sufficient attention from most surgeons until Oldfield et al[2] described the histology of the pseudocapsule and advocated using this pseudocapsule as a surgical capsule for pituitary adenomas. Subsequently, many researchers have reported the pseudocapsule operation, but there are still some problems with pituitary adenoma pseudocapsular surgery.

Regarding surgical technology, previous studies[3-8] have mainly used the surgical technology summarized by Oldfield on the basis of the microscopic transseptal transsphenoidal approach (MTSS), which is more suitable for microadenomas or small macroadenomas[7]. For surgery involving larger adenomas, it is hard to distinguish the pseudocapsule from the anterior surface of the adenoma, which limits the application of extraspseudocapsular resection[9]. Refinements of the endoscopic image quality and developments in the surgical technique have occurred over the years. The endoscopic transnasal transsphenoidal approach (ETSS) provides advantages over the traditional MTSS for tumor resection, but only a few studies have reported utilization of the pseudocapsule among macroadenomas in the pure ETSS, with little to no emphasis on the surgical technique.

In addition, the efficacy of pseudocapsular resection remains controversial, and the factors that influence pseudocapsular surgery have not been determined. Not all tumors are covered by a complete pseudocapsule[2]; under this condition, a mixture of the extraspseudocapsular technique and traditional piecemeal resection are used. In 2009, Lee et al[4] showed, compared with tradition piecemeal resection, that excising the pseudocapsule with the MTSS did not improve the surgical results. In 2015, Kim et al[10], however, used the same surgeon's database, but did not include all patients with an incomplete pseudocapsule in the extraspseudocapsular resection group and obtained the opposite conclusion. The surgery's effect among patients who only had a partial pseudocapsule was still unknown.

In our study, we collected a series of patients who underwent pure ETSS pituitary adenoma surgery and analyzed the following three aspects: (1) the intraoperative characteristics of the pseudocapsule, (2) the relationship between the extent of pseudocapsular resection and the surgical outcomes and (3) the impact factors of the pseudocapsule on improving the understanding of the pseudocapsule.

**Methods**

**patients**

The data collection for this study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanchang University. We retrospectively collected data from 237 patients who underwent endoscopic transsphenoidal pituitary adenoma surgery by a single surgeon (ZDW) from 1/2017 to
The data included a complete history, intraoperative observation, physical and neurological examinations, and radiological assessment. The distinction of the pseudocapsule is more difficult in tumors with a maximum diameter larger than 15 mm, according to the literature[9]. To reflect the difference in surgical technique between microadenomas and macroadenomas, 192 patients (tumor largest diameter 15-40mm) were included in this study.

The exclusion criteria were as follows:

1. patient had not undergone an MRI scan preoperatively or postoperatively (n=7)
2. follow-up time <3 months (n=27)
3. adenomas were intracranial extradural (Hardy D) as assessed according to the Hardy modification classification system[11] (n=15).

Adenomas that were classified as Hardy D were excluded because the pseudocapsule only covers intrasellar tumor tissue, and complete resection of extradural tumor tissue inevitably leads to intraoperative leakage of cerebrospinal fluid (CSF), which will influence the analysis of surgical complications. Invasive tumors, Hardy E, Knosp 3 or 4, were not ruled out because these adenomas still covered by incomplete pseudocapsules possibly and the resection does not necessarily cause CSF leakage. Following application of the inclusion and exclusion criteria, we performed a statistical analysis on a total of 143 patients.

Images were retrospectively reviewed by the first authors (WZQ and LGH) to determine the tumor grade according to the Knosp[12] and modified Hardy classification systems. The tumor volume was measured by Brainlab Systems[13]

**Surgical technique**

The location of the pituitary gland was identified by preoperative 3.0 T MRI and reconfirmed relying on Brainlab neuronavigation intraoperatively. surgeries were carried out using a standard binostril endoscopic approach (4 hand). In cases with a high risk of CSF leakage, a pediculate nasoseptal flap was harvested following the Hadad technique. The dura mater was opened widely, lateral to the cavernous sinus and superior to the tuberculum sellae, while attempting to leave the anterior surface of the pituitary (the pituitary capsule) intact.

