Pseudocapsular resection in elderly patients with non-functioning pituitary adenoma

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Abstract

Purpose

The safety of transsphenoidal surgery (TSS) for pituitary adenoma in elderly patients is becoming a new topic in our aging society. However, previous studies did not focus on the surgical procedures in elderly patients. We attempted to clarify the safety of TSS and the influence of pseudocapsular resection in elderly patients with non-functioning pituitary adenoma (NFPA).

Methods

A total of 272 patients undergoing initial surgery for NFPA were categorized into two groups as follows: 1) Elderly group (n = 66; age $\geq$ 70 years); and 2) Younger group (n = 206; age < 70 years). Furthermore, all patients were newly divided into the two following categories: 1) Resected group (n = 113, with total pseudocapsule resection); and 2) Non-Resected group (n = 159, without pseudocapsule resection). The main outcome measure was the incidence of perioperative complications and the rate of severe growth hormone deficiency (sGHD) after TSS.

Results

No data indicated a negative influence of aging on TSS. Furthermore, pseudocapsular resection did not increase the surgical risks in the Elderly group. On the other hand, sGHD only showed a significant improvement in the Younger group. However, the prevalence of sGHD did not change after TSS in the Elderly group, irrespective of whether the pseudocapsule was resected.

Conclusions

Aging does not increase the risk of TSS for NFPA, furthermore, pseudocapsular resection does not have any negative influence on the TSS of NFPA in elderly patients. However, in elderly patients, the likelihood of achieving an improvement in sGHD is lower, irrespective of whether the TSS is performed with a pseudocapsular resection.

Introduction

As the elderly population has increased in Japan, there has been an increase in the proportion of elderly patients with pituitary adenomas [1, 2]. The role of transsphenoidal surgery (TSS) in the treatment of pituitary adenomas in elderly patients should be further highlighted. Some recent studies have reported that the risk of complications associated with TSS was higher in elderly patients, hence it was recommended that TSS should be carefully conducted for elderly patients [3-5]. However, whether the risk of TSS is increased by aging is controversial.

Unfortunately, previous studies about TSS in elderly patients did not consider the differences among hypothalamic-pituitary tumors, including non-functioning pituitary adenoma (NFPA), functioning pituitary adenoma (FPA), craniopharyngioma and Rathke's cleft cyst (RCC). The hormonal state at FPA would influence the perioperative condition and could cause specific complications. Craniopharyngioma or RCC were treated with different surgical procedures in TSS and might require additional treatments. Thus, when examining the effects of age on TSS, the types of tumor pathology should be strictly defined. Another important discussion point is the surgical strategy and procedure of TSS for elderly patients. Some authors noted that neurosurgeons should exercise caution when performing TSS for elderly patients, but there have been no reports focusing on the specific procedures needed in elderly patients.

Pseudocapsular resection has become an essential technique in TSS for FPA [6]. The safety of pseudocapsular resection in TSS for NFPA has also been reported [7]. However, it has not been clarified in elderly patients. Preserving the pseudocapsule of a pituitary adenoma might help to avoid surgical complications in elderly patients; however, this might also result in an increasing risk of postoperative hemorrhage and recurrence from residual tumor cells. In this study, we focused on NFPA to evaluate the pure surgical effects and aimed to clarify the safety of TSS and the influence of pseudocapsular resection in elderly patients with NFPA.

Materials And Methods

After receiving institutional board review approval (Ethical Committee for Epidemiology of Hiroshima University, E-2022), we undertook a retrospective cohort study of patients who underwent initial surgery for NFPA at Hiroshima University Hospital, between January 2008 and March 2020. A total of 272 (male, n=155 [57%]; female, n=117 [43%]; mean age at surgery 58.4 years [range, 17-89 years]) patients were identified. All patients underwent preoperative 3-Tesla magnetic resonance imaging (MRI) examinations. These patients were diagnosed with NFPA according to preoperative endocrinological examinations and postoperative histological findings.

