



# Transsphenoidal microsurgical results of female patients with prolactinomas



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## ABSTRACT

**Objective:** We investigated surgical cure rate and surgical complications of patients with macroprolactinomas who desired pregnancy to evaluate the efficacy of transsphenoidal surgery.

**Methods:** Surgical cure rate was investigated in 138 female patients who were under 40 years old.

**Results:** We found a significant correlation between serum prolactin levels and adenoma volume ( $r=0.004$ ;  $p<0.0001$ ), adenoma volume and age ( $r=-0.213$ ;  $p<0.03$ ), and proliferative index of the adenoma and age ( $r=-0.15$ ;  $p<0.007$ ). Seventy-seven out of 81 patients with enclosed macroadenoma were considered cured, and therefore the overall surgical cure rate was 95%. However, during long-term follow-up, recurrence of adenomas with hyperprolactinemia was seen in 5 out of 81 patients (6%), and the long-term cure rate in patients with enclosed macroadenomas was 89%. Adenomas that did not invade the cavernous sinus showed a significantly higher surgical curability and lower serum prolactin levels, and a smaller size than those adenomas that invaded the cavernous sinus.

**Conclusions:** The long-term surgical cure rate was found to be 89% and this success rate far surpasses the complication rate of 39% during pregnancy by dopamine agonist therapy. Thus, transsphenoidal surgery should be considered as a first-line treatment for female patients who desire pregnancy.

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## 1. Introduction

Prolactinomas are an important cause of hypogonadism and infertility. The ultimate goal of therapy for prolactinomas is restoration or achievement of eugonadism through the normalization of hyperprolactinemia and control of tumor mass. Medical therapy with dopamine agonists (DAs) is highly effective in the majority of cases and represents the mainstay of therapy. As a result, transsphenoidal surgery for prolactinoma is indicated for a distinct number of indications such as non-responders to medical therapy, intolerance of DAs, and cerebrospinal fistula due to tumor invasion.

There is a significant negative correlation between age and the Ki-67 labeling index in female patients with prolactinoma [36]. Therefore, the younger their age, the higher the proliferative activity of the prolactinoma becomes. However, this negative correlation is not observed in male patients with prolactinomas [28]. The optimal management for patients with prolactinomas may vary according to sex, size of the adenoma, and age. In young female

patients, changes in hormone secretion in accordance with pregnancy and delivery have a severe effect on proliferative activity of adenomas. The placental estrogen surge during pregnancy has been shown to induce the mitotic activity of lactotroph cells [19,21]. Since prolactinoma cells express the estrogen receptor [18], it is reasonable that prolactinomas can greatly increase during pregnancy.

In pregnant women with microprolactinomas, the risk of symptomatic tumor enlargement is low [5,14]. Therefore, most pregnant women with microadenomas can be managed safely during pregnancy. However, the risk of tumor enlargement in pregnancy is substantially greater for patients with macroprolactinomas [5,14]. Therefore, specialist care and monitoring is generally required for women with macroprolactinomas during pregnancy [19]. Thirty-nine percent of pregnant women with macroprolactinomas have symptoms of tumor enlargement such as headaches or visual disturbance [6,9,13,23,26,27,33,37]. For these reasons, it is preferable to have a preventive therapeutic option to avoid serious complications and special care and monitoring during pregnancy. The most preventive approach to avoid serious complications during pregnancy is to perform a prepregnancy transsphenoidal surgical debulking of the tumor.

In this study, we evaluated young female patients (under 40 years old) and evaluated the surgical results and complications of

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transsphenoidal (TS) surgery to determine if it is appropriate for first-line treatment of female prolactinomas.

## 2. Methods

### 2.1. Patients

We conducted a retrospective study of female patients with prolactinomas who had undergone TS microsurgery performed by one neurosurgeon (HI) at Tohoku University School of Medicine, Kohnan Hospital, and Ohara Medical Center, Southern Tohoku General Hospital during the period from January 1989 to December 2010. The mean follow-up period was 12 years. Informed consent was obtained from each patient. The surgical cure rate was evaluated in 138 female patients who were under 40 years old and premenopausal.

Endoscopy assisted microsurgery was employed since 2005. The patients were classified into 4 groups: group 1 (invasive adenoma; 37 patients), group 2 (enclosed adenoma: 101 patients), group 3 (microadenoma; 21 patients), and group 4 (macroadenoma; 117 patients). In each group, the surgical cure rate was calculated. Microadenomas were <10 mm in diameter.