**Identification and establishment of the pseudocapsular surgical plane**

In our study, the pseudocapsule was identified by dissecting dura mater, pituitary capsule, and pituitary gland. When there is no obvious pituitary capsule, we separate the tumor capsule and the pituitary gland from the inner side of the pituitary gland[9]. This method is not fundamentally different from Taylor’s, which involves removing the tumor to expose the pituitary gland and establish a plane, however, in large
pituitary adenomas, the pituitary tends to be on one sides of the tumor and is not always on the posterior side of the tumor. After the dura was opened, the anterior surface was inspected primarily using a disc dissector to determine the possible presence of the thin pituitary gland or capsule, which was excised to expose the pseudocapsule after it was identified. If the position was on the lateral surface of tumor and the anterior surface of the tumor was covered by an intact capsule-like tissue, surgeons decompressed the tumors and attempted to establish a pseudocapsular plane along the capsule from the pituitary side. If the position was located on the posterolateral/superior surface of the tumor or there was not a visible capsule covering the anterior surface of the tumor, the majority of tumor tissue was resected until the pituitary gland was exposed.

According to the presence of a pseudocapsular plane and its continuity that were determined by surgical videos, patients were divided into the following three groups: Group A (whole capsulectomy), Group B (partial capsulectomy) and Group C (piecemeal resection). Each patient was initially grouped and characteristics of pituitary adenomas such as CSF leakage, apoplexy and fibrosis were evaluated anonymously by two authors (WZQ and LGH), and then checked by the author (ZDW).

Among the 143 patient, 58 (40.6%) patients (49 cases in Group A and 9 in Group B) had their pseudocapsules easily removed along with the main tumor mass. Thus, intraoperative biopsy of the removed capsule was not performed in these cases[14]. For the remained patients who had found a distinguishable capsule-like tissue from the pituitary gland, a biopsy for frozen histopathological examination was performed on them.

1. En bloc capsulectomy

The pseudocapsular plane was kept clear, and its integrity was maintained during the whole excision process, which was defined as en bloc capsulectomy. In this fashion, surgeons could ensure that adenomas had been removed with the capsule completely. After separating the pseudcapsule from the pituitary gland, the tumor was supported using a disc dissector from the extrapseudocapsule to keep high tension at the interface. Meanwhile, using an aspirator to separate the pseudcapsule from peritumor tissue, all processes were performed under a clear operative field, which avoided injury to the pituitary gland as much as possible. When the resection was carried out to the posterolateral surface of the tumor, the tumor volume was decreased again to avoid crushing the thin capsule. [video1 part1]

In our study, surgeons tried to achieve a bloc resection to prevent the loss of the surgical plane, but there were 12 case patients. For the convenience of excision, the part of the adenoma that had been separated from the peritumor tissue was removed earlier during the resection process, but these parts were assigned to Group A.

2. Partial capsulectomy
Partial capsulectomy was performed when the pseudocapsular plane was lost. The common reasons for this loss included bleeding in the operating area, tumor fibrosis, tumor invading the cavernous sinus, bone or finding the pseudocapsule after piecemeal resection. Most pseudocapsules were thin and transparent, which made them hard to find again once the surgical plane was lost. Under this condition, piecemeal resection was used as a substitute to completely resect the residual tumor.

There were 9 case patients. The pseudocapsule was completely removed with the intrasellar adenoma, but the adenomas broke through pseudocapsules and invaded the cavernous sinus or bone, them was assigned to Group B.

3. Piecemeal resection

If no pseudocapsule was found during the operation or detected by pathology, the surgery was defined as piecemeal resection. The tumor was removed by a 2-suction technique. With a 30° rigid endoscope, we searched for residual tumors in hidden corners. After hemostasis of the tumor bed with oxidized cellulose, we sometimes applied a synthetic dural graft and a dural sealant. At the end of the procedure, silicone rubber implants and nasal packing were placed.

Assessment of Surgical outcome

Intraoperative observation

The intraoperative observations included the integrity and characteristics of the pseudocapsule, adenomas texture, fibrosis, apoplexy, extent of adenomas invasion and intraoperative CSF leakage.

Most pituitary adenomas are soft, but some with a high collagen are sticky and Ceylan et al [15] showing that the fibrous composition of pituitary tumors is closely related to the aggressiveness of tumors, so adenomas fibrosis was roughly classified into two types (due to a lack of uniform standards[16,17]): 1) adenoma tissue was glutinous and some transparent and flimsy fibers could be observed and 2) the tumor was separated by white fibers or the white fibrous tissue adhered to the normal tissue. Type 1 adenomas were tumors with a high collagen content and without evidence of adherence to or invasion of surrounding tissue. Type 2 adenomas were separated by fibrous tissue or adhere to normal tissue tightly. Two cases of type 2 fiber tissue were resected with the capsule completely and placed into Group A (Fig 2). Adenoma apoplexy was judged according to surgical observations and preoperative MRI. Tumors that appeared to liquefy, coagulative necrotic tissue or black stale blood were identified as apoplexy. Inconspicuous hemorrhage of tumors was excluded from the statistics.

