Surgical Treatment of Prolactinomas: Potential Role as a First-Line Treatment Modality

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Purpose: Treatment with dopamine agonists (DAs) has been the first-line standard treatment for prolactinoma, and surgery has been reserved for drug intolerance and resistance for several decades. We evaluated whether surgery plays a primary role in prolactinoma management.

Materials and Methods: We conducted a retrospective study of 210 prolactinoma patients who had received surgical treatment at our institution. We analyzed the treatment outcomes according to tumor extent, sex, and preoperative DA medication.

Results: Overall hormonal remission was achieved in 164 patients (78.1%), and complete removal was achieved in 194 patients (92.4%). When the tumors were completely removed, the remission rate increased to 84.5%. Anterior pituitary function was normalized or improved in 94.6% of patients, whereas only 4.1% of patients showed worsening of hormone control. Hormonal remission was higher in patients who had not received DA preoperatively than in those who had received preoperative DA treatment. Smaller tumor size (<1 cm), no invasion into the cavernous sinus, and female sex were predictors of good surgical outcomes.

Conclusion: Although DAs remain the first-line standard treatment for prolactinomas, surgery can be an excellent option and should be considered as an alternative primary treatment modality when patients are predicted to achieve a good surgical outcome.

Key Words: Dopamine agonist, pituitary adenoma, prolactinoma, transsphenoidal surgery

INTRODUCTION

Prolactinomas are the most common type of functional pituitary adenoma, accounting for approximately 40% of all functioning adenomas, and their occurrence is most frequent in women aged between 20 and 50 years.[1] The clinical presentation of prolactinoma includes symptoms associated with elevated serum prolactin (PRL) levels, such as galactorrhea and gonadal and sexual dysfunctions, or tumor mass effects, such as visual disturbance due to cranial nerve palsy.[2]

The primary goals of prolactinoma treatment are as follows: 1) to normalize serum PRL levels and control the consequences of hyperprolactinemia, such as infertility and osteoporosis; 2) to prevent cranial nerve palsy by reducing the tumor mass size; 3) to preserve normal pituitary gland function; and 4) to prevent tumor progression.[1] Dopamine agonists (DAs), such as bromocriptine or cabergoline, have been found to effectively normalize PRL levels and to reduce the size of prolactinomas in many studies and are considered the first-line treatment for hyperprolactinemia.[3-5] DAs act as ligands of the G protein-type pituitary D2 receptor to inhibit the expression of PRL genes and lactotroph metabolism. However, because DAs exert various pharmacological actions on various receptors, patients often develop side effects, such as nausea, vomiting, headache, and dizziness.[6] Furthermore, several studies have shown an association between DA use and an increased risk of cardiac valve regurgitation in patients with Parkinson's disease and retroperitoneal and pulmonary fibrosis.[7-9]

A consensus for the withdrawal timing of DAs during pro-

lactinoma treatment has not been established.[10] The 2006 Pituitary Society guidelines recommend tapering and discontinuation of DAs if a normal PRL level has been maintained at least for 3 years with DA therapy and the tumor size has markedly reduced.[11] However, the 2011 Endocrine Society guidelines suggest the discontinuation of DA therapy after 2 years of hormone normalization and no evidence of a tumor on magnetic resonance imaging (MRI).[12] Recent meta-analysis studies have reported a hyperprolactinemia recurrence rate after DA withdrawal exceeding 50%.[13,14]

Because of side effects and treatment failure after their discontinuation of DAs and due to patient preferences, surgical treatment of prolactinomas has gained attention in recent years. With remarkable improvements in pituitary surgery over the past two decades,[15,16] complications from pituitary surgeries are decreasing. Furthermore, a few reports have advocated for the efficacy of surgical treatment in achieving long-term remission in patients with microprolactinomas.[17-19] Because medical treatment with DA remains the first-line treatment, a precise definition of the surgical indications for prolactinoma has yet to be established. This study was performed to evaluate the surgical outcomes of 210 prolactinoma patients from a single institution in an attempt to help characterize the indications for surgery.

