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ORIGINAL ARTICLE

Sexual Function

Transsphenoidal surgery for prolactinomas in male patients: a retrospective study

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Male patients with prolactinomas usually present with typical hyperprolactinemia symptoms, including sexual dysfunction and infertility. However, clinical factors related to sexual dysfunction and surgical outcomes in these patients remain unclear. This study aimed to investigate the outcomes of male patients with prolactinomas after transsphenoidal surgery and the risk factors affecting sexual dysfunction. This study was conducted on 58 male patients who underwent transsphenoidal surgery for prolactinomas between May 2014 and December 2020 at the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. We evaluated the sexual function of patients before and after surgery through International Index of Erectile Function-5 scores, libido, and frequency of morning erection. Of the 58 patients, 48 (82.8%) patients had sexual intercourse preoperatively. Among those 48 patients, 41 (85.4%) patients presented with erectile dysfunction. The preoperative International Index of Erectile Function-5 scores in patients with macroprolactinomas were significantly higher than those in patients with giant prolactinomas (17.63 ± 0.91 *vs* 13.28 ± 1.43; $P = 0.01$). Postoperatively, the incidence of erectile dysfunction was 47.9%, which was significantly lower than that preoperatively (85.4%; $P = 0.01$). Twenty-eight (68.3%) patients demonstrated an improvement in erectile dysfunction. Tumor size and invasiveness were significantly correlated with the improvement of erectile dysfunction. Preoperative testosterone <2.3 ng ml^{-1} was an independent predictor of improvement in erectile dysfunction. In conclusion, our results indicated that tumor size and invasiveness were important factors affecting the improvement of sexual dysfunction in male patients with prolactinoma. The preoperative testosterone level was an independent predictor related to the improvement of erectile dysfunction.

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INTRODUCTION

As the most common type of pituitary tumor, prolactinomas account for nearly 40% of all pituitary tumors.[1] Patients with prolactinomas usually present with hyperprolactinemia symptoms and tumor mass effect symptoms (*e.g.*, headache, visual defects, and hydrocephalus). In women, typical symptoms of hyperprolactinemia include menstrual disorders, galactorrhea, and infertility, whereas in men, sexual dysfunction (SD), including erectile dysfunction (ED) and decreased libido, and infertility are typical manifestations of hyperprolactinemia.[2] Compared with female patients, male patients with prolactinomas have larger tumor sizes and higher prolactin (PRL) levels at the time of diagnosis, and the symptoms of SD and infertility lack specificity.[3] Therefore, a considerable number of these patients are initially evaluated by the Department of Andrology due to SD and are occasionally diagnosed with prolactinomas. Patients with ED are unable to achieve and maintain sufficient erectile hardness for satisfactory sexual performance, which often affects their physical and psychological health.[4] The incidence of ED was positively correlated with age. Previous studies showed that 1%–10% of men younger than 40 years of age presented with ED, and this figure reached 2%–9% in males aged 40–49 years and 20%–40% in males aged 60–69 years. In addition, the prevalence of ED increased to 50%–100% in patients older than 70 years.[5,6] Causes of ED can be classified as psychogenic and organic (including nonendocrine and endocrine etiologies). In prolactinomas, ED is related to hyperprolactinemia, which is related to a low testosterone level.[4] In a cohort of 254 male patients with pituitary adenomas (PAs), the prevalence of ED and SD rates was 36.6% and 62.6%, respectively.[7] A retrospective study enrolled 28 elderly males with prolactinomas and found that 17 (61%) patients presented with SD and 11 (39%) patients complained of ED.[8] Phosphodiesterase 5 inhibitors (PDE5is; *e.g.*, sildenafil, vardenafil, and tadalafil) serve as first-line therapies for ED. However, PDE5is did not effectively improve ED symptoms in patients with prolactinomas due to the existence of hyperprolactinemia.[9–11] For prolactinomas and/or hyperprolactinemia, dopamine agonists (DAs) are considered the first-line treatment. A previous study showed that, after being treated with DAs, 46.4% (13/28) of the patients with prolactinomas and/or hyperprolactinemia demonstrated improvement in decreased libido/ED.[8] Another study indicated that, after surgical resection, 91.2% of patients with prolactinomas showed improvement of SD.[7] Nevertheless, clinical

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factors related to SD and the surgical outcomes in male patients with prolactinomas remain unclear.

