Early Prediction of Long-term Response to Cabergoline in Patients with Macroprolactinomas

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(Directed by Professor Eun Jig Lee)

Cabergoline is effective for treating prolactinomas. However, some patients display cabergoline resistance, and their early characteristics are not well known. We analyzed early indicators predicting the long-term response to cabergoline. We retrospectively reviewed 44 patients with macroprolactinomas who received cabergoline as first-line treatment; the patients were followed-up for a median of 16 months. The influences of various clinical parameters on outcomes were evaluated. Forty patients (90.9%) could be medically treated, displaying tumor volume reduction (TVR) of 74.7%, prolactin normalization (NP) rate of 81.8%, and complete response (CR; TVR>50% with NP, without surgery) rate of 70.5%. Most patients (93.1%) with TVR≥25% and NP at 3 months eventually achieved CR,

whereas 50% of patients with TVR≥25% without NP and no patient without TVR≥25% achieved CR. TVR at 3 months was strongly correlated with the final TVR (R=0.785). Patients with large macroadenomas exhibited a low NP rate at 3 months but eventually achieved TVR and NP rates similar to those of patients with smaller tumors. Surgery independently reduced the final dose of cabergoline (β=−1.181 mg/week), and two of four patients who underwent surgery could discontinue cabergoline. Determining cabergoline response using TVR and NP at 3 months after treatment is useful for predicting later outcomes. However, further cabergoline administration should be considered for patients with TVR>25% at 3 months without NP, especially with huge prolactinomas, because a delayed response may be achieved. As surgery can reduce the cabergoline dose with successful disease control, it should be considered for cabergoline-resistant patients.

Key words : Cabergoline, Dopamine, Macroprolactinoma, Hyperprolactinemia

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I. INTRODUCTION

Prolactinomas are the most frequent functioning pituitary adenomas, comprising approximately 40% of pituitary tumors [1,2]. Their prevalence in the general adult population was reported to range from 100 to 625 per million people [3,4]. Prolactinomas cause symptoms via two mechanisms, namely hormonal effects via hyperprolactinemia and mass effects via tumor expansion [1,5]. Hyperprolactinemia causes sexual and gonadal dysfunctions such as decreased libido, amenorrhea, erectile disorder, and infertility, as well as galactorrhea. Mass effects in patients with macroadenomas include bilateral hemianopsia, headache, hypopituitarism, and cranial neuropathy.

Dopamine agonists (DAs) are well established as first-line treatments for prolactinomas that can induce tumor shrinkage and normalization of prolactin (PRL) levels (NP) [1,5]. These agonists include bromocriptine, pergolide, cabergoline (CAB), and quinagolide, but only bromocriptine and CAB are currently available in Korea. Bromocriptine, which was introduced clinically

in the 1980s, is a traditional drug for the treatment of prolactinomas [1,6]. However, CAB, which was introduced more recently, is currently used more commonly than bromocriptine. CAB is a selective agonist of the D2 receptor, which is related with the resolution of hyperprolactinemia, contrary to bromocriptine, which has partial affinity for the D1 receptor and affinity for the D2 receptor [6]. This agent has superior tolerability and convenience, as well as higher rates of tumor shrinkage and control of hyperprolactinemia, compared with bromocriptine [7,8]. It also displayed effectiveness in patients with bromocriptine-intolerant or bromocriptine-resistant prolactinomas [9,10].

However, a considerable proportion of patients display resistance to CAB. CAB treatment was reported to respectively induce NP and successful tumor reduction in 61–92% and 55–100% of patients with prolactinomas [1]. Molitch et al. [11] defined pharmacologic resistance in prolactinoma as a failure to achieve NP and/or to decrease tumor size by ≥50%, and they described that the rate of CAB resistance was 10–15% in terms of PRL levels and tumor size. The treatment of patients with CAB resistance remains challenging, although a few articles suggested that surgical debulking or high-dose CAB therapy can be helpful for patients with resistance to DAs [12-15]. In addition, it is unclear how to identify these patients early.

A few years ago, we reported the long-term outcomes of patients with invasive prolactinomas who were treated with bromocriptine [16]. In that study, we documented that patients who achieved a tumor volume reduction (TVR)

of at least 25% with NP at 3 months had a high probability of achieving a long-term complete response (CR) defined as a TVR of at least 50% with sustained NP. However, patients who were treated with CAB as a first-line therapy could not be included because CAB was a newly introduced and expensive drug in Korea at that time.

In this study, we describe the result of CAB administration as a first-line treatment for 44 patients with macroprolactinomas who were followed up for a median of 16 months. To identify early predictors of the long-term response to CAB, we analyzed the influences of initial clinical parameters and early responses to CAB on later outcomes. We also evaluated which treatment factors could alter the outcomes of patients.

II. MATERIALS AND METHODS

1. Patient

We conducted a 6-year retrospective study of patients with macroprolactinomas who were treated with CAB as a primary drug at Severance Hospital, Seoul, South Korea, between 2008 and 2013. Macroprolactinoma was defined as (1) a PRL level of at least 150 ng/mL and (2) a maximal diameter at least 1 cm on baseline magnetic resonance imaging (MRI) scans of the sellar area. To evaluate the relationship between early and late parameters, the following additional inclusion criteria were applied: (1) a

full dataset of pituitary hormone assays (including PRL) and sella MRI at baseline, (2) follow-up PRL assay and MRI after 3 months of CAB treatment, and (3) total follow-up duration of at least 12 months.

2. Treatment and response assessment

In all the cases, oral CAB was started at a low dose (1–1.5 mg/week), and the dosage was gradually increased to 1.5–4 mg/week within 2–4 weeks. The increased dose was maintained until 3 months after treatment initiation to ensure a sufficient period of exposure to CAB. Evaluations of response were started after 3 months, and the dose of CAB and interval of follow-up were continuously adjusted in consideration of response, tolerance, and other clinical indicators. For patients with good response and tolerance, reduction of the dose of CAB was carefully tried, with relatively long interval of follow-up. For patients with poor response, higher dose of CAB and short interval of follow-up was applied. Because the follow-up intervals and treatment durations of the patients varied, three representative time points of response assessment were retrospectively defined as follows: early assessment, when the first sella MRI and PRL assay were performed after 3 months of CAB treatment; late assessment, when the first sella MRI and PRL assay were performed during the period of 12–24 months after treatment; and last assessment, when the last sella MRI and PRL assay were performed. Tumor volume was calculated according to Di Chiro and Nelson's formula

(volume=height×length×width×π/6) [17]. The degree of response was assessed using TVR and NP. When evaluating the relationship between early response and later outcomes, we used group criteria according to the early response to CAB, as suggested in our previous article, as follows [16]: group 1, TVR≥25% with NP; group 2, TVR≥25% without NP; group 3, TVR<25% with NP; and group 4, TVR<25% without NP [16]. A successful response at the late or last assessment was defined as follows: volume response, TVR≥50% without surgery; PRL response, NP without surgery; and CR, volume response with PRL response.