MATERIALS AND METHODS

Two hundred ten pituitary adenoma patients with histologically confirmed prolactinomas who had undergone surgery via a transsphenoidal approach (TSA) at our institution between January 2006 and April 2018 with at least a 3-year follow-up were retrospectively analyzed. The indications for surgery included DA resistance, drug intolerance due to side effects, patient preference for surgery, pituitary adenomas presumed to be other pathology preoperatively, pituitary apoplexy, and cerebrospinal fluid (CSF) leak after DA use (Fig. 1). Preoperative DAs were used in 164 patients: bromocriptine was used in 39 patients, cabergoline in 87 patients, and both in 38 patients. DA was started at a low dose (1 to 1.5 mg/wk for cabergoline, 2.5 mg/day for bromocriptine), and the dosage was gradually increased (1.5 to 4 mg/wk for cabergoline, 5 to 10 mg/day for bromocriptine) within 2–4 weeks. The maintenance dose was adjusted according to PRL levels. DA resistance was defined as failure to achieve normal PRL levels on maximally tolerated doses of DA and/or no decrease in tumor size. This study was conducted in accordance with the Declaration of Helsinki and approved by the Severance Hospital Institutional Review Board (IRB No. 2022-2392).

Preoperative evaluation
Each patient received endocrinological evaluation of basal serum hormone levels, including morning cortisol, adrenocor-
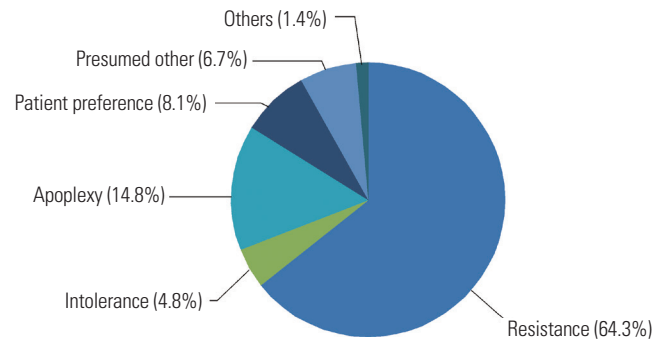

Fig. 1. Surgical indications for prolactinomas in our series. In the majority of cases, resistance to dopamine agonist treatment was the primary indication for surgery, which was followed by apoplexy and drug intolerance. In only 8.1%, surgical treatment was performed as a first-line treatment option to cure hyperprolactinemia by surgery alone.

ticotropic hormone (ACTH), free thyroxine (fT4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), insulin-like growth factor-1 (IGF-1), PRL, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels for male patients and estrogen for female patients. The combined pituitary function test (CPFT) was performed to evaluate anterior pituitary function and directly compare preoperative and postoperative CPFT; the procedure is described in detail in our previous report.[20] The criteria for normal response interpretation at our institution were as follows: peak growth hormone level >3 ng/mL; peak cortisol level >180 ng/mL or increase by >70 ng/mL from basal levels; peak PRL level increase by >2-fold of basal PRL levels; peak TSH level increase >5 μIU/mL from basal levels while fT4 was in the normal range; peak FSH increase >2 mIU/mL from basal levels; and peak LH increase >10 mIU/mL from basal levels.