Postoperative pituitary function
New pituitary deficits were determined based on new laboratory deficiencies or treatment with new supplemental medications without previously documented deficiencies or supplemental medications. Patients with preoperative panhypopituitarism (n=7) were excluded from the evaluation of new-onset deficits after surgery. Patients with a prior abnormal pituitary deficit that returned to normal during follow-up, stopped supplemental medications or lacked clinical symptoms at follow-up were considered to have recovered from a preoperative pituitary deficiency.

Follow-up

All patients underwent a comprehensive endocrine evaluation within 3 days before surgery, 3 days before discharge, at 3 months and every 1–2 years after surgery. A 3.0 T MRI scan of the head was performed on the second day after surgery; at 3 months postoperatively, which was the criterion that was used to judge the gross total tumor resection (GTR) in each group; and thereafter every 1–2 years, as appropriate.

Statistical Analysis

χ² tests and Fisher exact tests for independence were used to determine the statistical significance of differences in Knosp type, adenoma type, surgical remission rate, GTR, CSF and postoperative pituitary function between groups. A multiple logistic regression model was estimated to study the relationship between categorical outcome variables and independent variables. The level of significance was set at p < 0.05. All calculations were made using the statistical software package IBM SPSS version 24.

Results

Patients and pseudocapsule Characteristics

There were 49 patients in Group A (whole capsulectomy), 56 patients in Group B (partial capsulectomy) and 38 patients in Group C (piecemeal resection). The mean largest diameter (D) of tumors in Groups A, B and C was 25.41±4.13 mm, 25.75±5.49 mm and 26.21±8.17 mm, respectively. The adenoma volume (V) in Groups A, B and C was 6.76±3.53 cm³, 7.07±4.23 cm³ and 8.44±6.88 cm³, respectively. Comparing the diameter and volume of each group, although the mean size was gradually increase from Group A to B, there were not significant differences between each Group,(25.41±4.13 mm vs 26.21±8.17 mm, p_D=0.584; 6.76±3.53 cm³ vs 8.44±6.88 cm³, p_V=0.176).

In all, 24 patients (42.9%) in Group B and 17 patients (44.7%) in Group C had evidence of cavernous sinus invasion on preoperative MRI (p=0.857), while 18 patients (32.1%) in Group B and 14 patients (36.8%) in Group C had Knosp grades of 3 or 4 (p=0.637). On operation, 26 patients (46.4%) in Group B and 17 patients (44.7%) in Group C had evidence of cavernous sinus invasion (p=0.872). Other demographic characteristics are shown in Table 1.
A histological pseudocapsule was identified in 105 patients (73.4%) intraoperatively. There were 49 patients (34.3%) with an intact pseudocapsule, and in 56 patients (39.2%), the pseudocapsule was incomplete due to adenomas invasion or maldevelopment. Among these patients, the most common pseudocapsule visualized was described as transparent, thin and fragile, which was an off-white fibrous tissue after removal of the main tumor mass. As the thickness of the capsule increased, the pseudocapsule was yellowish or white. Some pseudocapsules appeared as calcified tissue, but the yellowish pseudocapsule was rare.

The number of type 1 fibroadenomas in Group B was greater than that in Group A (p=0.023, p<0.05) and Group C, but the number of type 2 fibroadenomas in Group C was more than that in Group A (p=0.034, p<0.05) and Group B. In addition, 5 patients (10.2%) in Group A and 26 patients (46.4%) in Group B were found to have pituitary apoplexy (p<0.001) (Table 3). However, fibrous pituitary adenomas were more frequent in aggressive and recurrent adenomas, which also influenced the integrity of the pseudocapsule and the size of the tumor in Group A to C is increasing. For these reasons, a multivariate analysis was carried out.

Because of the linear relationship between the groups, ordinal logistic regression was not used, and only Group A and Group B were used for logistic regression analysis of the influencing factors of tumor integrity. Partial correlation analysis was carried out between the tumor size and resection method.