The purpose of this study was to investigate the outcomes of male patients with prolactinomas after transsphenoidal surgery (TSS) and to analyze the potential risk factors affecting the improvement of SD.

PATIENTS AND METHODS

Study participants

The cohort consisted of 58 male patients with prolactinomas who underwent TSS at the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between May 2014 and December 2020. All patients were operated by LXY. The inclusion criteria were as follows: (1) male patients aged 18–60 years who underwent transsphenoidal microsurgery for the first time; (2) patients were diagnosed with prolactinomas based on the hormonal overproduction of PRL, clinical symptoms, and postsurgery immunohistochemistry; (3) preoperative and postoperative sexual function were fully evaluated; and (4) patients were followed in the outpatient department, by telephone and by e-mail 1 year after surgery. The exclusion criteria included the following: (1) patients who had previously received radiotherapy or adenoma resection; (2) plurihormonal prolactinomas; (3) patients who did not accept surgical resection; or (4) SD caused by other systemic diseases.[7]

Prolactinomas were divided into macroprolactinomas (1–3 cm) and giant prolactinomas (>3 cm), depending on the largest tumor diameter.[7] There were 58 males with prolactinomas, including 36 cases of macroprolactinomas and 22 cases of giant prolactinomas. The study did not include microprolactinomas because of the rarity of cases. Tumor invasiveness was evaluated by magnetic resonance imaging (MRI) in accordance with the Knosp classification as previously reported.[12] Based on the MRI performed 3 months after surgery, the degree of surgical resection was analyzed. Blood samples (*e.g.*, serum PRL and testosterone levels) were drawn in the morning before surgery and the 1st day, 3 months, and 6 months after surgery. The normal range of testosterone level before and after surgery in the study was 2.3–8 ng ml^{-1}, which has been described in the previous studies.[9,13] The normal reference ranges for thyroid hormones were as follows: thyroid-stimulating hormone (TSH; 0.56–5.91 μIU ml^{-1}); free T3 (fT3; 3.81–6.91 pmol l^{-1}); and free T4 (fT4; 7.5–21.1 pmol l^{-1}). DA resistance was considered if tumor size did not decrease by 50%, or after 6 months of DA treatment (2 mg cabergoline [CAB] weekly or 15 mg bromocriptine [BRC] daily), PRL levels were higher than 20 ng ml^{-1}.[14] All the participants were fully informed and consented to the research.

Evaluation of sexual function

Erectile function, morning erection, and libido were analyzed separately to evaluate SD in the study. The International Index of Erectile Function-5 (IIEF-5) scale was used to evaluate the erectile function of patients who had experienced sexual activity within the previous 6 months or who had future plans for sexual activity.[15] The study did not evaluate the erectile function of patients who were not engaged in or did not have future plans for sexual activity.

Patients whose IIEF-5 scores were 21 or less were diagnosed with ED. According to the IIEF-5 scale, the severity of ED was classified into five grades: normal (22–25), mild (17–21), mild–moderate (12–16), moderate (8–11), and severe (1–7).[5] Improvement of ED after surgery was considered when the severity of ED had decreased by at least one grade postoperatively.[7] Morning erection and libido were analyzed through a face-to-face interview and a series of questions from the questionnaire as described in a previous study.[16]

Statistical analyses

Statistical analyses were performed using SPSS Statistics (version 25.0; IBM, Armonk, NY, USA). All of the data were presented as the mean ± standard deviation (s.d.). One-way analysis of variance (ANOVA) was adopted to assess the differences between groups. Regression analysis was employed to analyze the associations between tumor size and preoperative PRL and testosterone levels. Predictors of postoperative improvement of ED were investigated by logistic regression analysis. Differences were considered statistically significant if $P < 0.05$.