3. PRL assays

Serum PRL levels were measured by a chemiluminescence immunoassay using commercial kits (Beckman Coulter, US). The within-run and total coefficients of variation for PRL concentrations were 3.66% and 3.77%, respectively. PRL levels <15 ng/mL for males and <25 ng/mL for females were regarded as normal. If serum PRL levels were normal or mildly elevated, PRL was measured again in diluted serum samples to exclude the hook effect, which causes falsely low results [18,19].

4. Statistical analyses

Data were presented as the median (interquartile range) or mean ± standard

deviation. The relationships between early responses and late or last responses were analyzed using the Pearson correlation coefficient and multiple linear regression tests. The Student t test, Kruskal-Wallis test, Mann-Whitney U test, and Fisher exact test were performed to compare multiple groups. The relationships between tumor volume or PRL levels at baseline and TVR, PRL levels, or the maintained dose of CAB after treatment were analyzed using the Spearman correlation coefficient. Statistical analyses were performed using SPSS version 20 (Chicago, IL, US). $p<0.05$ were considered statistically significant.

III. RESULTS

1. Baseline characteristics and overall treatment outcomes

Of 66 patients with macroprolactinomas who were treated with CAB as a primary drug during the study period, 47 patients had at least 1 year from their initial administration of CAB to the end of the data collection. One patient was lost to follow-up before 12 months, and 2 females who were pregnant before 12 months of CAB treatment were additionally excluded, because CAB had to be discontinued, irrespective of tumor size and PRL levels. Finally, in total 44 patients, including 28 males (63.6%), were included in the study (Tables 1 and 2). The mean age of the patients was 36.8 years, and the median follow-up duration was 16 months (interquartile range, 15–25.5 months). Eleven patients (25%) had visual field defects, and 28 patients

(61.4%) complained of sexual dysfunction including impotence, oligomenorrhea/amenorrhea, and/or infertility. The patients also complained of headache and dizziness (n=12; 27.3%), ocular movement abnormalities (n=2; 4.5%), and galactorrhea (n=6; 13.6%). The median PRL level and median tumor volume were 796.7 ng/dL (202.5–2431.3) and 3.71 cm3 (1.60–11.51), respectively. Tumor invasion of the cavernous sinus was noted in 20 patients (45.5%). Most patients (n=40; 90.9%) displayed sex hormone deficiency, defined as a testosterone level below the lower limit of the normal population for males, oligomenorrhea/amenorrhea in premenopausal females, and an inappropriately low gonadotropin level in postmenopausal female. Five patients (11.4%) displayed growth hormone (GH) deficiency, defined as a lower serum IGF-1 level than the age- and sex-specific lower limit of the normal population, whereas secondary hypothyroidism and adrenal insufficiency were found in one and zero patients, respectively. Compared with female patients, male patients were older (41.5 years vs. 28.5 years, $p<0.001$), less likely to complain of sexual dysfunction (46.4% vs. 87.5%, $p=0.010$), and more likely to have a visual field defect (39.3% vs. 0%, $p=0.003$), and they displayed higher tumor volume (10.64 cm3 vs. 0.87 cm3, $p<0.001$) and PRL level (923.3 ng/mL vs.428.5 ng/mL, $p=0.023$).

At the last assessment, a volume response, PRL response, and CR were achieved by 35 (79.5%), 36 (81.8%), and 31 patients (70.5%), respectively (Table 1). Two patients who exhibited transient mild PRL elevation (patients

nos. 18 and 24, who had PRL levels of 52.3 and 33.6 ng/mL, respectively.) related with very poor drug compliance at the last assessment were regarded to achieve a PRL response. Four patients (9.1%) underwent surgery in their treatment courses, and the median TVR of the patients who did not undergo surgery was 74.7% (61.7–85.4).

Table 1. Summary of 44 Patients with Macroprolactinomas

Variables	Total (n = 44)	Female (n = 16)	Male (n = 28)	P value
Demographic characteristics				
Age[a], years	36.8 ± 12.0	28.5 ± 12.0	41.5 ± 9.3	<0.001
Symptom and sign				
Visual defect[b], n (%)	11 (25.0)	0 (0)	11 (39.3)	0.003
Sexual dysfunction (Impotence, amenorrhea [female], infertility)[b], n (%)	27 (61.4)	14 (87.5)	13 (46.4)	0.010
Headache and dizziness[b], n (%)	12 (27.3)	2 (12.5)	10 (35.7)	0.160
Ocular movement abnormality[b], n (%)	2 (4.5)	0 (0)	2 (7.1)	0.526
Galactorrhea[b], n (%)	6 (13.6)	4 (25)	2 (7.1)	0.169
Baseline hormonal deficiency				
Sex hormone deficiency[b], n (%)	40 (90.9)	15 (93.8)	25 (89.3)	1.000
GH deficiency[b], n (%)	5 (11.4)	1 (6.3)	4 (14.3)	0.638
Secondary hypothyroidism[b], n (%)	1 (2.3)	1 (6.3)	0 (0)	0.364
Baseline prolactin and tumor volume				
Prolactin[c], ng/mL	796.7 (202.5–2431.3)	428.5 (165.6–932.6)	923.3 (545.6–3072.3)	0.023
Tumor volume[c], cm^3	3.71 (1.60–11.51)	0.87 (0.53–2.99)	10.64 (3.13–13.0)	<0.001
Final results of treatment				
Follow up duration[c], months	16 (15–25.5)	15 (15–22.5)	20.5 (15–29)	0.299
Tumor volume reduction without surgery[cd], %	74.7 (61.7–85.4)	82.6 (72.9–86.6)	69.6 (56.6–80.6)	0.040
Volume response[b], n (%)	35 (79.5)	15 (93.8)	20 (71.4)	0.124
Prolactin response[b], n (%)	36 (81.8	13 (81.3)	23 (82.1)	1.000
Complete response[b], n (%)	31 (70.5)	13 (81.3)	18 (64.3)	0.314
Surgery[b], n (%)	4 (9.1)	1 (6.3)	3 (10.7)	1.000

GH, Growth hormone. Data are presented as [a]the mean ± standard deviation, [b]the number (%), or [c]median (interquartile range). [d]Patients who underwent surgery before the final assessment were excluded. [a]The Student *t* test and [c]the Mann-Whitney *U* test were used for parametric and nonparametric analyses, respectively, and [b]the Fisher exact test was used for categorical data analyses.