In our study, we compared the characteristics of the pituitary adenomas in Group A and Group B based on forward stepwise logistic regression with predictive variables from Table 2 (i.e., adenoma apoplexy, adenoma fibrosis, recurrent adenomas and Knosp grades). Through logistic regression analysis, we showed that the integrity of the pseudocapsule was significantly dependent on tumor fibrosis (p=0.025), adenoma apoplexy (p<0.001). There was no significant correlation between the tumor size and surgical techniques ($R_D=-0.112, p=0.185; R_V=0.038, p=0.651$).

**Surgical Outcomes and Remission**

Radiographically, 121 patients (83.9%) achieved gross total resection. Patients who underwent complete pseudocapsular resection exhibited a higher GTR than patients who underwent piecemeal resection (100% vs 73.8%, p<0.001). There was no difference in the GTR between Group B and Group C (76.8% vs 73.8%, p=0.435); however, patients in Group B who had evidence of cavernous sinus invasion had a higher GTR than patients in Group C (73.1% vs 52.9%, p=0.176). The remission rate of patients in Group A (100%) was significantly higher than that of patients in Group C (71.4%) (p=0.004, p<0.05), and there was no significant difference in the endocrine remission rate between Group A and Group B (80.8% vs 71.4%, p=0.685) (Table 5). In general, complete pseudocapsular resection significantly improved surgical efficacy, but when the pseudocapsular plane was lost during surgery, there was no significant difference between extrapseudocapsular resection traditional piecemeal resection.
Complications

There was a significant difference in the incidence of intraoperative CSF leakage between Group A and Group C (51.0% vs 23.7%, p=0.010), but there was no difference in incidence between Group B and Group C (33.9% vs 23.7%, p=0.287). New postoperative endocrine deficits occurred in 22(16.2%) of 136 cases. There were 3 hypothyroidism and 1 low cortisol in Group A; 2 hypothyroidism, 5 low cortisol, 2 low GH and 1 hypogonadism in Group B; 2 hypothyroidism, 2 low cortisol, 3 low GH and 1 case with hypogonadism and hypothyroidism in Group C. There was a trend toward significance in the rate of postoperative endocrine deficits between Group A and Group C patients (8.5% vs 22.2%, p=0.078), but this was not statistically significant. However, there was a significant difference (3/42 vs 13/59, p=0.043) between patients (n=42) who underwent a whole pseudocapsular resection and the other patients (n=59) when excluded patients with knosp grade 3 or 4.

Discussion

The histologic pseudocapsule is a boundary between a pituitary adenoma and normal tissue[2]. The histologic pseudocapsule provides a surgical plane to excise the whole tumor accurately while avoiding injury to the normal pituitary gland. In the presence of an intact pseudocapsule, the anatomical structure of the sellar pituitary tumor can be divided into three layers[6]: the dura in the outermost layer, the pituitary and pituitary capsule[18] in the middle layer, and the pseudocapsule that surrounds the tumor (Fig 1A). In microadenoma, an obvious the pituitary capsule, as a reference, helps surgeons to identify the pseudocapsule by cutting through it to avoid mistaking a thin hypophysis for a pseudocapsule. However, there is not often a pituitary capsule or thin gland on the anterior surface of a large adenoma and characteristics of pseudocapsules vary widely, which makes pseudocapsule difficult to distinguish. To solve this problem, in 2006, Oldfield and Vortmeyer[2] proposed that the surgical plane could be established from the posterior margin of adenomas, which was demonstrated by Taylor et al[9] in 2018. However, either Oldfield and Vortmeyer or other researchers[19,5,4,10] have made contributions to the development of the pseudocapsular resection technique, all based on the MTSS. In recent years, although endoscopic technology has developed rapidly, few researchers have used endoscopy to explore the new characteristics of the pseudocapsule, especially based on surgery for pituitary macroadenomas.

The endoscope versus microscope debate has always confused pituitary surgeons. In the early phase of endoscopic development, surgeons believed that the ETSS had no obvious advantage over the MTSS[20]. However, in recent years, the advantages of the ETSS have gradually been shown. McLaughlin et al[21] proved that the ETSS can reduce residual tumors, and this advantage is more conspicuous in larger size tumors[22,23]. Endoscopy provides a wider exposure and a close-up view, which allows surgeons to achieve the pseudocapsular plane from different locations (Fig 1C and 1E).