RESULTS

Prevalence of ED in prolactinomas

Among the 58 enrolled patients, 48 (82.8%) patients, including 30 macroprolactinomas and 18 giant prolactinomas, had engaged in sexual activity within the previous 6 months or had plans to have sexual activity postoperatively. Among those 48 patients, 41 (85.4%) patients, including 24 macroprolactinomas and 17 giant prolactinomas, presented with ED preoperatively. The incidence of preoperative ED in macroprolactinomas was not significantly different from that in giant prolactinomas (80.0% *vs* 94.4%; $P = 0.231$; **Figure 1a**). The postoperative incidence of ED in those 48 patients was 47.9%, which was significantly lower than the preoperative incidence ($P = 0.01$; **Figure 1b**). Postoperatively, 9 patients (30.0%) with macroprolactinomas and 14 patients (77.8%) with giant prolactinomas had persistent ED ($P = 0.001$). Of the total patients, 34 patients (58.6%), including 18 macroprolactinomas and 16 giant prolactinomas, presented with hypogonadism preoperatively. The incidence of preoperative hypogonadism in macroprolactinomas was not significantly different from that in giant prolactinomas (50.0% *vs* 72.7%; $P = 0.088$; **Figure 1c**). The postoperative incidence of hypogonadism in all patients was 46.6%, which was significantly lower than the preoperative incidence ($P = 0.001$; **Figure 1d**). Fifteen patients

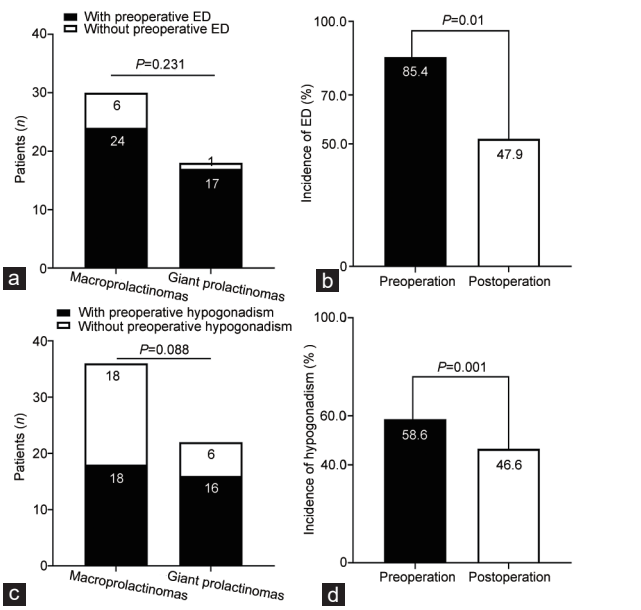

Figure 1: Prevalence of ED in prolactinomas. (**a**) Incidence of ED in macroprolactinomas and giant prolactinomas before surgery (Fisher's exact). (**b**) Comparison of the incidence of ED between preoperation and postoperation (Fisher's exact). (**c**) Incidence of preoperative hypogonadism in macroprolactinomas and giant prolactinomas (Chi-square test). (**d**) Comparison of preoperative and postoperative incidence of hypogonadism (Chi-square test). ED: erection dysfunction.

(41.7%) with macroprolactinomas and 12 patients (54.6%) with giant prolactinomas presented with hypogonadism postoperatively.

General characteristics of male patients with prolactinomas

Table 1 lists the general characteristics of the patients. The age (mean ± s.d.) of the patients was 38.0 ± 1.6 years (range: 18–60 years). Of the 58 patients, 36 of them (62.1%) had macroprolactinomas, and 22 of them (37.9%) had giant prolactinomas. The maximum tumor diameter (mean ± s.d.) of the macroprolactinomas was significantly lower than that of the giant prolactinomas (2.08 ± 0.09 cm *vs* 4.10 ± 0.21 cm; $P < 0.001$). The incidence of invasive prolactinomas in patients with macroprolactinomas was significantly lower than that in patients with giant prolactinoma (38.9% *vs* 100.0%; $P < 0.001$). Visual defects (including visual impairments and visual field defects) were found in 9 of the 36 (25.0%) cases of macroprolactinomas and 16 of the 22 (72.7%) cases of giant prolactinomas ($P < 0.001$). Forty-four patients (75.9%) were resected completely, including 31 macroprolactinomas and 13 giant prolactinomas ($P = 0.02$). In patients with giant prolactinomas, the preoperative PRL level (mean ± s.d.) was 2060.08 ± 578.79 ng ml^{-1}, which was significantly higher than that in patients with macroprolactinomas (525.76 ± 95.88 ng ml^{-1}; $P = 0.016$).