Radiologic evaluations included non-contrast brain computed tomography (CT) and brain MRI specifically focused on the pituitary and neighboring structures using a 1.5-Tesla system (Signa; General Electric, Minneapolis, MN, USA) or a 3.0-Tesla system (Achieva; Philips, Best, The Netherlands). The MRI evaluation comprised spin-echo T1-weighted (TR 500 ms/TE 20 ms) imaging, T2-weighted (TR 3500 ms/TE 100 ms) imaging, and dynamic contrast-enhanced (TR 400 ms/TE 10 ms) imaging after intravenous administration of gadolinium-diethylenetriaminepentaacetic acid (0.1 mL/kg of body weight) with a temporal resolution of 25 s. The extension of the lesions was classified according to a modified Hardy classification system.[21-23] A type I lesion was confined entirely within the sellae and had a size <1 cm. A type II lesion extended into the suprasellar space, up to <1 cm above the line of the diaphragm. A type III lesion extended into the suprasellar area, up to >1 cm above the line of the diaphragm or extended into the sphenoid sinus. A type IV lesion invaded the cavernous sinus.

Postoperative evaluation and management
Postoperative MRI was performed within 48 hours after sur-

gery to assess the extent of resection. Remission was declared at least 3 months after surgery in cases where total resection of the pituitary mass was achieved and where serum PRL levels were maintained within the normal range without using DAs. Normal serum PRL levels were defined as <15 ng/dL for men and <25 ng/dL for women. CPFT follow-up was performed to evaluate anterior pituitary function at 6 months after surgery and every 2 years thereafter. Changes in pituitary function from before and after surgery were classified into four categories: 1) from normal to normal, if no pituitary hormone deficiency was found before and after surgery; 2) improved hypopituitarism, if hypopituitarism improved or had completely recovered; 3) persistent hypopituitarism, if pituitary hormone deficiency persisted without improvement; and 4) worsened hypopituitarism, if the number and/or degree of pituitary hormone deficiency worsened after surgery. When hormonal remission was not achieved or tumor regrowth was noted, additional medical treatment with DAs, reoperation, or gamma-knife radiosurgery was implemented.

Statistical analysis

Chi-squared test, Fisher's exact test, and Student's t-test were performed to demonstrate statistically significant differences in the surgical outcomes using IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY, USA). p values less than 0.05 were considered as statistically significant.

RESULTS

The series comprised 23 male and 187 female. The mean age was 31.2 years, and the age range was 15 to 64 years. The mean follow-up duration was 51.3 months (range, 12–156 months). Based on the modified Hardy classification scheme, microadenoma (Hardy type 1) represented the largest proportion with 58.1%, followed by Hardy type 2 (22.4%), type 4 (13.8%) and type 3 (5.7%). The clinical characteristics of the patients are summarized in Table 1.

Overall outcomes

Among 210 patients who had received TSA for tumor resection, total resection was achieved in 194 patients (92.4%), while overall remission was reached in 164 patients (78.1%) (Fig. 2A). Regarding the 194 patients who had their tumors completely removed, the remission rate increased to 84.5%. Hormone remission was never achieved when the tumors were not completely removed.

In the analysis of the 171 patients in whom direct comparison between preoperative and postoperative CPFT was available, the outcome of anterior pituitary function showed that postoperative hormone function was normal in 81.1% of the

Table 1. Clinical Characteristics of Patients with Prolactinomas

	Remission (n=164)	Non-remission (n=46)	p value
Sex			<0.001*
Female	156 (95.1)	31 (67.4)	
Male	8 (4.9)	15 (32.6)	
Age (yr)	31.1 (15–63)	31.3 (16–64)	0.849
Extent of resection			<0.001*
Total	164 (100)	30 (65.2)	
Subtotal	0 (0)	16 (34.8)	
Size			<0.001*
Microadenoma	109 (66.5)	13 (28.3)	
Macroadenoma	55 (33.5)	33 (71.7)	
Presence of cavernous sinus invasion			<0.001*
Yes	13 (7.9)	16 (34.8)	
No	151 (92.1)	30 (65.2)	