These 272 patients were categorized into two groups based on past reports [5, 8, 9], as follows: 1) Elderly group (n=66; age ≥ 70 years); and 2) Younger group (n=206; age < 70 years). We further divided all of these patients into the following two categories: 1) Resected group (n=113; total resection of pseudocapsule was conducted); and 2) Non-Resected group (n=159; total resection of pseudocapsule was not conducted). In this study, pseudocapsular resection was defined as the separation of the tumor pseudocapsule and normal pituitary gland. Patients with total resection of the pseudocapsule underwent the removal of $>80\%$ of the pseudocapsule [7].

The following data were collected: maximum diameter of the tumor and Knosp grade on the preoperative MRI, American Society of Anesthesiologists (ASA) class, the rate of total tumor removal, peri-operative complications (intraoperative and postoperative cerebrospinal fluid (CSF) leakage, transient and permanent diabetes insipidus (DI), delayed hyponatremia, postoperative hemorrhage), period of hospitalization, incidence of preoperative and postoperative severe growth hormone deficiency (sGHD)

based on provocation tests, and identification of preoperative and postoperative anterior pituitary hormone replacement therapy (hydrocortisone, and/or levothyroxine sodium hydrate).

Endocrinological studies

The basal growth hormone (GH) levels of the anterior pituitary hormones and responses to induced hypoglycemia were evaluated in patients under 65 years of age. The other patients, who were older than 65 years of age or who had a history of heart disease or epilepsy, underwent arginine-loading tests to evaluate the GH axis, rather than hypoglycemia tests. In this present study, sGHD was defined as a GH peak of $<1.8 \mu\text{g/L}$ in a provocation test. The 217 patients received both of preoperative and postoperative provocation tests (at three months postoperatively). The insulin-like growth factor-1 (IGF-1) level was evaluated as the standard deviation score (SD score) based on a reference range established for the Japanese population according to both age and sex [10].

Surgical procedures

Transsphenoidal surgery was performed through one nostril under microscopic and endoscopic observation in all patients. A completely endoscopic procedure was adopted from 2010. Extracapsular dissection was attempted before internal decompression, or pseudocapsular resection was attempted after the internal decompression of the adenoma. The details of our surgical procedures were described in a previous report [7]. In this study, the pseudocapsular resection was not related to the total removal of the tumor. The total removal of the tumor means the complete resection of the adenoma, and does not consider whether the pseudocapsule is resected or not.

Statistical analysis

All statistical analyses were performed using the JMP[®] Pro 15.0 software program (SAS Institute Inc.). The values are expressed as the median. The median values were compared using the Mann–Whitney U-test, Kruskal-Wallis test, Fisher's exact test and chi-squared test with 95% confidence intervals. p values of <0.05 were considered to indicate statistical significance.

Results

Characteristics of the patients

The background characteristics of the patients are shown in Table 1. Sixty-six patients (mean age; 74.4 years) were included in the Elderly group and 206 patients (mean age; 53.3 years) were included in the Younger group. The ASA score in the Elderly group was higher than that in the Younger group ($p=0.0279$). There were no other significant differences in the background characteristics of the two groups (Table 1).

Surgical outcomes and complications

Table 2 shows the surgical outcomes and the incidence rates of perioperative complications. The rate of perioperative mortality was zero in this series. No data indicated that TSS was associated with greater risk in elderly patients. Furthermore, we examined the surgical outcomes and complications in super-elderly patients (≥ 75 years of age). There was no significant difference between the younger (< 75 years of age) and super-elderly (≥ 75 years of age) patients (data are not shown).