Detectable rate of pseudocapsule and Extent of resection
The determination of pseudocapsule mainly depends on intraoperative detection, which may be influenced by the experience of surgeons and surgical technology, so the rates of pseudocapsule detection during surgery in the literature are different. Kawamata et al[19] found that nearly all GH-secreting adenomas were covered by pseudocapsule-like tissue intraoperatively. Lee et al[4] found a pseudocapsule in 55.7% of patients. Jagannathan and Oldfield et al[3] found that 54% of ACTH-secreting microadenomas were covered by a pseudocapsule, but they believed that all pituitary adenomas possessed a well-defined pseudocapsule. In our study, most adenomas (73.4%) were found to have a pseudocapsule during surgery. These rates were similar to that found Kawamata and higher than that found by Kim et al. The majority of pituitary macroadenomas possess a pseudocapsule, but the detection rate of pseudocapsules was low due to the limitation of surgical observation tools and techniques in early studies.

The high rate of detectable pseudocapsules led to a high rate of extrapseudocapsular resections. In our series, the rate of complete extrapseudocapsular resections (49/143, 34.3%) was higher than that in previous research (8.2%–23.8%)[6,7,10] and in Group A, all patients had achieved GTR and hormone remission. This result was the same as Xie et al[7] and Kim et al[10]. However, there were no differences in the GTR (76.8% vs 73.8%, p=0.435) and hormone remission rate (80.8% vs 71.4%, p=0.685) between Group B and Group C. The ETSS approach also improved the GTR in piecemeal resection[24], and we performed a more active piecemeal resection would rather resect part of the compressed pituitary gland than completely remove the adenoma[25].

Achieving whole capsulectomy not only depends on surgical technology but also on the pseudocapsular thickness and integrity, but the factors impacting the integrity of the pseudocapsule are still unclear.

**Tumor size**

Excluding invasive tumors, the other factors that may influence the integrity of the pseudocapsule are still unknown. Lee et al and Kawamata et al thought, in larger tumors, that the microsurgical pseudocapsule tended to be discontinuous or disrupted, did not cover the entire tumor[19,4]. However, compared with the MTSS approach, the ETSS has obvious advantages in the resection of large adenoma[23,24]. the invasiveness of the tumor was related to the size of the tumor[26,27]. The size of the tumor in Group A to C is increasing but according to the results of partial correlation analysis that suppressed the interference of Knosp grades (R_D=-0.112, p=0.185; R_V=0.038, p=0.651), it was apparent that the tumor size did not impact pseudocapsular integrity.in some macroadenomas, that a multiply pseudocapsule,Onion like structure described by Oldfield and Vortmeyer in microadenomas,covered the tumor (video 2) which showed that the new capsule would possibly gradually replace the old one and explained the development of pseudocapsules in macroadenomas from a clinical view.

**Adenoma fibrosis**
Currently, it is generally accepted that the pseudocapsule is produced by the compressed pituitary gland[2,28]. however, the collagen content of pituitary adenomas also plays an important role in the development of the pseudocapsule. Farnoud et al[29]. believed pseudocapsules resulting from the condensation of the basement membranes of compressed peritumoral cell cords. Lee et al[4] demonstrated that the aggregation of fibroblasts, collagen fibers, and small cells forms the pseudocapsule in the background of myxoid materials. However, perhaps because of the lack of uniform standards, few studies have reported the relationship between tumor fibrosis and the pseudocapsule. In the literature, tumors with a high collagen content are beneficial to the development of the pseudocapsule, but our result was contrary to it. The ratio of tumor fibrosis in Group B was higher than that in Group A (24.5% vs 51.8%, p=0.004), and logistic analysis showed that tumor fibrosis was an independent factor (p=0.025) (Table 3). However, in our experience, a white and thick pseudocapsule was more frequently found in rubbery (Fig 2A). This difference may be because the grouping variable in the study was the surgical method, which depends on the intraoperative integrity of the pseudocapsule (not its thickness), and tumor fibrosis have a significant effect on resection even though the tumor did not invade the normal tissue(video1.part 2).

Adenoma apoplexy

Kim et al[10] found the nature of pseudocapsules could be influenced by adenoma apoplexy, which is consistent with our intraoperative observations. In our experience, the tumors covered by an intact capsule were more uniform in texture than other tumors. The ratio of patients who had evidence of adenoma apoplexy in Group A was less than that in Group B (10.2% vs 46.4% .p<0.001). Logistic regression analysis also demonstrated that adenoma apoplexy was an independent factor (p<0.001) related to the pseudocapsule. Adenoma apoplexy includes acute apoplexy and subclinical apoplexy[30]. Acute tumor apoplexy is rare but can lead to a dramatic increase in tumor volume. Subclinical adenoma apoplexy is frequent in pituitary adenomas. The prevailing view is that the imbalance of the high metabolism of adenomas and blood supply leads to adenoma apoplexy[31]. Farnoud et al[29] found an active process of adenoma expansion within normal parenchyma existed in the tumor with a pseudocapsule so the imbalance can possibly influence the development of a pseudocapsule. Pituitary adenoma apoplexy is more a result than a cause,can also occur in some large adenomas with an intact capsule. In these tumors, the capsule still had clinical significance, as it can help avoid accidental injury to pituitary tissue that has changed texture and color due to pituitary apoplexy[32].