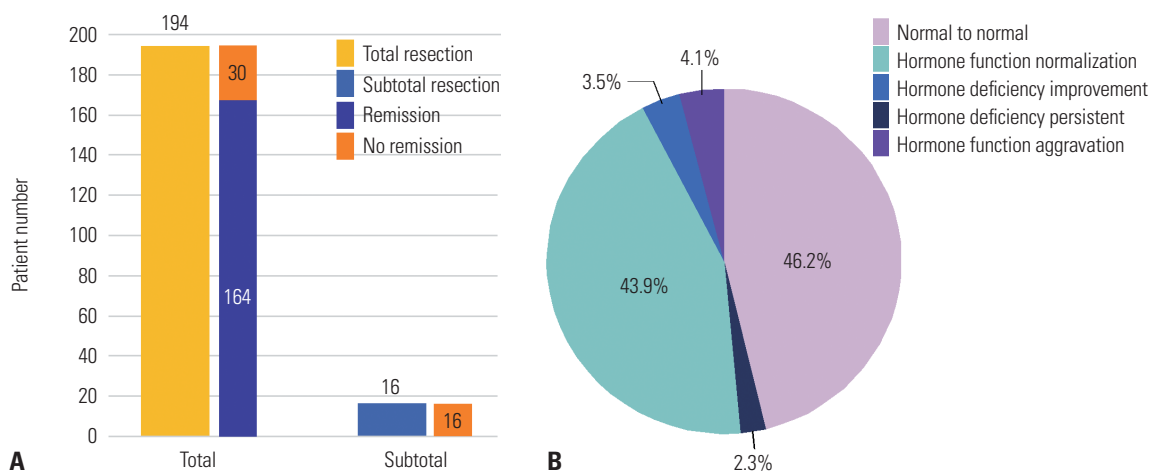Data are presented as mean (range) or n (%).
*p<0.05.

Fig. 2. Overall surgical outcomes. (A) Total resection was achieved in 194 patients (92.4%), while overall the remission was reached in 164 patients (78.1%). When tumors were completely removed, remission rate reached up to 84.5%. (B) Postoperative anterior pituitary function was normal or improved in 94.6% of patients.

patients. Compared with preoperative status, overall hormone function improved in 38.4%, worsened in 4.1%, and did not change in 2.3% (Fig. 2B). The incidence of gonadotropin deficiency, the most common anterior pituitary dysfunction in prolactinoma patients, was only 13.5% (23/171) before surgery and improved to 7.6% (13/171) after surgery. No deaths occurred due to surgery, and only two cases (1.0%) of postoperative CSF leakage occurred in those who eventually underwent additional surgery for reconstruction.

Surgical outcomes according to tumor extent

Hardy type 1 was the majority (58.1%) of our patients, which was followed by type 2 and 4 (Fig. 3A). Total resection was achieved in 100% (122/122) of Hardy type 1, 95.7% (45/47) of Hardy type 2, 83.3% (10/12) of Hardy type 3, and 58.6% (17/29) of Hardy type 4 tumors (Fig. 3B). When the tumor was completely removed, hormonal remission was achieved in 89.3% (109/122), 82.2% (37/45), 50.0% (5/10), and 76.5% (13/17) of Hardy type 1, 2, 3, and 4 tumors, respectively.

Surgical outcomes according to sex

In our cohort, 89.0% of our patients were female. Most of the female patients (63.1%) had Hardy type 1 tumors, whereas only 17.4% were microadenomas in male patients. In contrast, cavernous invasion confirmed either preoperatively or intraoperatively only occurred in 11.2% of female patients; however, cavernous sinus invasion was evident in 34.8% of male patients (Fig. 4A). Consequently, the surgical outcomes were very different between female and male patients. Total resection was achieved in 180 of 187 (96.3%) female patients, but only in 14 of 23 (60.9%) male patients (p<0.001) (Fig. 4B). Regarding endocrinological remission, 156 of 187 female patients (83.4%) attained remission after surgery; however, only 8 of 23 male patients (34.8%) achieved biochemical cure (p<0.001).