Tumor size and preoperative sexual function

Among the 58 patients with prolactinoma, 30 (51.7%) patients presented with decreased libido, including 14 macroprolactinomas and 16 giant prolactinomas ($P = 0.012$; **Table 1**). The levels of testosterone (mean ± s.d.) in giant prolactinomas were significantly lower than those in macroprolactinomas preoperatively (1.54 ± 0.25 ng ml^{-1} *vs* 2.29 ± 0.23 ng ml^{-1}; $P = 0.036$; **Table 1**). Although the incidence of preoperative ED in macroprolactinomas was not significantly different from that in giant prolactinomas, the preoperative IIEF-5 scores (mean ± s.d.) were significantly higher in macroprolactinomas than in giant prolactinomas (17.63 ± 0.91 *vs* 13.28 ± 1.43; $P = 0.01$; **Figure 2a**), which suggested that ED in giant prolactinomas was more significant than in macroprolactinomas. The frequencies of morning erection before surgery (mean ± s.d.) in giant prolactinomas and macroprolactinomas were 1.36 ± 0.30 days per week

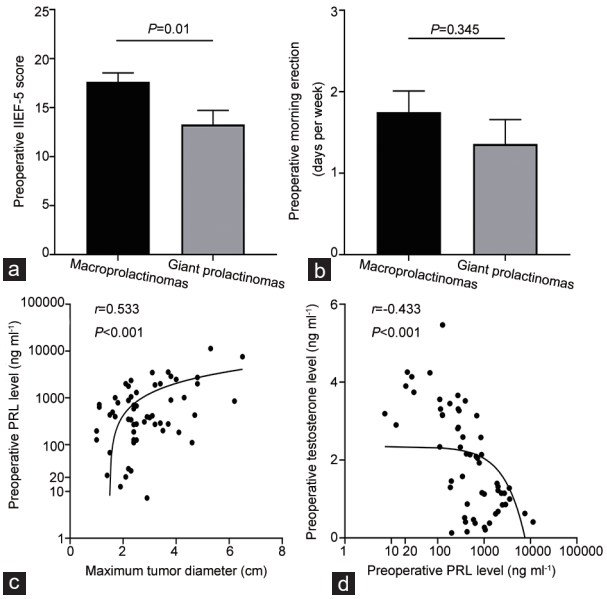

Figure 2: Tumor size and preoperative sexual function. (**a**) Preoperative IIEF-5 scores in macroprolactinomas and giant prolactinomas. (**b**) Preoperative morning erection in macroprolactinomas and giant prolactinomas (Student's *t*-test). (**c**) Correlation between tumor size and preoperative PRL levels (regression analysis). (**d**) Correlation between preoperative testosterone levels and PRL levels (regression analysis). IIEF-5: International Index of Erectile Function-5; PRL: prolactin.

Table 1: Baseline characteristics of all male prolactinomas patients

Clinical characteristic	*Total (n=58)*	*Macroprolactinomas (n=36)*	*Giant prolactinomas (n=22)*	*P*
Age (year), mean±s.d.	38.0±1.6	37.8±2.1	38.3±2.8	0.868[a]
Maximum tumor diameter (cm), mean±s.d.	2.85±0.16	2.08±0.09	4.10±0.21	<0.001[a]
Knosp grades, *n* (%)				<0.001[b]
I	5 (8.6)	5 (13.9)	0 (0)	
II	17 (29.3)	17 (47.2)	0 (0)	
III	19 (32.8)	10 (27.8)	9 (40.9)	
IV	17 (29.3)	4 (11.1)	13 (59.1)	
Headache, *n* (%)	25 (43.1)	14 (38.9)	11 (50.0)	0.407[c]
Visual defects, *n* (%)	25 (43.1)	9 (25.0)	16 (72.7)	<0.001[c]
Total resection, *n* (%)	44 (75.9)	31 (86.1)	13 (59.1)	0.020[c]
Tumor texture, *n* (%)				0.955[c]
Solid	34 (58.6)	21 (58.3)	13 (59.1)	
Cystic and solid	24 (41.4)	15 (41.7)	9 (40.9)	
Preoperative DA medication, *n* (%)				0.514[b]
Without medication	15 (25.9)	8 (22.2)	7 (31.8)	
Resistance to BRC	18 (31.0)	14 (38.9)	4 (18.2)	
Resistance to BRC and CAB	10 (17.2)	5 (13.9)	5 (22.7)	
Intolerance	10 (17.2)	6 (16.7)	4 (18.2)	
Resistance and intolerance	5 (8.6)	3 (8.3)	2 (9.1)	
Decreased libido, *n* (%)	30 (51.7)	14 (38.9)	16 (72.7)	0.012[c]
Sexual activity, *n* (%)	48 (82.8)	30 (83.3)	18 (81.8)	0.882[c]
Preoperative PRL levels (ng ml^{-1}), mean±s.d.	1107.74±245.03	525.76±95.88	2060.08±578.79	0.016[a]
Preoperative testosterone levels (ng ml^{-1}), mean±s.d.	2.01±0.17	2.29±0.23	1.54±0.25	0.036[a]