The rates of sGHD in the preoperative and postoperative periods are shown in Figure 1. In the Elderly group, five patients obtained an improvement of sGHD after TSS; however, five patients newly developed sGHD after TSS. In the Elderly group, the total rate of sGHD ($n=25/56$, 45%) did not change between the preoperative and postoperative periods. On the other hand, although seven patients newly suffered from sGHD after TSS in the Younger group, 28 patients recovered from preoperative sGHD after TSS. The total rate of sGHD decreased significantly from before surgery ($n= 64/161$, 40%) to after surgery ($n= 43/161$, 27%; $p=0.0178$). The incidence of newly developed sGHD after TSS in the Elderly and Younger groups did not differ to a statistically significant extent.

Effects of pseudocapsular resection

The effects of pseudocapsular resection were examined (Table 3). The rate of total tumor removal was significantly higher in the Resected group. Furthermore, we emphasize that postoperative hemorrhage did not occur in the Resected group. On the other hand, the incidence of perioperative complications in the Resected and Non-Resected groups did not differ to a statistically significant extent. These results were similarly observed in the Elderly and Younger groups.

Figure 2 shows the rates of preoperative and postoperative sGHD in the Resected and Non-Resected groups. In the Elderly group, the total rate of sGHD did not change after TSS, irrespective of whether pseudocapsular resection was performed. Furthermore, the rate of newly developed sGHD after TSS in the Resected and Non-Resected groups did not differ to a statistically significant extent. On the other hand, in the Younger group, the overall rate of sGHD decreased after surgery in both the Resect and Non-Resect groups. Only the Resected group showed a significant difference in the preoperative and postoperative rates of sGHD ($p=0.0165$): the rate of sGHD before surgery was 39%, while that after surgery was 21%.

Cutoff age of patients with the possibility of recovering from sGHD

As stated above, preoperative sGHD was not likely to improve after TSS in the Elderly group (≥ 70 years of age). We focused on the cutoff age of patients who had a possibility of recovering from preoperative sGHD after undergoing TSS. Figure 3 shows the rates of recovering from preoperative sGHD at intervals of five years of age. The preoperative sGHD was likely to improve in younger patients. The possibility of improvement was significantly higher in patients aged under 55 years old ($p=0.0015$). The rate of newly developed sGHD after TSS did not differ to a statistically significant extent in any of the groups: minimum 0% in the category of 55-59 years; maximum 8% in the categories of 50-54 years, 65-69 years, and ≥ 75 years.

Discussion

The present study showed that the perioperative risk of TSS did not increase in elderly patients. Recovery of sGHD after TSS was expected in patients younger than 55 years of age; however, pseudocapsular resection in elderly patients was not associated with the deterioration of GH secretion. To the best of our knowledge, the present study is the first report to focus on pseudocapsular resection in elderly patients.

Past studies have described the safety and the successful application of TSS in elderly patients, reporting that the outcomes were similar to those in younger patients. However, studies of large series have shown that elderly patients have a higher incidence of morbidity and inpatient mortality after pituitary surgery [4]. As TSS is generally less invasive than transcranial surgery and is associated with a lower incidence of perioperative complications, it is difficult to detect the difference between younger and elderly patients in small series of patients undergoing TSS. Although we also showed the safety of TSS in elderly patients with NFPA in this study, additional large studies are required to determine the effects of aging on TSS.

Pseudocapsular resection has contributed to the improvement of endocrinological remission rates in patients with FPA [6]; hence, this surgical technique is absolutely essential in the treatment of FPA. On the other hand, whether this technique should be applied to NFPA is controversial. We clarified the safety of pseudocapsular resection in patients with NFPA in a previous report [7], and this subsequent report confirmed the safety of pseudocapsular resection in elderly patients with NFPA.