Influence of preoperative DAS on surgical outcomes

Before surgery, DA medication was attempted in most of our patients (78.1%) (Fig. 5A). Of the 164 patients, 87 were medi-

cated with cabergoline alone, 39 with bromocriptine alone, and 38 with both. These patients required surgical removal of their prolactinomas for many reasons, including sustained hyperprolactinemia, an insufficient decrease in tumor size, and DA intolerance (Fig. 1). Their surgical outcomes were compared with those in others who were never treated with a DA (Fig. 5B). Overall, 123 of the 164 patients (75.0%) who received preoperative DA treatment achieved endocrinological remission after surgery. Regarding the 46 patients who did not receive DA treatment, their remission rate was 89.1%, and the difference in the remission rate between the two patient groups was statistically significant (p=0.041). Additionally, in subgroup analysis of the 191 patients whose tumors were completely removed, the difference in remission rate was more prominent: 82.6% of the patients treated with a DA preoperatively versus 97.6% of the patients who were not medicated before surgery (p=0.013).

Further treatments for non-remission patients

Overall, 46 patients (21.9%) did not attain remission status with surgery alone. In 30 of them, remnant tumors were not evident during intraoperative inspection and on postoperative MRIs. In the other 16 patients, the remnant tumors exhibited cavernous sinus or suprasellar invasion or extensive dural infiltration. Among them, 40 patients were regularly checked in the outpatient clinic with continuous DA medication alone. Six patients received additional non-medical treatment due to recurrence or regrowth even with the use of DA: four patients underwent gamma-knife radiosurgery, one received a second TSA surgery, and one received a second TSA surgery and chemotherapy with temozolomide because the patient was diagnosed with pituitary carcinoma with distant metastasis at the second surgery. No patient discontinued DA treatment.

DISCUSSION

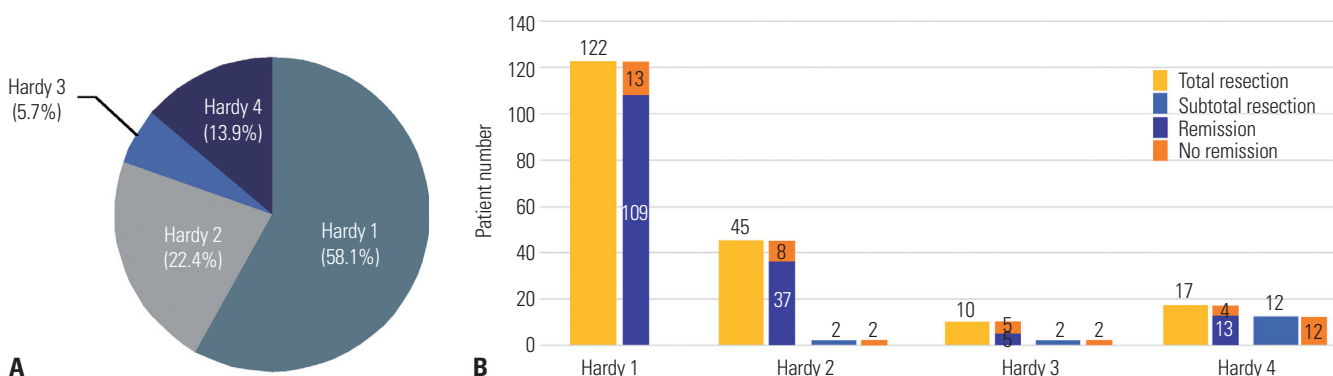Prolactinoma is the most common type of pituitary adenoma