Cerebrospinal fluid leakage

Although the technology for reconstruction of the skull base has developed substantially, cerebrospinal fluid (CSF) rhinorrhea still remains a difficult issue related to the ETSS. The root cause of CSF leakage is intraoperative injury of the diaphragma sellae. However, whether extrapseudocapsular resection increases or reduces the incidence of intraoperative CSF leakage is still unclear. Ceylan et al[6] and Kinoshita et al[8]
thought the rate of intraoperative CSF leakage was not influenced by pseudocapsules but Kim et al\[4\] believed pseudocapsular resection in MTSS will increase the incidence of intraoperative CSF leakage but that resecting the tumor en bloc with its pseudocapsule could avoid injury to the diaphragma sellae. But, in our study, the incidence of intraoperative CSF leakage in group A was higher than that in Group C (51.0% vs 23.7%, p=0.010), which was contrary to result of Kim et al. With the MTSS, small tumors can be easily removed with the complete pseudocapsule and the diaphragma sellae is protected by a thick pituitary gland\[2\]. However, in macroadenomas, the pituitary gland change position or too thin to protect the sella and the sella became larger and thinner due to compression of the tumor. Even if we carefully removed the pseudocapsule, it was still possible to cause CSF leaks due to stripping the pseudocapsule from the diaphragma sellae, In addition, intact membranes tend to be thicker and more adherent to surrounding tissue than poorly developed ones. This makes it easier to pull and tear the thin diaphragma sellae during separation, which was the same as the explanation by Kim et al\[10\] as to why partial pseudocapsular resection was more likely to cause intraoperative CSF leakage. Of course, this result may also be related to the methods and habits of the surgeon, which requires a multi-center argument. The intraoperative leaks always minor and the technique dose not cause obvious damage to normal pituitary gland that easily be damaged in piecemeal resection (shown in video 1 part 3). With use of the pediculate nasoseptal flap technique, there was no difference between Groups A, B and C (4.1%, 1.8% and 2.6% respectively) in the incidence of postoperative CSF leakage.

**Hypopituitarism**

Although excising part of the thin pituitary gland in pituitary adenoma surgery may not influence pituitary function, surgeons still try to protect the normal pituitary gland as much as possible. Oldfield et al\[2,4\] and Qu et al\[5\] emphasized that the extracapsular resection technique helped surgeons to identify and discriminate pituitary adenomas from the normal pituitary gland so that it reduced the risk of erroneous removal of a normal pituitary gland. However, there are no significant differences in hypopituitarism between extracapsular resection and traditional piecemeal resection in most studies\[4,6,8,10,33\]. The controversy was possibly caused by the surgical technique\[9\]. The pituitary gland was resected possibly due to misjudging the pituitary capsule as a pseudocapsule\[10\]. Taylor et al\[9\] demonstrated there were strong trend that the rate of new pituitary dysfunction after surgery in extrapseudocapsular resection is lower than normal technique. In the study, we attempt to exclude interference of partial pseudocapsular resection to prove the advantage of extrapseudocapsular resection in a short-time. The rate in Group A was less than Group C (4/47 vs 8/36, p=0.078), has a strong trend toward significance. And, among patients in knosp 0-2 grades, the rate of new hypopituitarism in pure extra-pseudocapsular resection (Group A) was less than that in the other technique (3/42 vs 13/59, p=0.043), shown in Table 6.

**Conclusion**

Pseudocapsules widely exist in pituitary macroadenomas, and their integrity is related to adenoma apoplexy and fibrosis, not adenoma size. The high collagen content of adenomas, however, is beneficial
to the development of pseudocapsules. In operative outcomes, extracapsular resection can improve the total resection rate and hormone remission rate and reduce the incidence of postoperative pituitary dysfunction.

Declarations

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Ethical approval: the ethics number is (2019) medicine research (140) approved by the medical Research Ethics Committee of The Frist Affiliated Hospital of Nanchang University.

