

In the Name of God

Journal presenter: Taiebeh Khajehali

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Long-term Follow-up of 84 Patients With Giant Prolactinomas—A Swedish Nationwide Study

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Prolactinomas are the **most common pituitary tumors**, with an annual incidence of 1.6 to 2.2 per 100 000 inhabitants. The tumors are classified, according to maximum diameter, as microprolactinomas (<10 mm) or macroprolactinomas (\geq 10 mm). A subset of patients with macroprolactinomas, termed giant prolactinomas.

Giant prolactinomas account for approximately 2% to 4% of all prolactinomas, are characterized by significant **extrasellar extension**, and are usually defined as a maximum tumor diameter (in at least 1 dimension) of **\geq 40 mm** in association with prolactin (**PRL**) **>1000 μ g/L** and **absence of concomitant** other hormonal secretion.

Macroprolactinomas, including giant prolactinomas, occur predominantly in **men**, in contrast to microprolactinomas, which are more common in women.

Macro- and giant prolactinomas in men are more often **invasive**, have higher Ki-67 and other markers of proliferation, and more commonly demonstrate aggressive growth.

Giant prolactinomas often cause typical symptoms due to hyperprolactinemia such as **hypogonadism** and **galactorrhea**. Because of their large size, the most striking symptoms are caused by the mass effect of the tumor, such as **headache**, visual field defects (**VFD**), other neurological symptoms, and **pituitary insufficiencies**.

Dopamine agonists (DA) are the **first-line** treatment for prolactinomas and lead to inhibition of PRL production and secretion, improved gonadal function, and reduced tumor size.

In a review of 12 studies of 309 patients with macroprolactinomas, including giant prolactinomas, treatment with cabergoline (CAB) was accompanied by normalization of PRL in 80% and significant tumor reduction in 87% of the patients, thus demonstrating a good response to DA even in larger tumors.

In many patients with giant prolactinomas, DAs rapidly reduce tumor size, although with increasing tumor size the proportion of patients achieving normalized PRL decreases. Giant prolactinomas may require **additional treatment** modalities, including surgery, radiotherapy, and/or chemotherapy.

Materials and Methods

The Swedish Pituitary Register (SPR) was established in 1991. It is a nationwide register run by the Regional Cancer Center (Stockholm-Gotland). The SPR collects prospectively registered information of patients with pituitary adenomas, craniopharyngiomas, and cysts. The SPR is organized by a multidisciplinary team of specialists.

Ethics Approval

SPR was approved by the Ethics Committee. Some data were not complete in the SPR, and a separate ethical approval granted by the Swedish Ethical Review Board for the present study allowed us to include missing data from medical records without additional consent.

Study Design and Case Findings

Patients diagnosed with a prolactinoma between December 1991 and December 31, 2018, were identified in the SPR (n = 1897).

The medical records were reviewed by endocrinologists.

A specific form was used to collect information on clinical presentation, PRL concentrations, pituitary function, tumor size, ophthalmologic examination, treatment modalities, maximum doses of DAs, histopathological data (Ki-67, PRL, and other hormonal immunoreactivity), follow-up time, and outcomes of treatment.

The treating physician decided on the DA drug to use, the start dose, and dose adjustments when considered appropriate.

Hormonal Assays and Imaging

Serum PRL and other hormones were analyzed locally with available methods that are in routine use. The serum PRL concentrations, expressed as mU/L, were converted to $\mu\text{g/L}$ by dividing by a conversion factor of 21.2.

Pituitary deficiencies were diagnosed according to the international guidelines. Stimulation tests for GH deficiency were not consistently performed, and thus, the total number of patients with GH deficiency is unknown. Magnetic resonance imaging (MRI) or (CT) was performed at diagnosis and during follow-up.

Follow-up and Response to Therapy

The last follow-up was defined as the last documented PRL or MRI of the pituitary (whichever was the latest). The last documented follow-up was in March 2020.

Normalization of PRL was defined as a serum PRL concentration within the normal reference range for the specific assay used at the last follow-up. The proportion of patients with PRL concentrations $< 2 \times$ upper level of normal (ULN) at the last follow-up was calculated.

Tumor response was defined as a $\geq 30\%$ decrease in the maximum tumor diameter at the last performed MRI, according to the **RECIST** definition. Tumor enlargement was defined as a $\geq 20\%$ increase in the sum of the accessible diameters. A combined response was defined as both normalization of serum PRL and tumor response as described earlier.

Statistical Methods

Statistical analysis was performed using IBM SPSS Statistics, version 26. Data are expressed as the median and interquartile range (IQR) for nonnormally distributed data.

Differences in normally distributed quantitative variables were calculated with Student's t test; otherwise they were calculated by the Mann Whitney U test. Categorical data are presented as absolute numbers or percentages; differences between the groups were evaluated with the chi-square or Fisher's exact test.

