Long-Term Effects of Intracapsular Debulking and Adjuvant Somatostatin Analogs for Growth Hormone-Secreting Pituitary Macroadenoma: 10 Years of Experience in a Single Institute

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OBJECTIVE: **Long-term effects of endoscopic endonasal transsphenoidal intracapsular debulking and adjuvant somatostatin analogs (SSAs) were evaluated in patients with growth hormone- (GH) secreting pituitary macroadenomas.**

METHODS: **We retrospectively reviewed the medical records of 45 patients with acromegalic macroadenoma who underwent endonasal endoscopic transsphenoidal intracapsular debulking and received adjuvant SSAs (octreotide) between 2006 and 2015 who had >1 year of follow-up. To evaluate the predictive factors for 1 year and long-term biochemical outcomes, univariate and multivariate analyses were performed.**

RESULTS: **Biochemical remission was achieved in 1 year in 20 of the 45 (44.4%) patients, and in 31 of the 45 patients after long-term adjuvant SSA treatment. Tumor control was achieved in 43 of the 45 (93.3%) patients. The univariate analysis showed age (≥55 years), tumor size (diameter ≤1.5 cm), premedication GH levels (≤2.8 ng/mL), premedication insulin-like growth factor 1 levels (≤2-fold of upper limit of normal range), cavernous sinus invasion (Knops grades 2, 3, and 4), and near-total tumor resection were associated with long-term outcomes. The multivariate analysis showed near-total resection was a significant predictor for long-term outcomes ($P = 0.019$). There were no new pituitary dysfunctions. The observed complications included one case of cerebrospinal fluid leakage and one case of epistaxis requiring intervention.**

CONCLUSIONS: **Intracapsular debulking and adjuvant SSAs are a safe and viable treatment for patients with GH secreting pituitary macroadenoma to achieve biochemical remission and tumor control. Although adjuvant SSA treatment enhances residual tumor control, cavernous sinus invasion impedes the remission of endocrine tumors.**

INTRODUCTION

Acromegaly is a rare and chronic disease, characterized by dysregulated growth hormone (GH) hypersecretion from a pituitary adenoma. The condition causes disproportionate skeletal, tissue, and organ growth that is associated with significant comorbidity and a higher mortality rate than that observed within the general population.[1-4] Crucial for the reduction of comorbidities and mortality is the normalization of the serum GH levels and insulin-like growth factor 1 (IGF-1).[5] In the 2010 consensus, endocrinological remission was defined as normal IGF-1 serum levels and either a nadir GH level of <0.4 ng/mL after an oral glucose load or a basal GH serum level <1 ng/mL.[6]

Transsphenoidal surgery is a first-line treatment and increases the possibility of immediate biochemical remission. The endonasal endoscopic approach is popular and achieves biochemical remission in 85% of patients with microadenoma and 40%–50% of patients with macroadenoma.[7-9] It is challenging to remove most of the invasive adenomas with parasellar, cavernous sinus invasion and sellar floor erosion surgically. Medical treatment can achieve significant effects on tumor size reduction and biochemical remission and is considered a preoperative or adjuvant therapy.[10-13] Of all the medications, somatostatin analog (SSA) is suggested as the first option.[6]

Key words
- Acromegaly
- Long-term
- Macroadenoma
- Somatostatin analog
- Transsphenoidal

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
GH: Growth hormone
IGF-1: Insulin-like growth factor 1
MRI: Magnetic resonance imaging
SSA: Somatostatin analog

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It is difficult to remove pituitary macroadenomas with invasion to the cavernous sinus, suprasellar region, or with intradural growth surgically. The extracapsular dissection of macroadenoma increases the remission rate, but usually requires bimanual dissection using a binasal approach.[14,15] The added destruction of the nasal cavity, secondary to the binasal transphenoidal approach, can be time-consuming to address, and cause rhinologic complications such as postoperative epistaxis or hyposmia at rates higher than those observed in patients treated using the single nostril approach.

The aim of this study was to evaluate the efficiency of intracapsular debulking with adjuvant SSAs (octreotide) in patients with GH-secreting pituitary macroadenomas, with a focus on the long-term outcomes.