[a]Values were analyzed using Student's *t*-test; [b]frequencies were analyzed using Fisher's exact; [c]frequencies were analyzed using the Chi-square test. DA: dopamine agonist; s.d.: standard deviation; BRC: bromocriptine; CAB: cabergoline; PRL: prolactin

and 1.75 ± 0.26 days per week, respectively, which were not statistically significant (P = 0.345; **Figure 2b**). Through regression analysis, we found that PRL levels were positively correlated with tumor size (r coefficient = 0.533; P < 0.001; **Figure 2c**). Testosterone levels were inversely correlated with PRL levels (r coefficient = −0.433; P < 0.001; **Figure 2d**). Therefore, tumor size was an important factor affecting preoperative sexual function.

Surgical outcomes

There were 5 (8.6%) patients with postoperative hypothyroidism. Overall, postoperative IIEF-5 scores (mean ± s.d.) were significantly higher than preoperative scores (20.77 ± 3.72 *vs* 16.00 ± 5.76; P < 0.001). Postoperative, IIEF-5 scores (mean ± s.d.) in macroprolactinomas rose to 22.33 ± 0.45, which was significantly higher than preoperative scores (P < 0.001; **Figure 3a**). Postoperative IIEF-5 scores (mean ± s.d.) in giant prolactinomas were significantly higher than preoperatively (18.17 ± 0.96 *vs* 13.28 ± 1.43; P = 0.002; **Figure 3a**). Using repeated-measures ANOVA, we found that the changes in the IIEF-5 scores between macroprolactinomas and giant prolactinomas were not statistically significant (F = 0.17, P = 0.898). However, tumor size significantly affected IIEF-5 scores (F = 15.05, P < 0.001).

In all enrolled patients, the frequencies of morning erection (mean ± s.d.) before surgery and 3 months and 6 months after surgery were 1.61 ± 1.50 days per week, 3.19 ± 1.33 days per week, and 3.91 ± 1.56 days per week, respectively. The differences among these three groups were statistically significant (both P < 0.001; **Figure 3b**). In macroprolactinomas, the frequencies of morning erection (mean ± s.d.) before surgery and 3 months and 6 months after surgery were 1.75 ± 0.26 days per week, 3.28 ± 0.21 days per week, and 3.97 ± 0.24 days per week, respectively. The differences among these three groups were statistically significant (P < 0.001 and P = 0.001, respectively; **Figure 3b**). The frequency of morning erection before surgery (mean ± s.d.) in giant prolactinomas was 1.36 ± 0.30 days per week. Three months and 6 months after surgery, the frequencies of morning erection (mean ± s.d.) increased to 3.05 ± 0.31 days per week and 3.82 ± 0.38 days per week, respectively. The differences among these three groups were also statistically significant (P < 0.001 and P = 0.004, respectively; **Figure 3b**). However, the changes in morning erection between macroprolactinomas and giant prolactinomas were not statistically significant (F_1 [macroprolactinomas] = 0.20, P = 0.654; F_2 [giant prolactinomas] = 0.06, P = 0.814). In addition, tumor size was not associated with morning erection (F = 0.61, P = 0.438).