Results

Eighty-four patients fulfilled the criteria for giant prolactinoma and were included in the study. There was a male predominance with a male-to-female ratio of **8:1** (Table 1). The mean age at diagnosis was 47 (± 16) years. The median PRL level was 6305 $\mu\text{g/L}$. The hook effect was reported in 2 patients, in year 2001 and 2009, in both cases due to discordance between the PRL concentrations and the clinical and radiological findings. The median of the largest tumor diameter was 47 mm (range 40-85). The extension of the adenomas was assessed according to the SIPAP classification. None of the tumors were classified as carcinomas at diagnosis.

The median duration of symptoms prior to diagnosis was **6 months**, with no difference between sexes ($P = .79$). The most common clinical findings or symptoms at diagnosis were **VFD** (71%), reduced visual acuity (47%), and headache (43%). Spontaneous cerebrospinal fluid (CSF) rhinorrhea was reported in one patient at diagnosis. In 8 patients (10%) the diagnosis was made incidentally on CT or MRI of the brain. **Gonadotropin deficiency** was reported in 84% of the patients (67/80), TSH deficiency in 30% (25/82), and ACTH deficiency in 17% (14/81).

None of the patients had antidiuretic hormone deficiency at diagnosis.

Table 1. Baseline characteristics of 84 patients with giant prolactinoma

	Entire cohort (n = 84)	Males (n = 75)	Females (n = 9)	<i>P</i> -value*
Age (years)	47 (\pm 16)	47 (\pm 16)	52 (\pm 23)	.49
PRL (μ g/L)	6305 (4095-11840)	6277 (4198-11792)	6836 (3969-12812)	.95
Tumor max diameter (mm)	47 (42-55)	47 (43-55)	41 (40-50)	.09
Visual field defects (%)	56/79 (71)	50/70 (71)	6 (67)	.77
Visual acuity impairment (%)	37/79 (47)	36/71 (51)	1/8 (13)	.06
Cranial nerve palsy (%)	7/67 (10)	5/58 (9)	2 (22)	.24
Headache (%)	36 (43)	31 (41)	5 (56)	.42
Galactorrhea (%)	4 (5)	3 (4)	1 (11)	.37
Apoplexy (%)	1 (1)	1 (1)	0	1.0
CSF leakage (%)	1 (1)	1 (1)	0	1.0
Hydrocephalus (%)	2 (2)	2 (3)	0	1.0
Incidentaloma (%)	8 (10)	6 (8)	2 (22)	.20
Pituitary insufficiency				
Gonadotrophin (%)	67/80 (84)	61/74 (82)	6/6 (100)	.26
TSH (%)	25/82 (30)	24/73 (33)	1/8 (13)	.26
ACTH (%)	14/81 (17)	12/72 (17)	2/8 (25)	.65
ADH	0	0	0	

Continuous data are presented as the mean \pm standard deviation or median and interquartile range (Q1-Q3). Categorical data are presented as numbers and percentages, the latter calculated from those with available data.

Abbreviations: ADH, antidiuretic hormone; CSF, cerebrospinal fluid; PRL, prolactin.

*Comparison between sexes.

There was a weak correlation between serum PRL and maximum tumor diameter at diagnosis (Spearman's $r = 0.35$, $P = .001$).