MATERIAL AND METHODS

Patients

We retrospectively reviewed the data of patients with GH-secreting pituitary macroadenomas who received endoscopic endonasal transsphenoidal intracapsular debulking. All the procedures were performed at the Taichung Veteran General Hospital in Taiwan between 2006 and 2015. All the participants were followed up for at least 1 year after surgery, and the patient data included complete and consecutive medical charts, including surgical records, medications, hormone tests, and magnetic resonance imaging (MRI). MRI scans were taken preoperatively, 3 months postoperatively, and after 1 year. The preoperative and postoperative MRI scans were used to evaluate the initial tumor invasion and the residue that remained after surgery. Tumors that were >1 cm in diameter were classified as macroadenomas. Instances of suprasellar and cavernous sinus invasion were classified according to both the Wilson-Hardy and Knosp classification systems, respectively.[16,17] The institutional review board at our institution approved this study and informed consent was obtained from all our patients.

Endocrinologic Evaluation

The basal fasting GH and IGF-1 levels were measured preoperatively, postoperatively, and during the follow-up period. The remission criteria, according to the 2010 consensus guidelines, were defined as normal IGF-1 serum levels and either a nadir GH level of <0.4 ng/mL after an oral glucose load or a basal GH serum level of <1 ng/mL. To identify hypopituitary complications, other pituitary axes, including adrenocorticotropic hormone-cortisol, thyroid, and gonadotropic hormones were tested.

Surgical Procedure

After the induction of general anesthesia, all the patients underwent an endonasal endoscopic approach without nasal speculum, performed through a single nostril. The 2-hand technique was used, with the endoscope in the nondominant hand and surgical instruments in the dominant hand. Intraoperative navigation was only used for unusual sphenoid pneumatization or other anatomic variations. During the nasosphenoid phase of the operation, the rotating Kerrison punch (Aesculap, USA) and a high-speed drill were used to achieve adequate removal of the anterior sphenoid wall and septa. We performed partial anterior sphenoidectomy mainly on the right vomer bone, in which there was enough space to maneuver instruments without collision. One silicone suction tube was placed on the clivus floor for drainage. During the sellar phase, a 1 cm section of the sellar floor was exposed. The dura was opened in a U-shape and was folded upward. Ring curettes were used to remove the tumor. The 30° rigid endoscope was used to evaluate the residual tumors near the bilateral cavernous sinus. We used abdominal fat grafts to fill the sellar defect and dural substitutes were used if intraoperative cerebrospinal fluid (CSF) leakage was encountered. We did not harvest mucosal or nasoseptal flaps to cover the sellar floors in our patients.

Extent of Surgical Resection

To evaluate the extent of tumor resection, the first postoperative MRI was performed within 3 months after the transphenoidal surgery. Near-total resection was defined as no segmentation of the residual tumor detected on the postoperative MRI. Subtotal resection was defined as segmentation of the residual tumor on the postoperative MRI, or according to the operative findings (Figure 1).

Adjuvant SSAs

All the patients received adjuvant SSA octreotide (Sandostatin LAR (long-acting release), Novartis, Basel, Switzerland) beginning at 3 months postoperatively and continuing for at least 1 year. The initial dose was 20 mg and, then, was gradually adjusted to 30 mg and 40 mg, depending on each patient's individual endocrinological condition. Health insurance payments in Taiwan supported the adjuvant SSA treatment.

Statistical Evaluation

SPSS software (SPSS, Inc., Cary, North Carolina, USA) was used to analyze all the data. A preliminary analysis showed a non-normal distribution of most of the variables. The continuous variables are shown as means ± standard deviations and ranges. The categorical values are shown as percentages. Associations among the effects of cavernous sinus invasion, suprasellar extension, and the extent of resection on endocrinological remission were calculated using the χ^2 test for categorical variables. The Mann-Whitney U test was used to compare tumor size and preoperative and postoperative GH and IGF-1 levels. Predictors for long-term biochemical remission were determined using the log rank test for univariate analysis and the Cox proportional hazards model for multivariate analysis. A P value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Over the study period, 45 patients with GH-secretion pituitary macroadenoma underwent intracapsular debulking and adjuvant SSA treatment. Table 1 shows the baseline preoperative characteristics of the cohort, composed of 19 men and 26 women with a mean age of 44.7 years. Preoperative imaging revealed 78.3% of the macroadenomas with a maximum diameter of >1.5 cm. Suprasellar tumor extension was present in 75.6% (Wilson-Hardy classification A, B, C, D, E) of the patients. Cavernous sinus invasion by the tumor was present in 73.3% (Knops grade 2, 3, 4) of the patients. The postoperative GH levels after primary surgery decreased significantly,