Table 2. Forty-four Patients with Macroprolactinomas

Patient number	Group	Age, years	Sex	Cavernous Sinus Invasion	Baseline		Post-Tx 3 months		Post-Tx 12 months (first follow-up after 12 months)			Post-Tx last			CAB dose, mg/week	
					Tumor volume, cm^3	Prolactin, ng/mL	Tumor volume, cm^3 (TVR, %)	Prolactin, ng/mL	Tumor volume, cm^3 (TVR, %)	Prolactin, ng/mL	Follow-up duration, months	Tumor volume, cm^3 (TVR, %)	Prolactin, ng/mL	Follow-up duration, months	Peak	Last
1	1	48.1	M	Yes	44.56	5280	22.77 (48.9)	4	12.7 (71.5)	4	15		As left		3	3
2	1	33.6	M	Yes	25.16	3268	11.57 (54)	0.7	7.62 (69.7)	0.5	15		As left		3	2
3	1	30.4	M	Yes	14.31	623	5.21 (63.6)	<1	2.19 (84.7)	0.21	21	2.04 (85.7)	<0.25	64	1.5	0.5
4	1	39	M	Yes	13.66	3789.6	10.19 (25.4)	1.1	8.55 (37.4)	0.5	15		As left		3	2
5	1	42.3	M	No	11.86	1475.5	8.06 (32)	3.4	4.84 (59.2)	1.1	22		As left		3	2
6	1	53.7	M	Yes	11.8	3326	7.49 (36.5)	0.7	3.67 (68.9)	0.3	21		As left		3	3
7	1	25.4	M	No	10.95	795.56	4.35 (60.3)	0.8	0.52 (95.3)	0.8	20		As left		2	0.7
8	1	49.6	M	Yes	10.74	2844.1	4.24 (60.5)	1.4	3.84 (64.2)	0.7	15		As left		3	2
9	1	48	M	No	10.54	904.4	6.88 (34.7)	8.6	4.9 (53.5)	8.1	21	5.67 (46.2)	11	33	3	1
10	1	41	M	No	10.15	148.5	3.9 (61.6)	0.4	3.22 (68.3)	1.7	22		As left		3	2
11	1	35.7	M	Yes	9.22	942.2	5.16 (44)	1.8	4 (56.6)	2.1	12		As left		2	3
12	1	45	M	Yes	9.2	799.67	4.98 (45.9)	0.5	3.09 (66.4)	0.5	25		As left		3	2
13	1	42.9	M	No	8.34	628.3	5.32 (36.2)	0.8	4.58 (45.1)	0.3	12	1.97	76.4	1.97 (76.4)	3	0.5
14	1	16.6	F	No	7.04	3982.1	2.69 (61.8)	1.2	1.14 (83.8)	0.8	21		As left		3	2
15	1	49.3	F	Yes	3.72	894.7	2.73 (26.6)	18.1	1.84 (50.5)	16.1	21		As left		3	2
16	1	48.4	M	No	3.6	797.8	2.18 (39.4)	6.2	1.76 (51.1)	0.8	15		As left		3	2
17	1	43.6	M	No	2.8	651.6	0.52 (81.4)	4.1	0.35 (87.5)	3.4	15	0.33 (88.2)	5.1	27	3	1
18	1	21	F	Yes	2.29	1271	1.21 (47.2)	7.73	0.77 (66.4)	3.99	15	0.64 (72.1)	52.3	48	1.75	1
19	1	64.9	M	Yes	2.11	1501.3	1 (52.6)	<0.25	0.46 (78.2)	<0.25	15		As left		3	1.5
20	1	24.2	F	No	1.51	614.8	0.41 (72.8)	0.8	0.19 (87.4)	0.4	15		As left		3	0.5

21	1	15.6	F	No	0.93	197	0.33 (64.5)	2.21	0.14 (84.9)	2.74	16	0.13 (86)	1.2	59	2	1
22	1	26.1	F	No	0.8	501	0.27 (66.3)	1.2	0.12 (85)	0.6	15		As left		3	1
23	1	21.1	F	No	0.78	356	0.44 (43.6)	2.4	0.23 (70.5)	1.5	15		As left		3	1
24	1	22.6	F	No	0.69	168.1	0.38 (44.9)	0.7	0.12 (82.6)	33.6	15		As left		3	1
25	1	38.3	M	No	0.65	131.9	0.19 (70.8)	1.2	0.07 (89.2)	1.2	15		As left		3	2
26	1	46.3	F	No	0.54	156.92	0.28 (48.1)	0.7	0.12 (77.8)	0.4	15		As left		1	0.7
27	1	32.6	F	No	0.52	163	0.25 (51.9)	8.3	0.25 (51.9)	8.9	15		As left		2	1.5
28	1	27.1	F	No	0.43	159.3	0.12 (72.1)	0.4	0.06 (86)	0.3	15		As left		2	0.5
29	1	26	F	No	0.36	151.11	0.25 (30.6)	0.4	0.16 (55.6)	<0.25	12	0.03 (91.7)	0.3	24	2	0.25
30	2	27.5	M	Yes	89.96	13096.4	27.01 (70)	734.9	21.96 (75.6)	423.7	15		As left		4.5	4.5
31	2	45.3	M	Yes	20.44	8759	10.04 (50.9)	57.5	2.72 (86.7)	19.5	21	2.42 (88.2)	11.5	32	3	2
32	2	35	M	Yes	19.65	2876.5	6.63 (66.3)	22.78	3.67 (81.3)	13.9	16	3.24 (83.5)	8.1	41	3	2
33	2	55.1	F	Yes	5.87	1018.2	2.16 (63.2)	58.7	1.03 (82.5)	5.1	14		As left		2	1
34	2	33.1	F	No	3.69	970.4	1.18 (68)	32.15	0.55 (85.1)	28.05	15	0.43 (88.3)	47.7	26	2	1
35	2	39.9	M	No	3.45	468.2	1.29 (62.6)	189.6	0.99 (71.3)	196.3	15		As left		4.5	4.5
36	2	16.5	F	Yes	2.28	656.5	1.09 (52.2)	33.5	0.6 (73.7)	29.9	15		As left		4.5	4.5
37	2	31.5	M	No	2.22	176.2	1 (55)	17	0.43 (80.6)	12.3	21		As left		3	1
38	3	27.5	M	No	17.67	2042	18.36 (-3.9)	0.6	0 (100)[a]	2.2[a]	15	0 (100)[a]	7.9[a]	32	3	0.7
39	3	37.4	M	Yes	11.21	4256	10.03 (10.5)	5.8	6.81 (39.3)	8.7	18	6.79 (39.4)	8.1	31	3	3
40	3	37.3	M	No	2.27	207.9	1.93 (15)	2.6	1.46 (35.7)	2.8	15		As left		3	2
41	3	56.6	M	Yes	1.68	165.3	1.54 (8.3)	0.5	1.26 (25)	0.6	21		As left		2	0.5
42	3	22.5	F	No	0.35	196.3	0.33 (5.7)	6.7	0 (100)[a]	15.3[a]	15		As left		3	0
43	4	51.4	M	Yes	22.06	2820.5	17.19 (22.1)	23.1	0 (100)[a]	13.2[a]	15		As left		3	0
44	4	42.2	M	Yes	2.34	317.1	2.39 (-2.1)	58.2	2.42 (-3.4)	699.4	15	Uncertain[ab]	393.8[a]	17	3	1