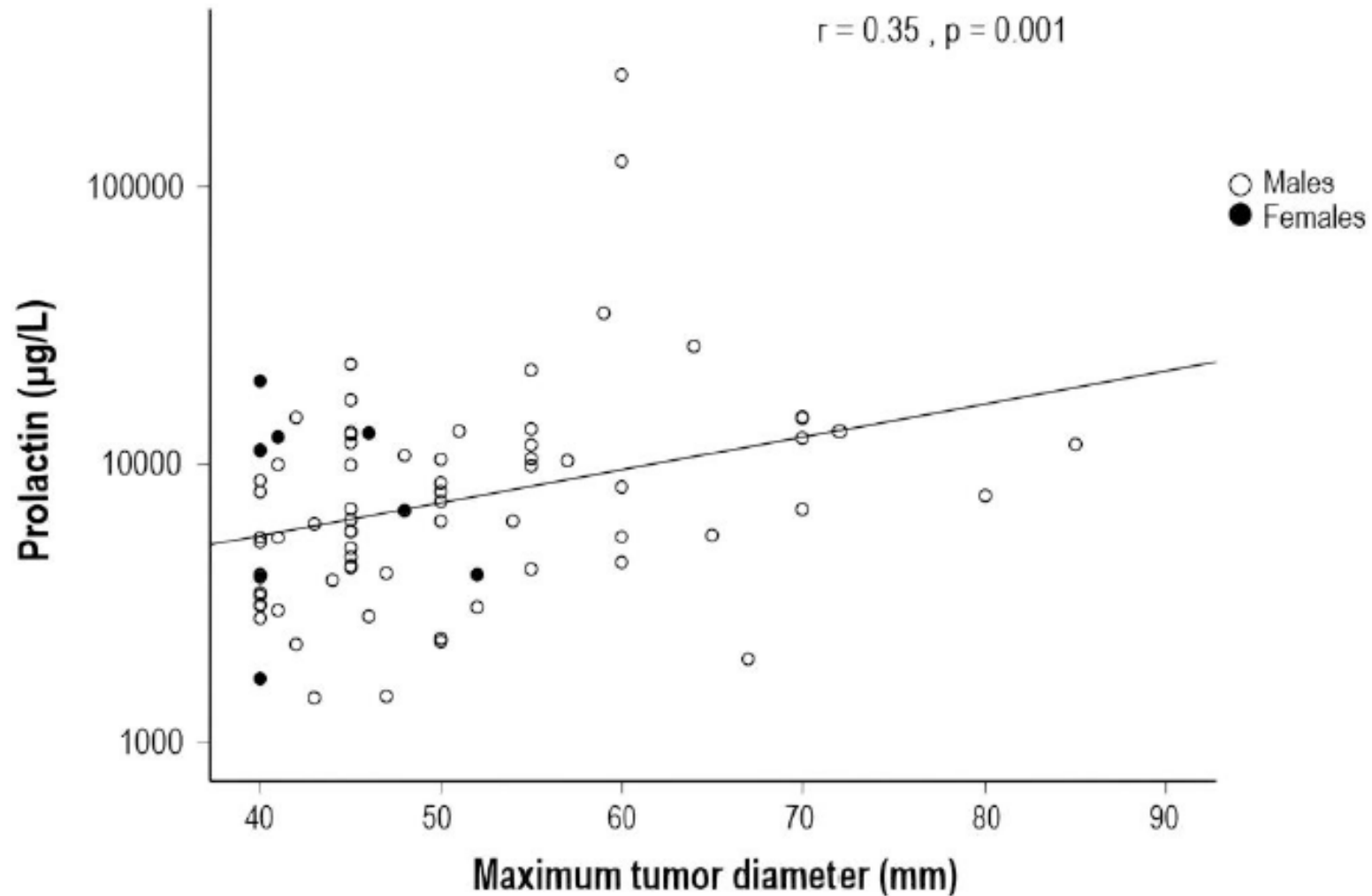


Figure 1. Correlation between PRL and maximum tumor diameter at baseline ($n = 79$), excluding 5 patients with serum PRL > 5000 µg/L but with no information on the exact value. Abbreviations: PRL, prolactin.

Treatment Modalities

All patients were treated with a DA at some point during the study period, either as primary treatment (n = 79) or after initial surgery (n = 5). In the primary DA-treated patients, 23% (18/79) received additional therapy (surgery and/or radiotherapy and/or other medical therapy) after a median time of 14 months (IQR 4-29). In 14 patients, this was due to a **lack of effect** on PRL and/or tumor size, and in 4 patients, it was due to **CSF leakage** during DA treatment.

Nineteen patients (23%) underwent pituitary surgery (13 with transsphenoidal, 6 with transcranial techniques).

The proportion of patients who had surgery was similar over the time period [7/24 patients diagnosed from 1991-2004 vs 12/60 diagnosed from 2005-2018 ($P = .36$)].

Surgery was the primary treatment in 5 patients due to reduced visual acuity, VFD, or pituitary apoplexy. Three patients underwent reoperation. Six patients received radiotherapy [conventional radiotherapy ($n = 4$), gamma knife radiosurgery ($n = 1$), or proton radiation therapy ($n = 1$)]. Additional medical treatments were **anastrozole** ($n = 3$), **pasireotide** ($n = 1$), **temozolomide** (TMZ) ($n = 1$), and **lomustine** ($n = 1$).