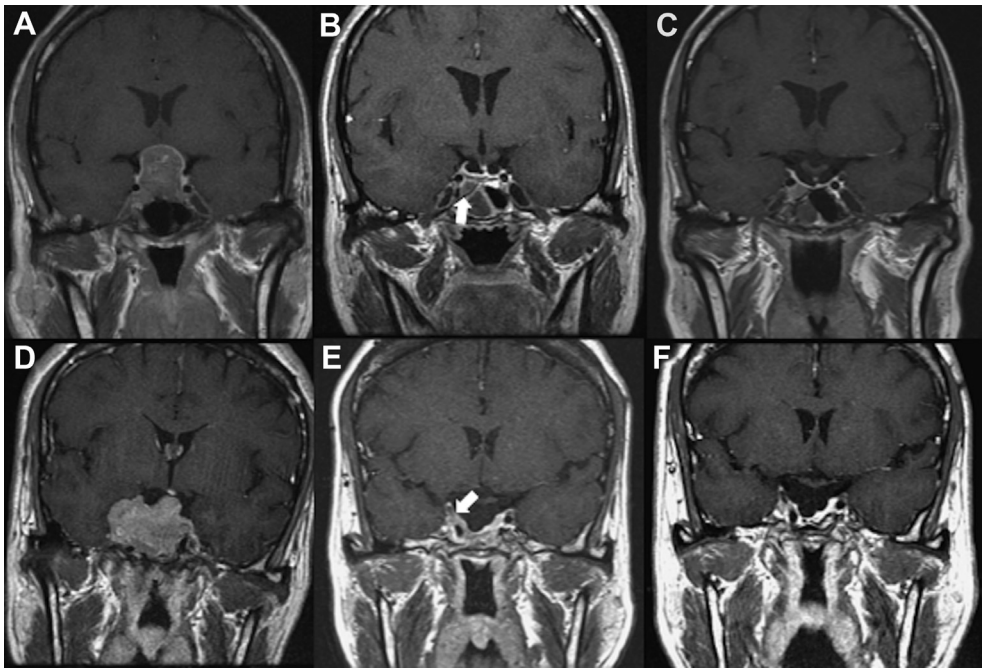

Figure 1. T1-weighted contrasted coronal images of 2 cases. Case 1: (**A**) preoperative and (**B**) postoperative 1-month images; the arrow indicates "tumor segmentation" and subtotal resection of the tumor. (**C**) The 9-year image of an adjuvant somatostatin analog. Case 2: (**D**) preoperative and (**E**) postoperative 1-month image; the arrow indicates residual pseudocapsule and near-total resection of the tumor. (**F**) The 3-month image of adjuvant somatostatin analog.

compared to the preoperative levels. This report focuses on 2 topics, specifically: 1) 1-year and 10-year long-term biochemical remission, and 2) predictive values of variables influencing biochemical remission.

Biochemical Remission: 1 Year and 10 Years

After transsphenoidal surgery and adjuvant SSA therapy, the biochemical remission rate reached 44.4% after 1 year of treatment. The 1-year outcome was divided into remission and non-remission groups for predictive analytics (Table 2). After 1 year of treatment, the Mann-Whitney U test showed significant differences in the remission and non-remission groups regarding age, premedication GH and IGF-1 serum levels, cavernous invasion, and extent of resection. These factors were associated with the effects of adjuvant SSA therapy on short-term outcomes. The extent of the cavernous sinus invasion and tumor resection might have affected the short-term outcomes more significantly.

Regarding the long-term outcomes, Table 3 illustrates the univariate and multivariate Cox proportional hazard results of age ($\geq$55 and $<$55 years), premedication GH serum levels ($>$2.8 ng/mL and $\leq$2.8 ng/mL), premedication IGF-1 serum levels (2-fold of upper limit of normal range), extent of resection (near-total and subtotal resection), and cavernous sinus invasion after 10 years of follow-up. The multivariate analysis showed that long-term biochemical remission was positively affected by the extent of tumor resection (hazards ratio, 3.32; 95% CI, 1.29–9.06; $P = 0.019$). Figure 2A shows the cumulative incidence rates of biochemical remission between the near-total and subtotal tumor resection groups, within 10 years of follow-up. Here, near-total resection of the tumor increased the successful biochemical remission after long-term adjuvant SSA therapy. The overall biochemical remission rate after long-term adjuvant SSA therapy was 68.9% within 10 years of follow-up (Figure 2B).