Most of the young females under 40 who visited the gynecological clinic complained of menstrual problems and desired to be pregnant in the future. The rest of the female patients were referred to our hospital because of sudden onset of headache and nausea, with MRI revealing intratumoral hemorrhage. In our series there were two patients who had apoplexy during the third trimester of pregnancy and had emergency caesarian sections. 72 out of 138 women received dopamine agonist therapy before surgery.

Thirty patients complained of drug resistance, 40 patients complained of drug intolerance, 30 patients preferred to have operations, and 38 patients had intratumoral hemorrhage.

In addition to high prolactin (PRL) levels, pituitary hormone deficiencies were observed in five patients preoperatively. One patient had adult GH deficiency, two patients had hypothyroidism, and two patients had both adrenal and thyroid axis deficiency.

### 2.2. Criteria for cavernous sinus invasion

The invasiveness of pituitary adenomas was evaluated based on preoperative magnetic resonance (MR) imaging and intraoperative findings. Cavernous sinus invasion (=invasive adenoma) was defined as present when adenoma tissue was located lateral to the cavernous sinus portion of the internal carotid artery on MR imaging, or the medial wall of the cavernous sinus was found to be destroyed by tumor invasion at intraoperative examination. Adenomas other than invasive adenoma were defined as “enclosed adenomas”.

### 2.3. Neuroradiological assessment

The tumor size and presence of intra-cavernous invasion were determined using MR images obtained with a 1.5T system (Magnetom, Siemens, Erlangen, Germany) and 3.0T MR unit (Achieva Quasar Dual 3.0T, Philips, Netherlands). T1- and T2-weighted thick sagittal and coronal spin-echo MR images were obtained as 2–3-mm-thick slices. Additional T1-weighted axial, sagittal and coronal MR images (500/15 ms) were obtained immediately after injection of 0.1 mmol/kg gadolinium-diethylenetriaminepenta-acetic acid (Schering, Berlin, Germany). Images were reconstructed by 2-dimensional Fourier transformation on a 256 × 256 image matrix. The tumor size was measured on the axial, sagittal and coronal MR images. Tumor volume was calculated as 0.5 × (tumor height × width × depth) mm<sup>3</sup>.

Informed consent was obtained from all patients, and research using human blood and tumor tissue was approved by the ethics committee at Tohoku University.

### 2.4. Histological evaluation

Tumor specimens were fixed immediately after removal at the operation. Specimens were fixed in 10% neutral buffered formalin. The samples were then embedded in paraffin blocks, and sections of 3 μm thickness were cut. The sections were used for hematoxylin and eosin staining and immunohistochemical staining by the ABC method using the following antibodies: polyclonal adrenocorticotrophic hormone (Dako, Tokyo, Japan), polyclonal growth hormone (Dako), polyclonal prolactin (Dako), monoclonal thyroid-stimulating hormone-beta (Neo markers, CA, USA), monoclonal luteinizing hormone-beta (Neo markers), monoclonal follicle-stimulating hormone-beta (Neo markers), polyclonal alpha-subunit (Dako) and monoclonal Ki-67 (Dako). Ki-67-labeled cells were determined by counting the number of positive cells in more than 1000 tumor cells in at least 4 representative high power fields (400×) across the slide.

### 2.5. Statistical analysis

To clarify specific biological characteristics of the young female prolactinomas, the relationships between linear and/or factorial variables among the clinical and histological parameters, such as age, tumor volume, serum prolactin values, and proliferative activity of the adenoma, were investigated by simple regression, correlation coefficients, Spearman's rank correlation, and analysis of variance tests. The significance of differences between 2 groups was tested by the nonparametric Mann–Whitney's *U* test. A level of  $p < 0.05$  was taken to be statistically significant. Values are given as mean ± SD.

Chi-square for independence test was applied to evaluate a significant association between pre-operative dopamine agonist treatment and surgical cure rate.

### 2.6. Definition of cure by surgical treatment

Serum prolactin levels were measured before surgery, several times after surgery and during the follow-up period. The criterion for success of the operation was restoration of normal serum prolactin values (<30.5 ng/ml for premenopausal women).

Postoperative serum prolactin levels were determined for all patients in this study at 7–10 days, 6 months, and 1–5 years after surgery. The patients were instructed to visit the hospital whenever the menstrual cycle became irregular.

### 2.7. Evaluation of the results of medical treatment for female prolactinoma

We reviewed studies of female macroprolactinomas published in the last 40 years, and calculated the risk of DA therapy during pregnancy. As a result, we collected 171 cases of female macroprolactinomas and found that unfavorable events during pregnancy such as rapid growth of adenomas, visual disturbance, and hemorrhage within adenomas occurred in 66 patients (39%) (Table 4). The risk of this complication rate (39%) without prepregnant debulking of the macroadenoma during pregnancy was compared with the results of transsphenoidal surgery.

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