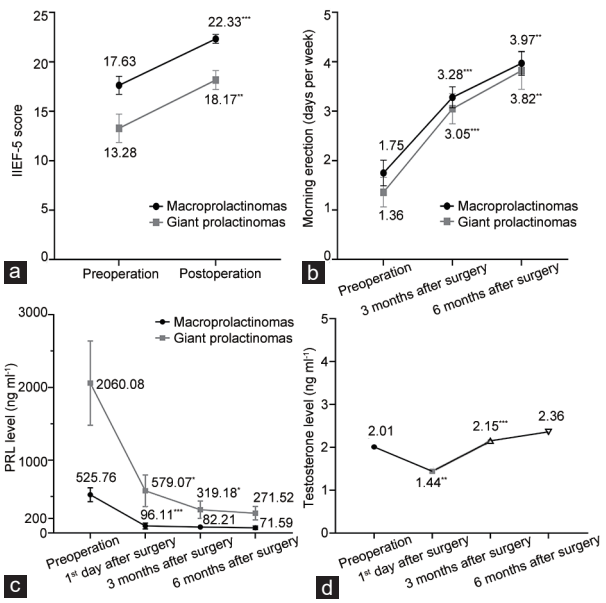

Figure 3: Surgical effects on macroprolactinomas and giant prolactinomas. (**a**) Changes in IIEF-5 scores before and after surgery in macroprolactinomas (black line) and giant prolactinomas (gray line; Student's t-test). (**b**) Changes in the frequencies of morning erection in macroprolactinomas (black line) and giant prolactinomas (gray line; Student's t-test). (**c**) Changes in PRL levels in macroprolactinomas (black line) and giant prolactinomas (gray line; Student's). (**d**) Changes in testosterone levels in total prolactinomas (Student's t-test). $^*P$ < 0.05, $^{**}P$ < 0.01, $^{***}P$ < 0.001. IIEF-5: International Index of Erectile Function-5; PRL: prolactin.

Figure 3c shows the changes in PRL levels of the patients before surgery and the 1st day, 3 months, and 6 months after surgery. On the 1st day after surgery, the PRL levels (mean ± s.d.) of macroprolactinomas and giant prolactinomas dropped sharply compared with preoperative levels (96.11 ± 39.32 ng ml^{-1} *vs* 525.76 ± 95.88 ng ml^{-1}, P < 0.001; 579.07 ± 217.86 ng ml^{-1} *vs* 2060.08 ± 578.79 ng ml^{-1}, P = 0.002; respectively; **Figure 3c**). There were no differences in PRL levels (mean ± s.d.) between 3 months and 6 months after surgery in macroprolactinomas (3 months after surgery: 82.21 ± 33.39 ng ml^{-1}, P = 0.195; 6 months after surgery: 71.59 ± 23.37 ng ml^{-1}, P = 0.449; **Figure 3c**). In giant prolactinomas, PRL levels (mean ± s.d.) at 3 months after surgery decreased to 319.18 ± 119.17 ng ml^{-1} compared with the 1st day after surgery (579.07 ± 217.86 ng ml^{-1}, P = 0.021; **Figure 3c**). However, the differences between the PRL levels (mean ± s.d.) at 3 months and 6 months in giant prolactinomas were statistically insignificant (271.52 ± 91.98 ng ml^{-1} *vs* 319.18 ± 119.17 ng ml^{-1}, P = 0.202; **Figure 3c**). The present study indicated that the changes between the 1st day and 3 months after surgery in macroprolactinomas and giant prolactinomas were statistically significant (F_1 = 11.03, P = 0.002; F_2 = 8.89, P = 0.004). The changes between in PRL levels at 3 months and 6 months after surgery in macroprolactinomas and giant prolactinomas were not statistically significant (F = 3.63, P = 0.062). Nevertheless, tumor size had a significant impact on PRL levels (F = 10.07, P = 0.002).

In all patients, the testosterone levels (mean ± s.d.) before the operation and the 1st day, 3 months, and 6 months after surgery were 2.01 ± 0.17 ng ml^{-1}, 1.44 ± 0.18 ng ml^{-1}, 2.15 ± 0.21 ng ml^{-1}, and 2.36 ± 0.16 ng ml^{-1}, respectively (**Figure 3d**). Compared with the preoperative testosterone level, the testosterone level decreased significantly on the 1st day after surgery (P = 0.001; **Figure 3d**). However, testosterone levels markedly increased at 3 months after surgery (P < 0.001; **Figure 3d**). No statistically significant difference was found in testosterone levels at 3 months and 6 months after the surgery (P = 0 .133; **Figure 3d**).