Fig. 3. Surgical outcomes according to tumor extent. (A) The majority of tumors were microprolactinomas (58.1%). (B) The surgical outcomes of microprolactinomas were excellent as total resection was achieved in 100% of Hardy type 1 tumors. Endocrinological remission rate was 89.3% in microprolactinomas. Endocrinological remission was achieved only in 44.8% of our Hardy type 4 patients.
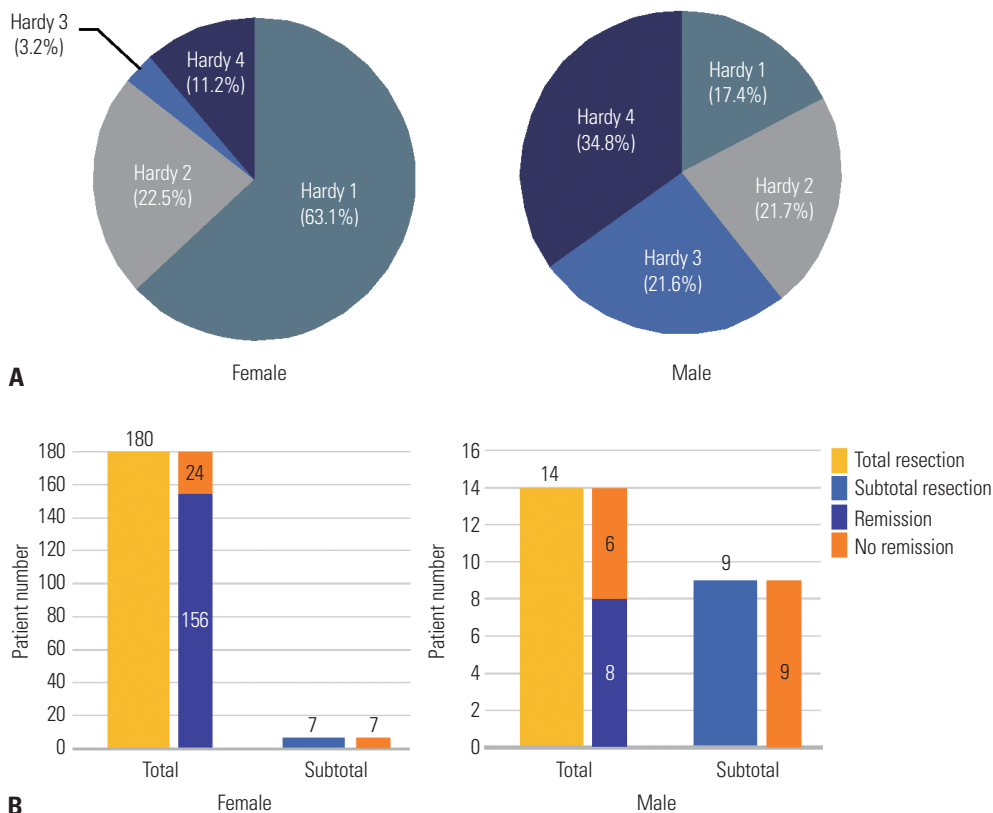
Fig. 4. Surgical outcomes according to sex. (A) The size and extent of tumors were very different between male and female patients. The majority of tumors were Hardy type 1 (63.1%) in females, whereas only 17.4% were in males. Moreover, 34.8% of male patients presented with cavernous sinus invasion. (B) Consequently, the surgical outcomes showed striking sex differences.
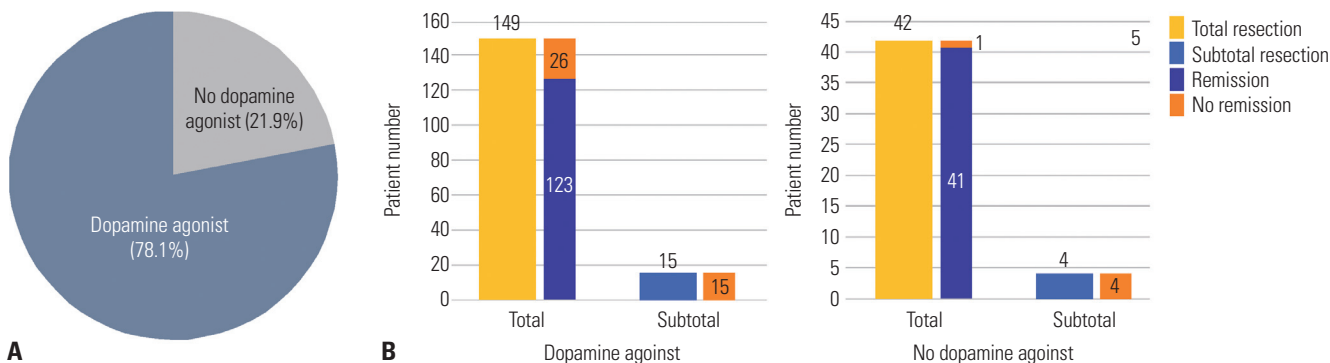