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Tables
TABLE 1. Univariate analysis of demographic data of Group A, Group B and Group C patients
| Demographics          | Group A | Group B | Group C | Total    |
|-----------------------|---------|---------|---------|----------|
| No. of patients       | 49      | 56      | 38      | 143      |
| Male sex (%)          | 29(59.2%) | 33(58.9%) | 18(47.4%) | 80(55.9%) |
| Age, years            | 46.8±10.7 | 51.2±11.2 | 53.1±12.01 | 51.47±12.96 |
| Tumor diameter D (mm) | 25.41±413 | 25.75±5.49 | 26.21±8.17 | 25.76±5.91 |
| Tumor volume V (cm³)  | 6.76±3.53 | 7.07±4.23 | 8.44±6.88 | 7.33±4.89 |
| No. of patients w/ CSI|         |         |         |          |
| On preop imaging      | 5(10.2%) | 24(42.9%) | 17(44.7%) | 46(32.2%) |
| On operation          | 0(0.0%)  | 26(46.4%) | 17(44.7%) | 43(30.1%) |
| Tumor type            |         |         |         |          |
| GH                    | 9(18.4%) | 15(26.8%) | 10(26.3%) | 34(23.8%) |
| ACTH                  | 7(14.3%) | 8(14.3%)  | 7(18.4%)  | 22(15.4%) |
| PRL                   | 8(16.3%) | 4(7.1%)   | 5(13.2%)  | 17(11.9%) |
| TSH                   | 0(0.0%)  | 2(3.6%)   | 1(2.6%)   | 3(2.1%)   |
| NFPA                  | 25(51.0%)| 27(48.2%) | 15(39.5%) | 67(46.9%) |
| No. of patients w/ preop deficits | 27(55.1%) | 35(62.5%) | 26(68.4%) | 88(61.5%) |
| Preop deficits        |         |         |         |          |
| Hypothyroidism        | 9(18.4%) | 8(14.3%)  | 6(15.8%)  | 23(16.1%) |
| Low cortisol          | 3(6.1%)  | 3(5.4%)   | 2(5.3%)   | 8(5.6%)   |
| Low GH                | 3(6.1%)  | 9(16.1%)  | 5(13.2%)  | 17(11.9%) |
| Hypogonadism          | 15(30.6%)| 27(48.2%) | 16(42.1%) | 58(40.6%) |
| Panhypopituitarism    | 2(4.1%)  | 3(5.4%)   | 2(5.3%)   | 7(4.9%)   |
| DI                    | 1(2.0%)  | 1(1.8%)   | 2(5.3%)   | 4(2.8%)   |
| Knosp grade           |         |         |         |          |
| 0                     | 4(8.2%)  | 4(7.1%)   | 2(5.3%)   | 10(7.0%)  |
| 1                     | 12(24.5%)| 18(32.1%) | 11(28.9%) | 41(28.7%) |
| 2                     | 28(57.1%)| 16(28.6%) | 11(28.9%) | 55(38.5%) |
| 3                     | 5(10.2%) | 17(30.4%) | 12(31.6%) | 34(23.8%) |
| 4                     | 0(0.0%)  | 1(1.8%)   | 2(5.3%)   | 3(2.1%)   |
CSI = cavernous sinus invasion; DI = diabetes insipidus; GH = growth hormone; NFA = nonfunctioning adenoma; TSH = thyroid-stimulating hormone.

**TABLE 2. Characteristics of pituitary adenomas in different group**

| variable                  | Group A | Group B | Group C | Total |
|---------------------------|---------|---------|---------|-------|
| No of patients            | 49      | 56      | 38      | 143   |
| Tumor fibrosis            | 12(24.5%)<sup>a</sup> | 29(51.8%) | 15(39.5%) | 56(39.2%) |
| Type 1                    | 10(20.4%)<sup>a</sup> | 23(41.1%) | 7(18.4%)  | 40(28.0%) |
| Type 2                    | 2(4.1%)<sup>b</sup> | 6(10.7%)  | 8(21.1%)  | 16(11.2%) |
| Recurrent Tumors          | 2(4.1%)  | 4(7.1%)   | 3(7.9%)   | 9(6.3%)    |
| adenoma apoplexy          | 5(10.2%)<sup>a</sup> | 26(46.4%) | 15(39.5%) | 46(32.2%) |

<sup>a</sup>: Significant according to χ² test (p<0.05) compared to Group B.