Tx, treatment; CAB, cabergoline; and TVR, tumor volume reduction.

[a]Surgery was performed before measuring the variables; [b]Residual tumor was not distinguished from postoperative change in last MRI.

2. Influences of baseline tumor burdens on latter outcomes

The baseline tumor volume or PRL levels were not directly correlated with TVR or PRL levels at the early, late, and last assessments (Spearman correlation coefficients, all $p>0.05$). However, 6 patients with large tumors (larger group), whose baseline tumor volume exceeded 18 cm3 and whose PRL levels exceeded 2000 ng/mL, displayed higher PRL levels than the other patients (smaller group) at 3 months after treatment (22.9 ng/mL vs. 1.6 ng/mL, $p=0.043$; Fig. 1A). Interestingly, these differences in PRL levels between the groups lost their statistical significance at 9 months (Figs. 1A), and the TVR of patients who did not undergo surgery was not different between the groups during the entire treatment course (Fig. 1B).

3. Relationships between early response and late or last response

To assess the influence of the early response on the late or last response, we primarily categorized patients into four groups according to their early responses to CAB. Of the total 44 patients, 29 patients belonged to group 1 (TVR≥25% with NP), eight patients were included in group 2 (TVR≥25% without NP), five patients belonged to group 3 (TVR<25% with NP), and two patients were included in group 4 (TVR<25% without NP; Fig. 2A). Most patients in group 1 (93.1%) achieved a CR as expected, but two patients (6.9%) could not achieve TVR≥50% until the last assessment. Four (50%) of eight patients in group 2 eventually achieved a CR, whereas no patient in groups 3 and 4 achieved a CR. The proportion of CRs

significantly differed between the groups (group 1 vs. 2 vs. 3 vs. 4: 93.1% vs. 50% vs. 0% vs. 0%, $p<0.001$). The last maintenance dose of CAB differed according to the last responses (CR vs. volume response without NP vs. PRL response without TVR≥50% vs. surgery: 1.5 mg/week (1.0–2.0) vs. 4.5 mg/week (2.75–4.5) vs. 2.0 mg/week (1.0–2.0) vs. 0.5 mg/week (0.0–0.7), overall $p=0.006$), but no differences were observed between the four groups according to early responses ($p=0.109$).

Because half of the patients in group 2 eventually achieved a CR, we conducted further analysis of change in PRL levels to identify the distinguishing characteristics of these patients (Fig. 2B). Of the four patients who achieved NP, three patients displayed normal PRL levels at 6–9 months (patients no. 32, 33, and 37), and the remaining patient, who had a giant prolactinoma (patient no. 31; maximum tumor diameter=4.8 cm, tumor volume=20.4 cm3, and PRL level=8759 ng/mL at baseline) maintained a slightly supranormal range of PRL until 15 months (18.6 ng/mL at 9 months and 19.5 ng/mL at 15 months), but displayed NP at 21 months. The median PRL levels did not differ until 3 months between the patients who achieved NP (delayed response subgroup; n=4) and those who did not achieve NP (sustained resistance subgroup; n=4; 1947.4 ng/mL vs. 813.5 ng/mL, $p=0.886$ at baseline; 55.3 ng/mL vs. 115.3 ng/mL, $p=0.686$ at 3 months). However, a meaningful difference in the median PRL levels between the two subgroups could be found after 9 months of CAB treatment (median PRL level=13.0 ng/mL vs. 117.9 ng/mL, $p=0.029$). The median TVR was not different between the subgroups (59.1% vs. 65.3%, $p=0.486$ at 3 months; 81.9% vs. 74.7%, $p=0.200$ at 15 months).

We also attempted to determine whether the absolute value of early TVR itself is predictive of response or whether only a certain cutoff such as 25% is meaningful. The Pearson correlation analysis demonstrated that late TVR had a very strong correlation with early TVR ($R=0.869$, $p<0.001$) according to the following regression equation: late TVR = 0.851 × early TVR + 26.606 (Fig. 3). Last TVR also displayed a correlation with early TVR, although the strength of the correlation was slightly lower ($R=0.785$, $p<0.001$). Multiple regression analysis was subsequently performed using sex, natural logarithm of the CAB maintenance duration between early and late assessment (Ln[weeks]), and the cumulative dose of CAB between early and late assessments (mg) as the independent variables. In this analysis, a greater TVR at the early assessment and a longer CAB maintenance duration were independent predictors for a greater TVR at the late assessment ($\beta=0.849$, $p<0.001$; and β for Ln[weeks]=16.978, $p=0.016$, respectively), whereas sex and the cumulative dose of CAB were not predictive ($p=0.074$ and $p=0.613$, respectively).