Fig. 5. Influence of preoperative dopamine agonists on surgical outcomes. (A) Dopamine agonist medication was preceded before surgical treatment in the majority of our patients (78.1%). (B) Patients who had not experienced dopamine agonist treatment before surgical treatment showed better outcome than the other patients with preoperative dopamine agonist (89.1% vs.75.0%). For the patients whose tumors were totally removed, the difference in remission rate was more prominent (97.6% vs. 82.6%).

and accounts for more than 50% of all medically treated pituitary adenomas.[24,25] When tumors are less than 1 cm in size (microprolactinomas), patients generally present with galactorrhea, hypogonadism, and infertility because of excessive PRL secretion. In contrast, macroprolactinomas often result in compressive neuropathy, hypopituitarism, and even hydrocephalus due to the effects of the tumor mass. Although treatment goals include the normalization of PRL, alleviation of hyperprolactinemia symptoms, relief of tumor mass effects, and

prevention of tumor growth, these should be individualized according to sex, age, and tumor nature.[26]

Unlike most other types of pituitary adenomas, surgical resection can be reserved as a second-line treatment option in prolactinoma management because medical therapy is highly effective not only to normalize PRL levels but also to rapidly reduce the tumor size.[12,27] Thus, for decades, the consensus was that DA therapy was the first-line treatment option for prolactinoma patients.[11,12] At our institution, we have adhered to this

guideline, and DA therapy was always recommended to our patients as the initial treatment option. [28] Among 210 patients with surgically removed prolactinomas, DA medication was initiated in more than 70% of our study population, who later underwent surgery because of drug resistance and intolerance (Fig. 1). Although the definition of drug resistance may vary substantially based on the stringency of the treatment goal, at our institution, it was defined as either the failure of PRL normalization (a PRL level higher than 15 ng/mL in male and 25 ng/mL in female) or insufficient volume shrinkage (less than 50% of volume reduction) after 3 months of DA medication. The overall surgical outcomes in our cohort comprised total resection in 92.4% and endocrinological remission in 78.1%, which are comparable with other groups in the literature.[27,29] Only five cases (3.0%) of recurrence were identified among 164 patients who had initially achieved endocrinological remission after surgery. Because most cases were microprolactinomas, complications, such as postoperative CSF leakage and the deterioration of pituitary function, were rarely encountered. The anterior pituitary function of our patients, which was evaluated pre- and postoperatively and followed up on a long-term basis, revealed that it was normalized or improved in 94.6% of patients, whereas only 4.1% of patients showed worsening of hormones in at least one axis. Considering that the indications for surgical treatment are not uniform in our patient group, the efficacy of surgical treatment for prolactinomas could be much higher than that reported in the present study. Our subgroup analysis supports this idea. Seventeen patients (8.1%) refused long-term medication and chose surgery as their treatment preference (Fig. 1). In these patients, radical surgical resection was thought to be possible and thus was performed as a first-line treatment option. Total resection was achieved in all patients, and endocrinological remission was achieved in 16 (94.1%).