The rate of recurrence in elderly patients was reported to be lower than that in younger patients [11], and the tumor volume doubling time of residual NFPA in elderly patients (≥ 61 years of age) was approximately 2-fold longer than that in younger patients (< 61 years of age) [12]. From the viewpoint of prevention of tumor recurrence, pseudocapsular resection might not be so important in some elderly patients, while some tumors may recur at older age and require additional treatments, such as radiotherapy or re-operation when the patient is older. Moreover, we would like to emphasize the importance of pseudocapsular resection in hemorrhagic tumors causing postoperative hematoma, and hard or fibrous tumors. Pseudocapsular resection cannot be conducted in all cases; however, pseudocapsular resection can contribute to reducing the surgical risk and reducing the incidence of tumor recurrence in some cases without increasing the perioperative risk. In the present study, we showed that pseudocapsular resection was not associated with the deterioration of the pituitary functions in elderly patients with NFPA; moreover, pseudocapsular resection might reduce the risk of postoperative hemorrhage. Further studies are needed to confirm the advantage from the aspect of the recurrence rate.

We showed that it was difficult to improve sGHD in elderly patients. Jahangiri et al. reported that younger age predicted the recovery from preoperative pituitary dysfunction after TSS for NFPA [13]. Liu et al. also reported that elderly patients had significantly more difficulty in recovering from preoperative hypopituitarism [14]. No studies in the relevant literature have reported that elderly patients show superior recovery from preoperative hypopituitarism. We also showed that the elderly patients (≥ 55 years of age) were not likely to recover from preoperative sGHD after surgery. On the other hand, the improvement of sGHD was obtained especially in younger patients, especially those with pseudocapsular resection. This

result was probably associated with the background characteristics of patients with pseudocapsular resection, who tended to have small-size tumors [7]. From the beginning, younger patients who received pseudocapsular resection were likely to recover from sGHD, irrespective of whether the pseudocapsule was resected. We recognize that pseudocapsular resection does not contribute to recovery from preoperative hypopituitarism, but that appropriate pseudocapsular resection procedures have no negative influence on the pituitary function, even in elderly patients. These results also suggest that the application of pseudocapsular resection can be considered in elderly patients with FPA. We assume that pseudocapsular resection is not necessary for all elderly patients with NFPA, but that surgeons should not be hesitant in applying this technique because of their elderly age.

The present study was associated with some limitations. First, the number of elderly patients was relatively small. The incidence rates of perioperative complications are intrinsically low in TSS; thus, studies in larger populations are needed to assess the safety of TSS in elderly patients. Second, the application of pseudocapsular resection is depends on the pituitary surgeon. The selection of patients with pseudocapsular resection is not free from some bias. Third, some patients did not receive preoperative and postoperative pituitary provocation tests. The incidence of sGHD would be affected by the selection bias in the patients who receive provocation tests.

Conclusions

Aging was not a negative factor in TSS for NFPA, moreover pseudocapsular resection did not increase the risk of surgical complications, even in elderly patients. However, postoperative recovery from sGHD was expected in younger patients, irrespective of whether pseudocapsular resection was performed.

Declarations

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Code availability: Not applicable.

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Ethics approval: This study was approved by the Ethical Committee for Epidemiology of Hiroshima University, E-2022.

Consent to participate: For this type of study, formal consent is not required.

Consent for publication: Not applicable.

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Tables

Table 1 Patients characteristics			
	Elderly (≥70 years)	Younger (<70 years)	<i>p</i> value
<i>n</i>	66	206	
Age (mean, years)	74.4	53.3	<0.0001
Sex (male)	39 (59%)	116 (55%)	0.7755
Tumor diameter (mm)	25.8	25.3	0.3705
Knosp Grade G0-2	44 (67%)	140 (68%)	0.8803
ASA class			0.0279
1	2	32	
2	62	169	
3	2	5	
4	0	0	
Preoperative IGF-1 SD score (mean)	-0.9	-1.0	0.7665
ASA American Society of Anesthesiologists, <i>IGF-1</i> insulin-like growth factor-1, <i>SD</i> standard deviation			