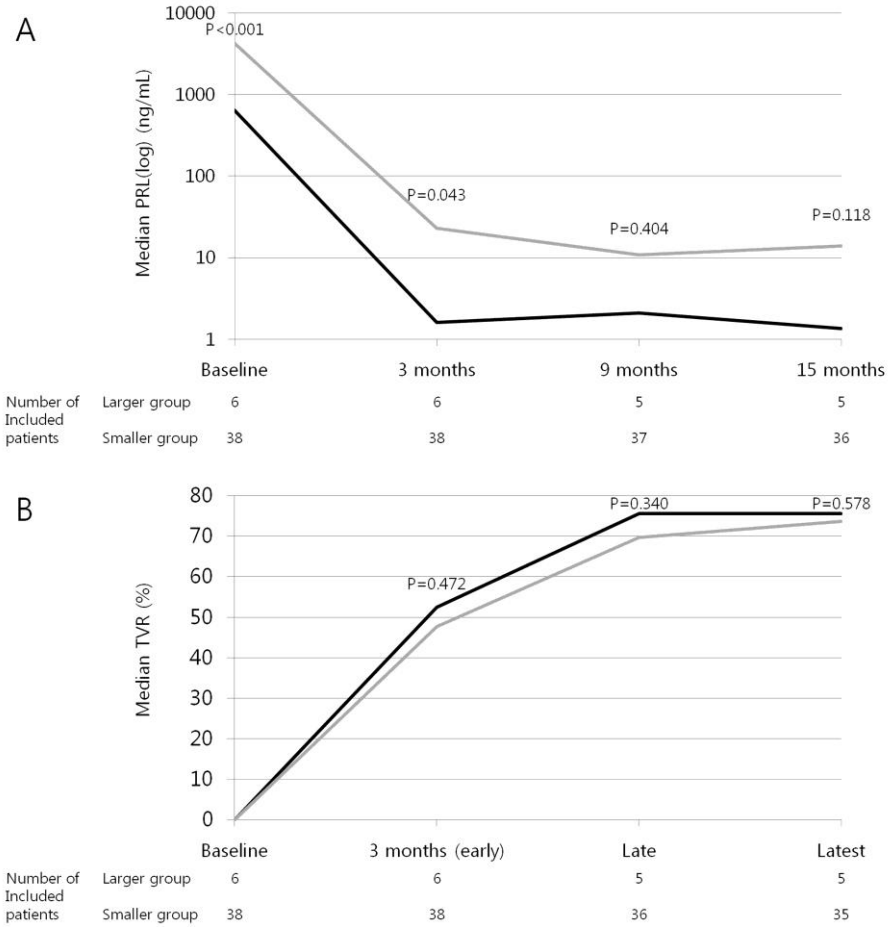

Fig. 1 Changes in PRL levels and TVR in the two groups according to the baseline tumor volume. Black lines indicate patients with larger tumors (larger group); and gray lines, patients with smaller tumors (smaller group). The cutoff between the two groups was a baseline tumor volume of 18 cm^3. Each p value between the groups was calculated at each time point with the Mann-Whitney *U* test. At each time point, the patients who underwent surgery before the assessment were excluded. (A) Changes in the median PRL levels. (B) Changes in the median TVR.

PRL, prolactin; TVR, tumor volume reduction.

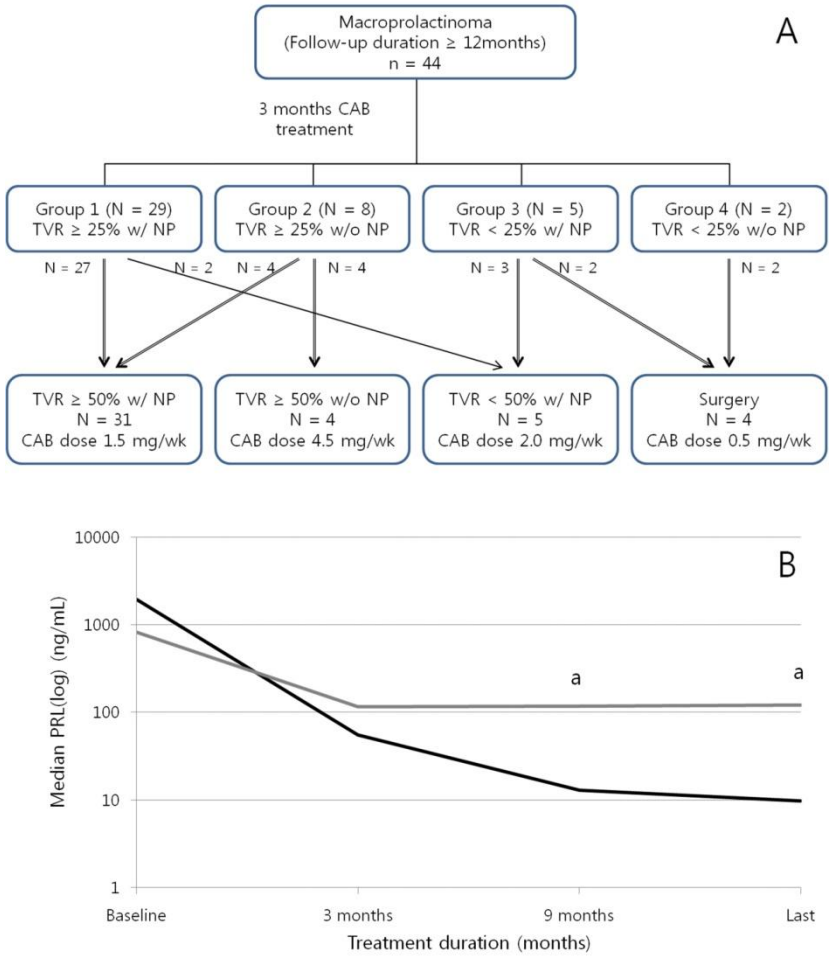

Fig. 2 Fate of 44 patients with macroprolactinomas according to the early response. (A) Overall progress of patients according to categorization by early responses. (B) PRL levels of the patients in group 2. Black line indicates patients who eventually achieved NP (delayed response subgroup); and gray line, patients who did not achieve NP (sustained resistance subgroup).

TVR, tumor volume reduction; NP, normalization of prolactin level; PRL, prolactin.

[a]$p<0.05$ between the subgroups; the p value was calculated with the Mann-Whitney *U* test.