Apart from the effectiveness of DA treatment, concerns for recurrence after the discontinuation of DA treatment and its long-term safety have been increasing.[29-31] Additionally, many advances have been made in surgical techniques and materials, markedly enhancing surgical radicality and lowering surgical morbidities. Considering the excellent surgical outcomes demonstrated by recent studies in the literature,[27] we believe that the role and indications for surgical treatment should be re-established in prolactinoma management. In the same context, many have proposed that surgical options should be at least discussed as a standard treatment option when the following two conditions are met: 1) tumors can be removed radically and safely, and thus remission is highly likely to be achieved, and 2) patients are managed by experienced pituitary surgeons.[27,29]

Under current guidelines, surgical candidates are chosen based on DA responsiveness, and thus, it is critical to identify risk factors, such as male sex, tumor invasiveness, larger tumor size, high PRL levels, and MRI signal characteristics.[32,33] However, in order to clarify the role of surgery as a first-line treat-

ment option for prolactinomas, surgical indications should be re-established. Not all patients are suitable candidates for surgery; thus, the selection of good candidates must be a critical step to refine guidelines for prolactinoma management. Most clinicians agree that large macroprolactinomas are not likely to be cured by surgery alone because radical removal is not feasible in most cases. However, regarding microprolactinomas, the surgical outcomes are excellent and comparable to those of DA medical treatment. A recent review on the surgical outcomes of microprolactinomas demonstrated remission was achieved in 71%–100% of patients.[27,31] This difference was also noted in our study (Fig. 3). In 41 patients with suprasellar- and parasellar-invading tumors, the total resection rates and endocrinological remission rates were 83.3% and 41.6% in Hardy type 3 and 58.6% and 44.8% in Hardy type 4, respectively. In contrast, the surgical outcomes for microadenomas were excellent: 122 Hardy type 1 tumors were completely removed in 100% of patients, with 89.3% achieving endocrinological remission. Sex is another strong predictor of a less favorable surgical outcome. The tumors in male patients were larger and more invasive, as more than 50% of tumors belonged to Hardy type 3 and 4. Consequently, their surgical outcomes were much worse than those in female patients (Fig. 4). Focusing on microprolactinomas, although total resection was achieved in all four male microadenomas, only two achieved endocrinological remission after surgery.

Several studies have reported that preoperative DA treatment induces tumor fibrosis, which may result in a less favorable surgical outcome.[34,35] Our data showed that the surgical outcomes of patients who had undergone first-line surgical treatment without DA medication were better than those of patients who were treated with DAs. Considering most of our patients with preoperative DA treatment were medicated for only 3 months, we can postulate that long-term DA treatment may decrease the chance of surgical remission. Additionally, if we provide a surgical option to good candidates as a first-line treatment, the overall surgical outcomes are likely to be more favorable than our current practice of using DA as a first-line treatment before surgery.

In summary, while medical treatment with DAs remains the first-line standard treatment for prolactinomas, surgery may also play a primary role in the management of prolactinomas. When patients are predicted to achieve a good surgical outcome, surgery can be an excellent option and should be considered as an alternative primary treatment modality. A smaller tumor size (<1 cm), no invasion into the cavernous sinus, and female sex are predictors of a good surgical outcome. A higher chance of endocrinological remission is expected when surgery is performed without prior DA treatment.

AUTHOR CONTRIBUTIONS

Conceptualization: Sun Ho Kim. Data curation: Eui Hyun Kim, Choel Ryong Ku, and Eun Jig Lee. Formal analysis: Eui Hyun Kim and Junhyung Kim. Funding acquisition: Eui Hyun Kim. Methodology: Eui Hyun Kim. Software: Eui Hyun Kim. Supervision: Sun Ho Kim. Validation: Eui Hyun Kim and Sun Ho Kim. Visualization: Eui Hyun Kim. Writing—original draft: Eui Hyun Kim and Junhyung Kim. Writing—review & editing: Eui Hyun Kim and Sun Ho Kim. Approval of final manuscript: all authors.

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