Clinical factors affecting the improvement of ED after TSS

Among 41 patients who complained of ED preoperatively, there were 28 (68.3%) patients, including 22 macroprolactinomas and 6 giant prolactinomas, whose ED was alleviated. The present study found that patients with giant prolactinomas showed a lower improvement rate of ED than patients with macroprolactinomas using univariate logistic regression (odds ratio [OR]: 0.050, 95% confidence intervals [95% CI]: 0.009–0.287; P = 0.001; **Table 2**). Moreover, patients with noninvasive prolactinomas had a higher improvement rate (OR: 0.054, 95% CI: 0.006–0.475; P = 0.009). Patients with preoperative testosterone ≥2.3 ng ml^{-1} had higher improvement rate of ED (OR: 0.120, 95% CI: 0.022–0.636; P = 0.013). Growth hormone (GH) levels (mean ± s.d.) on the 1st day after surgery in patients with alleviated ED were not significantly different from those in patients without alleviated ED (1.05 ± 1.55 μg l^{-1} *vs* 0.99 ± 1.26 μg l^{-1}, P = 0.794). Age,

Table 2: Predictors related to the improvement of erection dysfunction after surgery in male prolactinomas

Predictor	*Univariate logistic regression*		*Multivariate stepwise logistic regression*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age >50 year	0.923 (0.076–11.201)	0.950	-	-
Resection degree	3.750 (0.805–17.477)	0.092	-	-
Tumor texture	0.687 (0.169–2.788)	0.599	-	-
Maximum tumor diameter	0.050 (0.009–0.287)	0.001	0.270 (0.018–3.997)	0.341
Invasiveness	0.054 (0.006–0.475)	0.009	0.104 (0.004–2.867)	0.181
Preoperative testosterone <2.3 ng ml^{-1}	0.118 (0.022–0.636)	0.013	0.100 (0.013–0.778)	0.028
Preoperative PRL ≥200 ng ml^{-1}	0.242 (0.045–1.304)	0.099	-	-
GH levels on the 1st day after surgery	1.034 (0.644–1.660)	0.891	-	-

CI: confidence interval; OR: odds ratio; PRL: prolactin; GH: growth hormone; -: not available

resection degree, preoperative PRL levels, and GH levels on the 1st day after surgery were not associated with the improvement of ED after surgery. The study demonstrated that preoperative testosterone <2.3 ng ml^{-1} was an independent predictor related to the improvement of ED through multivariate stepwise logistic regression (OR: 0.100, 95% CI: 0.013–0.778; P = 0.028). Tumor size and invasiveness were not independent predictors related to the improvement of ED (P = 0.341 and P = 0.181, respectively). In summary, tumor size and invasiveness were important risk factors affecting the improvement of ED. The preoperative testosterone level (<2.3 ng ml^{-1}) was an independent predictor related to the improvement of ED.

DISCUSSION

ED, a systemic and common SD in males, has many possible causes. It has been reported that 52% of men aged 40–70 years suffered from mild-to-moderate ED.[4] The prevalence of ED in our study was 85.4%. A previous study found that patients with functioning PAs showed a higher incidence of SD than those with nonfunctioning PAs.[7] The proposed mechanism of SD in nonfunctioning PAs is that the tumor mass effect not only leads to suppression of gonadotropin secretion but also induces hypothyroidism or GH deficiency.[17–19] In our study, the incidence of postoperative hypothyroidism was 8.6%. A previous study indicated that testosterone levels at 6 months after surgery were an important predictor for the improvement of SD in patients with PAs. This study also found that tumor invasiveness and tumor size were important predictors affecting the improvement of ED.[7] In the present study, our results indicated that the preoperative testosterone level was an independent predictor related to the improvement of ED in male patients with prolactinomas. Tumor size and invasiveness were important factors related to SD. First, compared with patients with preoperative testosterone <2.3 ng ml^{-1}, patients with preoperative testosterone ≥2.3 ng ml^{-1} had a higher improvement rate of ED. Multivariate stepwise logistic regression showed that preoperative testosterone <2.3 ng ml^{-1} was an independent risk factor affecting the improvement of ED. Second, the rate of invasiveness in giant prolactinomas was significantly higher than that in macroprolactinomas (100.0% *vs* 38.9%). This finding can be explained by the fact that, in addition to affecting hormone secretion, a larger tumor size results in more serious pituitary stalk compression. Compared with noninvasive prolactinomas, invasive prolactinomas have more effects on the normal pituitary gland, which leads to more serious pituitary stalk compression. Furthermore, the tumor size in invasive prolactinomas is usually larger than that in noninvasive prolactinomas, which is positively related to preoperative PRL levels. In our study, patients with giant prolactinomas had higher PRL levels than those with macroprolactinomas. A reverse relationship between testosterone levels and PRL levels was also detected. Testosterone levels in giant prolactinomas were significantly lower than those in macroprolactinomas. A previous study indicated that SD was significantly related to free testosterone levels <64 pg ml^{-1} or total testosterone levels below 3.2 ng ml^{-1}.[20] Moreover, it was reported that the level of testosterone required to maintain the erectile function was 2.3 ng ml^{-1}.[21] This might explain why ED in giant prolactinomas was more serious than that in macroprolactinomas preoperatively. Our study found that the preoperative incidence of ED in patients with macroprolactinomas was similar to that in those with giant prolactinomas (80.0% *vs* 94.4%), but the degree of ED in patients with giant prolactinomas was more serious than that in patients with macroprolactinomas preoperatively. Previous studies have demonstrated that hyperprolactinemia led to SD or infertility by inhibiting the secretion of gonadotropin-releasing hormone and gonadal steroidogenesis. In addition to decreasing the level of testosterone, hyperprolactinemia could also reduce libido directly.[22–24] In the present study, patients with giant prolactinoma suffered a higher proportion of decreased libido than those with macroprolactinomas (72.7% *vs* 51.7%).