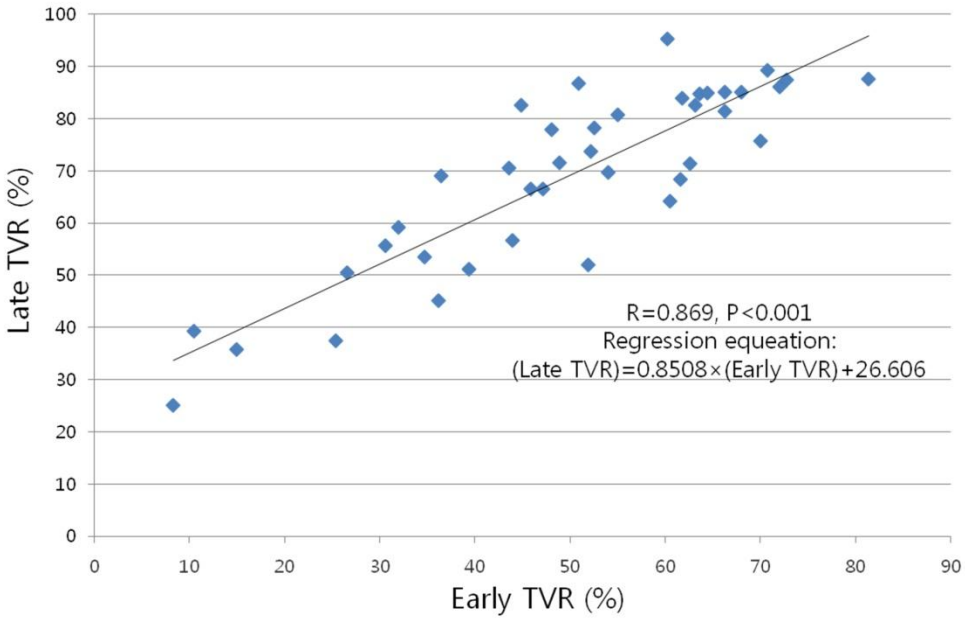

Fig. 3 Correlation between the Late TVR and early TVR.

TVR, tumor volume reduction.

The Pearson correlation analysis was used for statistical analysis.

Table 3. Summary of Patients Who Underwent Surgery

	Patient 38	**Patient 42**	**Patient 43**	**Patient 44**
Age, years	27.5	22.5	51.4	42.2
Sex	M	F	M	M
Cavernous sinus invasion	No	No	Yes	Yes
Visual field defect	Yes	No	Yes	No
Ocular movement Abnormality	No	No	Yes	No
Baseline volume, cm^3	17.67	0.35	22.06	2.34
Baseline PRL level, ng/mL	2042	196.3	2820.5	317.1
TVR at 3 months, %	−3.9	5.7	22.1	-2.1
Preoperative PRL level, ng/mL	0.5	168.6	23.1	699.4
Preoperative dose of CAB, mg/week	3	3	3	3
Reason for surgery	Acute hemorrhage with headache	No change of tumor size	Sustained visual field defect and diplopia	Increased tumor size
Time of surgery, months of treatment	3	12	5	16
Immunohistochemistry	All (−)[a]	PRL (+)	PRL (+)	PRL (+)
Residual tumor on MRI	No	No	No	Uncertain
Last PRL level, ng/mL	7.9	15.3	13.2	393.8
Last CAB dose, mg/week	0.7	0	0	1
Last hormone deficiency	GH/TSH/cortisol	None	Sex/GH/TSH/cortisol	None
Follow-up duration, months	32	15	15	17

PRL, prolactin; TVR, tumor volume reduction; CAB, cabergoline; MRI, magnetic resonance imaging; GH, growth hormone; and TSH, thyroid-stimulating hormone. [a]It was regarded as a false-negative result owing to acute hemorrhage.

4. Influences of surgery on final maintenance dose of CAB

Because the patients who underwent surgery maintained the lowest dose of CAB (Fig. 2A), we sought to confirm whether surgery could reduce the CAB dose independently. Thus, we performed multiple linear regression analysis with four independent variables as follows: undergoing surgery, baseline PRL level (mg/mL), 1/baseline volume (1/cm3), and natural logarithm of the treatment duration (Ln[months]). The baseline volume was transformed reciprocally to ensure linearity of the model. The analysis confirmed that undergoing surgery ($\beta=-1.181$, $p=0.013$), a lower baseline PRL level ($\beta=0.161$, $p=0.008$), a smaller baseline volume (β for 1/baseline volume$=-0.448$, $p=0.026$), and a longer treatment duration (β for Ln[months]$=-0.882$, $p=0.010$) were independent predictors for a lower dose of CAB at the last assessment.

5. Summary of patients who underwent surgery

Four patients underwent transsphenoidal surgery (Table 3; patient nos. 38, 42, 43, and 44). The first patient (patient no. 38) underwent surgery after 3 months of CAB treatment because of acute hemorrhage in the tumor accompanied by severe headache. Immunohistochemical analysis for all pituitary hormones including PRL was negative, but the PRL result was regarded as a false-negative result due to destruction of tumor cells following acute hemorrhage because a nonfunctioning pituitary adenoma could not

explain the patient's extremely high baseline PRL level (2042 ng/mL). His headache was completely resolved after surgery, although he developed panhypopituitarism. His CAB dose was reduced from 3 to 0.7 mg/week, and his serum PRL levels were within the reference range. The second patient (patient no. 43) underwent surgery at 5 months because of a progressive visual field defect and diplopia. Immunohistochemical analysis of the excised tumor revealed PRL immunoreactivity. His symptoms were dramatically improved after surgery, although panhypopituitarism developed. He was able to discontinue CAB with sustained NP, and MRI revealed no residual tumor. The third patient (patient no. 42) underwent elective surgery after 12 months of CAB treatment owing to CAB resistance. Her early TVR was only 5.7%, and her preoperative PRL level was 168.6 ng/mL. Immunohistochemical analysis demonstrated PRL reactivity. She was able to discontinue CAB with sustained NP without a residual tumor. The fourth patient (patient no. 44) also underwent elective surgery after 16 months of CAB treatment due to CAB resistance. His tumor size was increased by 2.1% despite 3 months of CAB treatment, and the tumor size continued to increase after 12 additional months of treatment without NP. Immunohistochemical staining revealed immunoreactivity for PRL. Postoperative MRI could not clearly confirm whether there was residual tumor or only postoperative changes, and PRL levels were not normalized despite surgery. However, the CAB dose could be markedly decreased (from 3 to 1 mg/week) with a partial reduction in her

serum PRL levels (from 699.4 to 393.8 ng/mL).

Overall, none of the patients, including those with (patient nos. 38 and 42) and those without NP (patient nos. 43 and 44), achieved TVR≥25% at 3 months.

The CAB dose was decreased after surgery, and two patients were able to discontinue CAB without residual tumors or PRL elevation.

6. Changes of pituitary hormones and the characteristics of patients without recovery of testosterones

Among the patients who did not undergo surgery, the CAB treatment improved the baseline abnormalities of other pituitary hormones in most of them. All subnormal IGF-1 levels (patient nos. 6, 8, 9, 13, and 24) and secondary hypothyroidism (patient no. 34) were gradually restored. All premenopausal women with oligomenorrhea/amenorrhea demonstrated improvement of symptoms following the reduction of PRL levels, and the subnormal gonadotropin level of one postmenopausal woman was also improved. However, six male patients with NP and two male patients without NP displayed subnormal serum testosterone levels at the last assessment.