Tumor Growth Control and Complication

Of our patients, 97.8% (42/45) achieved successful control of tumor growth. The 3 cases of refractory macroadenoma had received secondary transphenoidal surgery, high doses of adjuvant SSA therapy, and Gamma Knife radiosurgery. However, with these 3 patients, we still failed to achieve biochemical remission and tumor growth control. Epistaxis was found in 1 of our patients 1 week after surgery and local treatment. One case of postoperative CSF leakage was treated by lumbar drainage, and this patient sustained no permanent impairments consequently. During the regular hormone monitoring of our patients, we observed no new-onset cases of pituitary dysfunction.

DISCUSSION

Intracapsular debulking and adjuvant SSAs provide a safe and viable approach for patients with GH-secreting pituitary macroadenomas to achieve biochemical remission and tumor control.

Table 1. Baseline Characteristics

Variable	Number (%)
Male/Female	19/26 (M, 42.2%)
Age	44.7 ± 11.7
Suprasellar extension of Wilson-Hardy classification	
0	11 (24.4)
A	11 (24.4)
B	21 (46.7)
C, D, E	2 (4.5)
Knosp grade	
0	7 (16.6)
1	5 (11.1)
2	9 (20)
3	16 (35.6)
4	8 (17.8)
Tumor size (mm)	2.2
>1.5	36 (78.3)
≤1.5	9 (19.7)
Preoperative	
GH (ng/mL)	28.2 ± 28.7
IGF-1	670.5 ± 167
Postoperative/pre-SSA	
GH (ng/mL)	6.3 ± 6.2
IGF-1	509.5 ± 157
Complication	2 (4.4)
Epitaxis	1
CSF leakage	1
New onset of pituitary dysfunction	0
Dose of SSAs (octreotide LAR), mg/4 weekly	
20	31 (68.9)
30	11 (24.4)
40	3 (6.7)

M, male; GH, growth hormone; IGF-1, insulin-like growth factor 1; SSA, somatostatin analog; CSF, cerebrospinal fluid; LAR, long-acting release.

Near-total resection of the tumor has a positive result on both early and long-term biochemical remission.

Previous studies on acromegalic macroadenoma surgery yielded 40%–60% biochemical remission rates. Cavernous invasion was associated with residual tumors and remission failure after surgery.[7,18,19] The extended transsphenoidal extracapsular approach provided higher rates of remission, but required more destruction of the nasal cavity and sphenoidal sinus. Extended transsphenoidal debulking is time-consuming and technique-dependent, making it difficult for neurosurgeons to achieve consistent results. Furthermore, surgical trauma on normal pituitary glands possibly caused postoperative pituitary dysfunction.[20] Carvalho et al.[21] conducted a meta-analysis of surgery-induced hypopituitarism in 12.79% of acromegalic patients. The intracapsular debulking we performed in this study did not remove the pseudocapsular part of the tumor, lowering the possibility of injury to the normal pituitary gland. Additionally, because we performed all the endoscopic transsphenoidal operations through a single nostril, we were able to preserve half of the vomer bone while we completed the central debulking of the tumor. The dural layer under the tumor was not opened widely, although in some cases, single sutures were required to close the opened dura and to strengthen the fat graft base. There was only 1 case of postoperative CSF leakage, in which we used lumbar drainage to treat. To prevent the destruction of the normal pituitary gland, the tumors were evacuated gently. None of our cases showed new pituitary dysfunctions after surgery. In most of our patients, >75% of the tumor mass was evacuated, although the operations were limited if the residual tumor was located near the cavernous sinus bilaterally.