<sup>b</sup>: Significant according to χ² test (p<0.05) compared to Group C

**TABLE 3. Partial Correlation between size of tumors and fashions of resection**

| Control Variables | Variable | R   | p Value |
|-------------------|----------|-----|---------|
| Knosp grades      | diameter | -0.112 | 0.185  |
|                   | volume   | 0.038 | 0.651  |

**TABLE 4. Logistic Regression Analysis of pseudocapsules integrity**
| Covariates        | Exp(B) | 95% CI       | p Value |
|-------------------|--------|--------------|---------|
| apoplexy          | 10.577 | 3.030-36.921 | <0.001  |
| Tumor fibrosis    |        | 0.025        |         |
| type1             | 0.243  | 0.037-1.607  | 0.142   |
| type2             | 1.035  | 0.144-7.428  | 0.973   |
| Recurrent tumors  | 3.016  | 0.276-14.812 | 0.488   |
| knosp             |        | 0.099        |         |
| knosp 0           | Ref    |              |         |
| knosp 1           | 0.922  | 0.129-6.581  | 0.935   |
| knosp 2           | 1.222  | 0.282-5.294  | 0.788   |
| knosp 3           | 0.320  | 0.082-1.247  | 0.101   |
| knosp 4           | Ref    |              |         |

**TABLE 5. Surgical outcome**

| Variable        | No. of Patients* | Group A               | Group B               | Group C               | Total               |
|-----------------|------------------|-----------------------|-----------------------|-----------------------|---------------------|
| Remission rate  | 22.26.21.69      | 22(100%)a             | 21(80.8%)             | 15(71.4%)             | 58(84.1%)           |
| knosp 0-2       | 19.15.14.48      | 19(100%)              | 13(86.7%)             | 11(78.6%)             | 43(89.6%)           |
| knosp 3         | 3.11.6.21        | 3(100%)               | 8(72.7%)              | 4(66.7%)              | 15(71.4%)           |
| Knosp4          | 0.0.1.1          | 0(0.0%)               | 0(0.0%)               | 0(0.0%)               | 0(0.0%)             |
| CSI at op       | 0.14.9.23        | 0(0%)                 | 11(78.6%)             | 5(55.6%)              | 16(69.6%)           |
| GTR             | 49.56.38.143     | 49(100%)a             | 43(76.8%)             | 28(73.8%)             | 120(83.9%)          |
| Knosp 0-2       | 44.38.24.106     | 44(100%)              | 31(81.6%)             | 21(87.5%)             | 96(90.6%)           |
| Knosp 3         | 5.17.12.34       | 5(100%)               | 12(70.6%)             | 7(58.3%)              | 24(70.6%)           |
| Knosp 4         | 0.1.2.3          | 0(0.0%)               | 0(0.0%)               | 0(0.0%)               | 0(0.0%)             |
| CSI at op       | 0.26.17.43       | 0(0%)                 | 19(73.1%)             | 9(52.9%)              | 28(65.1%)           |

* Presented as Group A, Group B, Group C and total patients, respectively.

a: Significant according to χ² test(p<0.05) compared to Group C

**TABLE 6. Univariate analysis of intraoperative CSF leak, worsened endocrine function after surgery**
| Variable                                    | No. of Patients* | Group A | Group B | Group C | Total  |
|--------------------------------------------|-----------------|---------|---------|---------|-------|
| Rate of endocrine deficits based on technique | 47.53.36.136    | 4(8.5%) | 10(18.9%) | 8(22.2%) | 22(16.2%) |
| knosp0-2                                   | 42.36.23.101    | 3(7.1%) | 7(19.4%) | 6(26.1%) | 16(15.4%) |
| knosp3-4                                   | 5.17.13.35      | 1(20.0%) | 3(17.6%) | 2(15.4%) | 6(17.1%) |
| CSF                                        |                 |         |         |         |       |
| Intra CSF                                  | 49.56.38.143    | 25(51.0%) | 19(33.9%) | 9(23.7%) | 53(37.1%) |
| Post CSF                                   | 49.56.38.143    | 2(4.1%) | 1(1.8%) | 1(2.6%) | 4(2.8%) |

*Presented as Group A, Group B, Group C and total patients, respectively, and Groups A, B, and C each had 2, 3, and 2 patients with panhypopituitarism.

a: Significant according to χ² test (p<0.05) compared to Group C

b: Significant according to χ² test (p=0.043) compared to the other patients in Group B and Group C (n=59)

**Supplementary Files**

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