To elucidate the early characteristics of patients who could not achieve normalization of testosterone levels despite NP, we compared various clinical parameters of these patients (subnormal group; n=6) with those of male patients with normal testosterone levels and NP at the last assessment (normal group; n=16). Three patients who underwent surgery and one patient who

received exogenous testosterone replacement before the first visit to our institution were excluded from this analysis to minimize confounding factors. The subnormal group had lower baseline IGF-1 (median 112.0 ng/mL vs. 212.1 ng/mL, p=0.013) and testosterone levels (median 57.9 ng/dL vs. 159.4 ng/dL, p=0.010) than the normal group. Although patients in the subnormal group tended to be older (48.4 years vs. 39.8 years, p=0.052), this group had a higher proportion of patients with age-specific subnormal IGF-1 levels (50% vs. 6.3%, p=0.046). The baseline tumor volume, PRL levels, proportion of patients with symptoms related with volume effects, and responses to CAB in terms of TVR and residual volume did not differ between the groups.

IV. DISCUSSION

We described the clinical outcomes of 44 patients with macroprolactinomas who were treated with CAB, and this is the first report of CAB treatment in Korea with a relatively large sample size. Previously, only one article about the efficacy of CAB was reported in Korea [20]. This study concluded that CAB could be effectively used even for invasive giant prolactinoma; however, its sample size was relatively small (n=10), and patients treated with other modalities such as TSA during their treatment courses was excluded. In our study, the CR rate (TVR≥50% with NP) of CAB treatment at the last assessment was 70.5% (total 31/44; group 1: n=27, group 2: n=4). This rate

was not superior to the result of bromocriptine treatment (CR rate=69.4%) that we reported previously, but this appears to have resulted from the shorter follow-up duration (15 months vs. 44 months) [16]. Previous reports of the treatment results of CAB varied widely according to the different inclusion criteria, cutoff of "responsiveness," and treatment duration [1,19,21]. In a retrospective study of 455 patients with hyperprolactinemia, TVR≥50% was noted in 31% of 190 evaluable patients and NP was achieved in 77% of 181 patients with macroprolactinomas after a median of 28 months of CAB treatment [22]. In another retrospective study of 56 de novo patients with macroprolactinoma, a remarkable tumor reduction defined as a ≥30% reduction of the maximal tumor diameter was achieved in 89.1% of patients, and NP was achieved in 82.1% of patients [7]. In a prospective study of 26 drug-naive patients with macroprolactinomas, NP was achieved in 80.7% of patients after 6 months of treatment, the mean volume was reduced by 67.5% after 1 year, and the mean TVR was 92.1% after 3 years of CAB treatment [23]. Our outcomes regarding TVR and NP were in line with the findings of these previous reports.

In our study, we primarily focused on discovering early indicators that could reliably predict the long-term response to CAB. Early identification of CAB-resistant patients is valuable considering the following facts. First, recent large studies of patients with CAB-resistant prolactinomas demonstrated that pharmacological resistance to CAB is associated with more

aggressive disease, the potential risk of malignant evolution, and genetic predisposition to pituitary adenomas [15]. Second, there is a concern about the safety of long-term high-dose CAB treatment in patients with resistant prolactinomas. CAB was found to increase the frequency of valvular heart disease in a dose-dependent manner in studies of patients with Parkinson disease [24-27]. Although many studies indicated that a lower dose of CAB used in the treatment for hyperprolactinemia or prolactinoma was not related with valvular dysfunction [28], some studies reported that the risk of tricuspid valve dysfunction was increased in patients with prolactinomas who were treated with long-term, high-dose CAB regimens [29,30]. Finally, long-term treatment with DAs may cause peritumoral fibrosis, which makes removal of the entire tumor difficult, although it is unclear whether this phenomenon is reproduced with CAB [31,32].

In our study, we determined that grouping patients after 3 months of CAB treatment using the criteria of TVR≥25% and NP was a potentially reliable approach. Groups with TVR≥25% with NP, TVR≥25% without NP, and TVR<25% at 3 months after CAB treatment could be regarded to have early responsiveness, early partial resistance, and early resistance respectively, considering the different long-term CR rates of 93.1%, 50%, and 0%, respectively. We reconfirmed that TVR=25% at 3 months might be a reliable cutoff because TVR at 3 months was very strongly correlated (R>0.8) with TVR at 15 months, and the estimated regression equation revealed that

TVR=50% at 15 months, the cutoff of resistance [11], corresponds to TVR≈25% at 3 months. These results are in line with our previous reports demonstrating that TVR≥25% and NP after 3 months of bromocriptine treatment are useful predictors of the responsiveness to DAs [16].

In addition, patients with early partial resistance should be reassessed after several months to confirm whether they achieved a delayed response. Among patients with TVR≥25% without NP at 3 months, the PRL levels of patients who achieved a CR were lower than those of patients who did not achieve a CR after 9 months. This is similar to the result for bromocriptine treatment, in which three of five patients with TVR≥25% without NP at 3 months achieved NP at 5–9 months [16]. Moreover, patients with giant prolactinomas might require a longer treatment duration to achieve NP than patients with smaller tumors even if the giant tumors have sufficient responsiveness to CAB. Patients with the largest tumors and very high PRL levels displayed higher PRL levels at 3 months, even though they achieved similar TVR rates and PRL levels as patients with smaller tumors after 9 months of treatment. Similarly, in a study of 10 male patients with invasive giant prolactinomas (tumor diameter >4 cm with PRL levels>1000 ng/mL), none achieved PRL levels<15 ng/mL at 3 months, although six patients (60%) exhibited PRL levels<15 ng/mL at the final assessment with continuous CAB treatment [20].

The modality that is most effective for patients with resistance to standard-dose CAB remains unclear. In this situation, high doses of CAB,

transsphenoidal surgery, and occasionally radiotherapy can be applied, and temozolomide therapy can be used for patients with malignant prolactinomas [8,19,21]. Recently, Laurent et al. [15] reviewed the outcomes of 92 patients with resistance to CAB, defined as a failure to achieve NP on a CAB dose of 2.0 mg/week. Of the 17 patients treated with high-dose CAB regimens (≥3.5 mg/week) without surgery, only five patients (26.3%) achieved NP. Surgery had significant usefulness for controlling PRL levels and reducing the CAB dose, whereas radiotherapy did not have a significant benefit. With these results, the authors suggested that surgery could improve the outcomes of patients with CAB resistance [15].