For decades, the pharmacologic management of acromegaly to achieve biochemical remission and control of tumor growth has been considered first-line therapy for patients who are not candidates for surgery. Of all the potential pharmacologic therapies, SSAs are the first option because of their better effects on tumor shrinkage and ability to reduce endocrine, GH, and IGF-1 levels. Among all the clinically available somatostatin analogs, pasireotide LAR showed superior biochemical efficacy compared to octreotide LAR, lanreotide SR, and lanreotide ATG, but may contribute to the side effect of hyperglycemia.[22-24] Compared to lanreotide SR, octreotide LAR is more efficacious for achieving GH and IGF-1 targets.[12,25] The few studies comparing octreotide LAR and lanreotide ATG show that these formulations have equivalent biochemical efficacy.[11,26] A number of studies also report that partial tumor removal or surgical debulking of pituitary tumors improves the outcomes of SSAs[27-30]; however, these investigations lack long-term results pertaining to biochemical and tumor control. Fukuda et al.[31] reported the 10 year multidisciplinary therapeutic outcomes of acromegaly in Japan. In this investigation, they observed a 79% 10-year biochemical remission rate for patients with macroadenoma.[31] In our study, the mean serum GH and IGF-1 levels decreased yearly, and biochemical remission rates improved from 44.4%–67.4%. Long-term follow-up found that subtotal resection of the adenoma required additional adjuvant SSA therapy to achieve biochemical remission; patients who received subtotal resection also reached remission later than near-total resection.

Figure 2 shows the difference in 10 year cumulative remission rates for the near-total and subtotal resection groups. The segmentation of residual adenomas required long-term SSA therapy and achieved <50% remission. Yamada et al.[32] reported a 58.5% remission rate in patients with remaining or recurring pituitary adenomas who underwent repeated transsphenoidal surgery for acromegaly. However, owing to a lack of impressive outcomes, the benefits of repeat transsphenoidal surgery remain controversial; thus, cavernous sinus invasion should also be considered. Repeated transsphenoidal surgery could be considered when long-term adjuvant SSA therapy fails to show results. Preoperative images of residual adenomas should be evaluated carefully to see if the adenomas are accessible. We

Table 2. Predictive Factors of Early Treatment

	1-Year Biochemical Remission	1-Year Non-Remission	*P* Value
Age (years), mean ± SD	47 ± 12	39 ± 10	*0.032
≥55	8 (40%)	2 (8%)	*0.014
<55	12	23	
Sex, male:female	8:12	11:14	1
Preoperative GH, ng/mL	20.5 ± 10.9 (2.8–104)	34.3 ± 36.5 (8.4–120)	0.159
Pre-SSA GH, ng/mL	3.9 ± 5.3 (0.7–25.1)	8.5 ± 6.3 (2.1–50)	*0.015
Preoperative IGF-1	676 ± 167 (432–1166)	666 ± 170 (352–987)	0.748
Pre-SSA IGF-1	404 ± 91 (310–805)	598 ± 146 (231–937)	0.332
Suprasellar extension (Wilson-Hardy classification)			*0.038
A	13 (65%)	8 (32%)	
B, C, D, E	7	17	
Cavernous sinus invasion (Knosp)			*0.002
0, 1	9 (45%)	1 (4%)	
2, 3, 4	11	24	
Sphenoid sinus extension			1
Yes	4 (20%)	4 (16%)	
No	16	21	
Resection			*0.002
Near-total	9 (45%)	1 (4%)	
Subtotal	11	24	
Tumor size (cm)			
≥1.5	12 (60%)	24 (96%)	*0.006
<1.5	8	1	

SD, standard deviation; GH, growth hormone; SSA, somatostatin analog; IGF-1, insulin-like growth factor 1.
*$P < 0.05$ was considered significant.

suggest repeated surgery for residual adenomas that do not invade the lateral tangents of the carotid arteries bilaterally.

Three of our cases showed no effects in tumor growth or biochemical condition after treatment. Subsequently, they received repeated surgery and Gamma Knife radiosurgery that also failed to control tumor growth and achieve biochemical remission. Additionally, these patients required life-long treatment for panhypopituitarism complications. All of their uncontrollable

Table 3. Predictive Factors of Long-Term Biochemical Remission

		Univariate Analysis			Multivariate Analysis		
	Category	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (years)	≥55	2.5	1.13–5.53	*0.024	1.44	0.53–3.90	0.471
Tumor size	≥1.5 cm	2.68	1.15–6.25	*0.023	1.98	0.76–5.14	0.162
Pre-SSA GH level, ng/mL	≤2.8	3.58	1.7–7.55	*0.001	2.15	0.96–4.84	0.064
Pre-SSA IGF-1 level	≤2 fold of ULN	3.15	1.49–6.65	*0.003	2.29	0.95–5.52	0.064
Extent of resection	Near-total resection	4.79	2.11–10.88	*<0.001	3.32	1.21–9.06	*0.019

OR, odds ratio; CI, confidence interval; SSA, somatostatin analog; GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limits of normal.
*$P < 0.05$ was considered significant.