A morning erection is associated with sexual self-confidence, and a poor morning erection has a negative impact on a man's sexual life.[16] It has been reported that testosterone levels <2 ng ml^{-1} were, in most cases, related to SD and morning erections.[25] Another study also found that the testosterone threshold for morning erections was approximately 2 ng ml^{-1}, which was lower than the normal laboratory range. In addition, the correlation between morning erections and serum testosterone levels was statistically insignificant in patients with normal serum testosterone levels.[26] In the present study, we found that the difference in the frequencies of morning erection between macroprolactinomas and giant prolactinomas was statistically insignificant preoperatively. Nevertheless, the frequencies of postoperative morning erection either in macroprolactinomas or in giant prolactinomas were significantly higher than those preoperatively, which corresponded with the significantly increased levels of testosterone at 3 months after surgery. However, compared to before the operation, testosterone levels on the 1st day after surgery were much lower, which suggested that there was a temporary postoperative effect on testosterone levels. This might be explained by the fact that intraoperative destruction of normal pituitary tissue or compression of the pituitary stalk can lead to hypopituitarism.[27] The present study found that 47.9% of patients suffered from ED after receiving TSS, which was significantly lower than that before the operation. These ED symptoms were improved in 68.3% of the patients after surgery. The study also found that the PRL levels in macroprolactinomas and giant prolactinomas decreased significantly on the 1st day after surgery compared to preoperative levels. PRL levels at 3 months after surgery in

giant prolactinomas were significantly lower than those on the 1st day after surgery. These results provide a unique view that TSS is effective in improving SD in male patients with prolactinomas.

In patients who do not respond to DAs or cannot tolerate the side effects of DA therapy, it is well known that TSS serves as an important therapeutic choice.[28] Researchers previously reported that DA treatment could effectively improve testosterone levels and libido in male patients with hyperprolactinemia.[9] Another study demonstrated that, after experiencing TSS, ED symptoms were significantly improved in all enrolled patients with PAs. Moreover, testosterone levels increased significantly at 6 months after surgery compared with before the surgery.[7] A literature review suggested that men with testosterone <2.3 ng ml^{-1} usually benefit from testosterone replacement therapy, based on the data of young hypogonadal men.[13] Therefore, for those patients who still suffer from SD and have testosterone <2.3 ng ml^{-1} at 3 months after surgery, testosterone treatment serves as an important therapy for SD. Jiang *et al*.[29] reported four cases in which prolactinoma therapy reversed the nonresponse to PDE5is treatment in men with ED. However, the cases included in the study were limited. The role of PDE5is in male patients with prolactinomas who had ED after surgery warrants further investigation. The study has inherent weaknesses, such as the cohort was not large enough and the follow-up was not long enough due to the limited research time. Moreover, during the treatment of patients with prolactinomas, we did not perform glucagon stimulation and further growth hormone-releasing hormone/arginine testing, so patients who presented with GH deficiency postoperatively could not be confirmed.

CONCLUSIONS

The present study demonstrates that tumor size and invasiveness are important factors affecting the improvement of SD in male patients with prolactinomas. The preoperative testosterone level could be an independent predictor related to the improvement of ED.

AUTHOR CONTRIBUTIONS

WJS and HCC were responsible for the design of the study. WJS, HCC, and GCY performed the analysis of clinical information and drafting of the manuscript. KJH, HLW, YBY, and HXT performed the follow-up. CHD and LXY supervised the study and critically revised the article. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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