In our study, surgery demonstrated its usefulness for disease control and reducing the dose of CAB. Three of the four patients who underwent surgical interventions achieved complete tumor resolution on MRI with NP even though they had TVR<25% and/or no NP at 3 months. Two patients were able to discontinue CAB early, and multiple regression analysis of all the 44 patients also revealed that surgery could reduce the CAB dose independently. Conversely, a higher cumulative dose of CAB did not alter TVR upon correction for treatment duration. CAB inhibits PRL production in a dose-dependent manner [1], and resistance to DAs is occasionally overcome by high-dose CAB treatment [13,14]. Therefore, guidelines suggest escalating the CAB dose in patients with resistance [8,19]. This difference between our result and previous reports may be due to the relatively narrow range of our CAB dose.

Generally, a CAB dose exceeding 3 mg/week is rarely necessary for prolactinomas [1,8,19], but doses as high as 11 mg/week may be required to overcome pharmacological resistance [13,14]. In our study, the median peak CAB dose was 3 mg/week with an interquartile range of only 1 mg, and this dose may be insufficient to reverse resistance of some patients. However, it is necessary to remember that a marked increase of CAB dose might be associated with cardiac valve disease, as discussed previously.

Another interesting finding was that the baseline IGF-1 level was associated with final restoration of sex hormones. Unlike other pituitary hormones, suppression of sex hormones can be a result of hyperprolactinemia-induced hypogonadism and compression of the gonadotropic cells by the tumors [21]. However, CAB treatment results in normalization or a marked reduction of PRL levels rapidly in most patients, and thus, persistent subnormal sex hormone levels would primarily result from volume effects rather than hyperprolactinemia. In our study, six of the eight nonsurgically-treated male patients with hypogonadism at the last assessment displayed NP; thus, these patients were regarded to have hypogonadism induced by compression. In terms of pituitary hormone deficits induced by tumors, GH deficiency is the second most common deficit after hypogonadism [33-36]. In our study, six patients with persistent hypogonadism despite NP had lower IGF-1 levels at diagnosis than the other male patients, whereas their baseline tumor volume or residual volume after treatment was

not larger. These findings suggest that a low IGF-1 level at diagnosis might be a useful indicator for predicting persistent hypogonadism induced by volume effects, which might not be directly proportional to tumor size itself.

This study has some limitations. First, this study is single center retrospective study, and there were not fully standardized protocol for adjusting dose of CAB and interval of follow-up. For further precise data, prospective study with the preset protocol is warranted. Second, prevalence of adrenal insufficiency might be underestimated, because stimulation tests were not be routinely performed. However, basal pituitary hormone test is used as an important screening test in clinical field, and gonadal function and thyroid function could be properly interpreted with basal hormone test and symptom/signs. So the descriptive data of basal hormone test itself might be somewhat meaningful. Third, our 16 months of follow-up duration might be relatively short to represent the long term response. So, further cumulative data collection with CAB treatment will be able to give us additional information.

V. CONCLUSION

CAB was very effective in two-thirds of the patients with macroprolactinomas. Assessing response using TVR and NP after 3 months of treatment is a useful approach for predicting long-term response and

resistance to CAB. When patients achieve TVR≥25% without NP at 3 months, the assessment resistance should be delayed for several months to rule out a delayed response, especially in patients with large tumors. Surgical treatment can help to reduce the CAB dose with successful disease control, and it should be considered in CAB-resistant patients.

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ABSTRACT (IN KOREAN)

프로락틴 분비 거대선종 환자의 장기적인 카버골린 치료 반응의 초기 예측 지표

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이 영 기

카버골린(Cabergoline)은 프로락틴 분비 선종에 대한 우수한 치료 약제이다. 그러나 일부 환자들은 카버롤린에 대한 저항성을 보이며, 이러한 환자군의 초기 임상적 특성에 대해서 명확히 알려져 있지 않다. 따라서 본 연구에서는 치료 초기에 카버골린에 대한 장기적 반응을 예측할 수 있는 임상적 지표를 규명하고자 하였다. 본 후향적 연구는 카버골린을 초치료로 적용받은 44명의 프로락틴 분비 거대선종 환자를 대상으로 진행되었다. 환자들의 추적 관찰기간의 중위값은 17개월이었으며, 다양한 초기 임상 지표와 장기적인 예후와의 연관성을 분석하였다. 대상 환자 중 약물만으로 치료할 수 있었던 환자는 40명 (90.9%)이었으며, 이들의 종양 크기의 감소율 (TVR)의 중위값은 74.7%이었고, 그 중 36명 (81.8%)의 환자가 혈중 프로락틴의 정상화를 보였다. 최종적으로 완전 반응 (CR; 약물만으로 TVR>50%와 프로락틴 정상화를 보인 경우)을 보인 환자는 31명 (70.5%)이었다. 3개월째의 평가 시점에서 TVR≥25%와 프로락틴 정상화를 보인 환자들의 대부분 (93.1%)은 최종 평가 시점에 CR을 보였으나, 프로락틴의 정상화 없이 TVR≥25%만을 보인 환자들의 경우 절반만이 최종적인 CR을

보였고, TVR<25%에 해당하는 환자의 경우 CR에 이른 사례가 없었다. 3개월째의 TVR 값은 최종 평가 시점의 TVR 값과 유의한 상관관계 (R=0.785, p<0.001)가 있었다. 진단 당시 상대적으로 종양 크기가 큰 환자들은 치료 후 3개월째 프로락틴의 정상화 비율이 낮았으나, 최종 평가 시점에는 TVR과 프로락틴 정상화 비율 모두에서 차이가 없었다. 다중회귀분석 결과 수술적 치료가 카버골린 유지 용량을 줄일 수 있었다 (β=−1.181 mg/wk, p=0.013). 본 결과는, 치료 시작 후 3개월째의 TVR 및 프로락틴 정상화 여부가 장기적인 카버골린 치료 반응에 대한 효과적인 예측 인자가 될 수 있음을 시사한다. 다만 종양 크기가 큰 환자에서는 치료 후 3개월째에 프로락틴 수치 정상화가 없더라도 지연성 반응의 가능성을 고려하여 추가적인 경과를 관찰하는 것이 필요하겠다. 또한, 수술을 통하여 성공적인 질병 조절과 카버골린 용량 감량을 이룰 수 있었기에, 카버골린 저항성을 보이는 환자들에서는 수술을 적극적으로 고려하여야 하겠다.

핵심되는 말 : 카버골린, 도파민, 프로락틴 분비 거대선종, 고프로락틴혈증