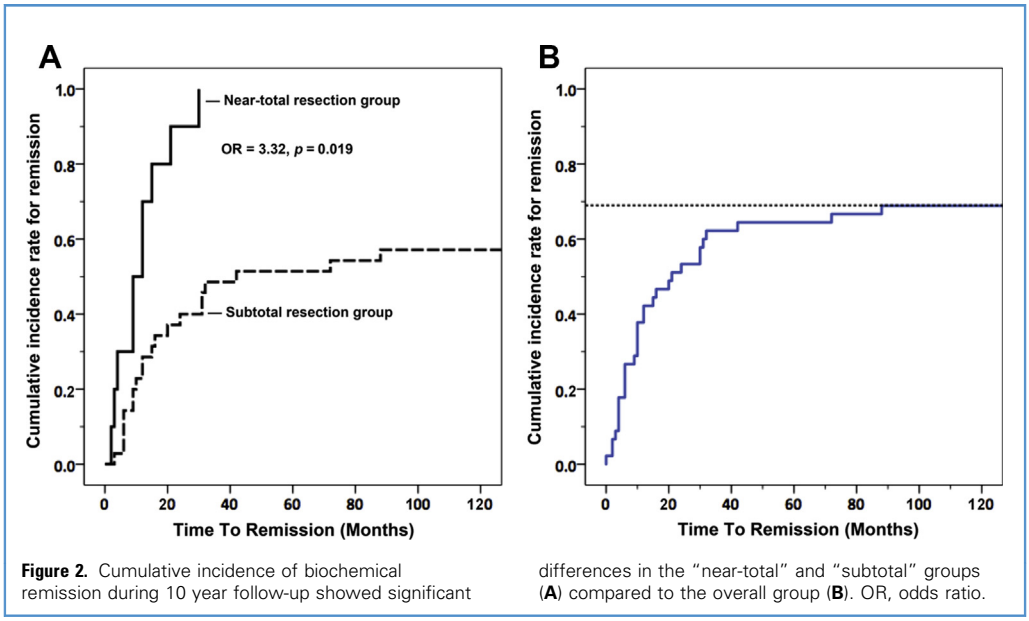

Figure 2. Cumulative incidence of biochemical remission during 10 year follow-up showed significant differences in the "near-total" and "subtotal" groups (**A**) compared to the overall group (**B**). OR, odds ratio.

adenomas expanded over the cavernous sinus, into the extradural and intradural temporal base (Hardy-Wilson grade D, E and Knops score 4), and we were only able to extract <50% using the transsphenoidal approach. The transcranial approach might be considered for further tumor evacuation.

In this study we observed that a greater amount of adenoma mass reduced by surgery, and higher rates of biochemical remission were associated with adjuvant SSA treatment. Cavernous invasion of the pituitary macroadenoma was associated with the quality of resection and reduction of tumor mass by surgery. Adjuvant SSA treatment effectively reduced and stabilized the serum GH and IGF-1 levels. For patients with residual adenomas that cannot be extracted by repeated surgery, long-term use of SSAs should be considered.

A limitation of this retrospective cohort study is that it is likely it contains random errors and selection bias that may affect the validity of our findings. Compliance of patients and insurance payment issues complicated the adjustment of the SSA doses. In this study, we showed changes in the GH and IGF-1 levels after long-term SSA use; however, further studies of the additional long-term effects of adjuvant SSA use are recommended. Also, additional cost-effectiveness analysis should also be considered.

CONCLUSIONS

Intracapsular debulking and adjuvant SSAs comprise a safe and viable approach for patients with GH-secreting pituitary macroadenoma to achieve biochemical remission and tumor control. The extent of the tumor resection determines the outcomes of long-term adjuvant SSA treatment. Repeated transsphenoidal surgery could be considered for patients with residual adenomas with segmentation that do not expand over the carotid arteries bilaterally. In addition, the side effects of long-term SSA treatment should be monitored.

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