Table 2 Surgical outcome and complications			
	Elderly (≥70 years)	Younger (<70 years)	<i>p</i> value
N	66	206	
Total removal of tumor ¹⁾	54 (82%)	173 (84%)	0.7048
Total resection of pseudocapsule	21 (32%)	92 (45%)	0.0846
Postoperative IGF-1 SD score (mean)	-0.9	-1.1	0.4049
Intraoperative CSF leakage	19 (29%)	71 (34%)	0.4535
Postoperative CSF leakage	0	1 (0.5%)	1.000
Delayed hyponatremia	19 (29%)	60 (29%)	1.000
Transient DI	10 (15%)	47 (23%)	0.2248
Permanent DI	1 (1.5%)	3 (1.5%)	1.000
Postoperative hemorrhage	2 (3.0%)	3 (1.5%)	0.5978
Newly replacement of anterior hormones ²⁾	1 (1.5%)	3 (1.5%)	1.000
Hospitalization (mean, days)	14.3	13.5	0.1417
¹⁾ “Total removal of tumor” did not consider whether the pseudocapsule was resected or not. ²⁾ “Anterior hormones” included hydrocortisone and levothyroxine sodium hydrate. <i>IGF-1</i> insulin-like growth factor-1, <i>SD</i> standard deviation, <i>CSF</i> cerebrospinal fluid, <i>DI</i> diabetes insipidus			

Table 3 Comparison between the patients with and without total pseudocapsule resection in the Elderly and Younger groups.						
	Elderly (≥ 70 years)			Younger (< 70 years)		
	Resected	Non-Resected	<i>p</i> value	Resected	Non-Resected	<i>p</i> value
<i>n</i>	21	45		92	114	
Total removal of tumor ¹⁾	21 (100%)	33 (93%)	0.0068*	86 (93%)	87 (76%)	0.0010
Intraoperative CSF leakage	8 (38%)	11 (24%)	0.3815	33 (36%)	38 (33%)	0.7686
Postoperative CSF leakage	0	0	1.000	0	1 (0.9%)	1.000
Delayed hyponatremia	3 (14%)	16 (36%)	0.0886	25 (27%)	35 (31%)	0.6446
Transient DI	3 (14%)	7 (16%)	1.000	18 (20%)	29 (25%)	0.4040
Permanent DI	1 (4.8%)	0	0.3182	0	3 (2.6%)	0.2549
Postoperative hemorrhage	0	2 (4.4%)	1.000	0	3 (2.6%)	0.2549
Newly replacement of anterior hormones ²⁾	0	1 (2.2%)	1.000	0	3 (2.6%)	0.2549
Hospitalization (mean, day)	13.4	14.8	0.2976	13.0	14.0	0.1720
¹⁾ “Total removal of tumor” did not consider whether the pseudocapsule was resected or not. ²⁾ “Anterior hormones” included hydrocortisone and levothyroxine sodium hydrate. <i>CSF</i> cerebrospinal fluid, <i>DI</i> diabetes insipidus						

Figures

Rates of sGHD in the Elderly and Younger groups

Figure 1

A graph showing the rates of severe GH deficiency (sGHD) at the preoperative and postoperative time-points in the Elderly and Younger groups. Although some patients showed recovery from sGHD and some suffered from newly developed sGHD after TSS, the total rate of sGHD did not change in the Elderly group. In the Younger group, there was significant decrease in the rate of sGHD from the preoperative time-point (40%) to the postoperative time-point (27%; *p=0.0178).

Figure 2

A graph showing the rates of severe GH deficiency (sGHD) at the preoperative and postoperative time-points in the Resected and Non-Resected groups. In the Elderly group, the total rate of sGHD did not differ between in the Resected and Non-Resected groups. Furthermore, the rates of newly developed sGHD after TSS did not change, irrespective of whether pseudocapsular resection was performed. In the Younger group, the total rate of sGHD decreased, especially in the Resected group (* $p=0.0165$).

Rates of recovery from preoperative sGHD according to age

Figure 3

A graph showing the rate of recovery from preoperative severe GH deficiency (sGHD) after TSS at intervals of five years of age. The likelihood of improvement of sGHD decreased in older patients (≥ 55 years of age).