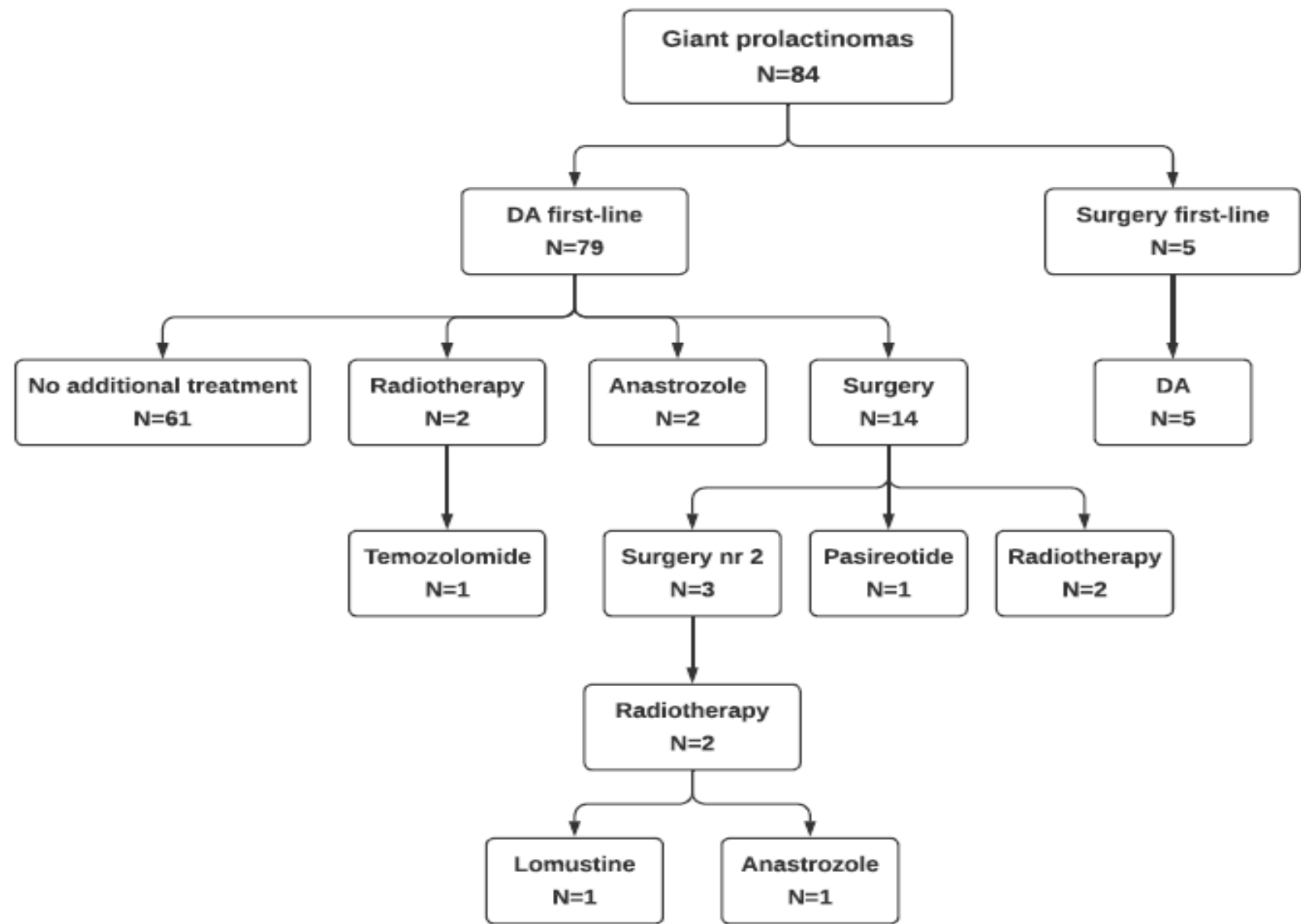


Figure 2. Flowchart of the treatment modalities in a cohort of 84 patients with giant prolactinomas.

The **initial DA was bromocriptine** (BRC) in 60% of the patients (n = 50), CAB in 38% (n = 32), and quinagolide in 2% (n = 2).

During the first time period (1991-2004) the initial DA was BRC in 73% (16/22) of the patients and CAB in 27% (6/22), while from 2005 to 2018 BRC was initially in 57% (34/60) and CAB in 43% (26/60) of the patients ($P=.19$). The median maximum dose of BRC was 5 mg/day (range 1.25-30), for CAB it was 2 mg/week (range 0.25-10.5), and for quinagolide it was 187 µg/day (range 75-450).

Twenty-seven of 50 patients (54%) initially treated with BRC switched to CAB and 1 of 32 patients (3%) from CAB to BRC. At the last follow-up, 79 patients were treated.

with DA, 23% (n = 18) with BRC, 68% (n = 54) with CAB, and 9% (n = 7) with quinagolide.

Compared to the patients treated with DA monotherapy (n = 61), the patients received multimodal treatment [DA + surgery and/or radiotherapy and/or other medical treatment (n = 23)] had **larger tumors** [maximum tumor diameter 55 mm (IQR 45-60) vs 45 mm (IQR 41-52) ($P=.003$)], had higher rates of **VFD** [91% vs 63% ($P= .02$)], and more frequently had **TSH and ACTH deficiency** at diagnosis [50% vs 23% and 33% vs 12% ,respectively ($P= .02$ for both comparisons)].

There were no significant differences in age at diagnosis, sex, or baseline serum PRL concentrations between the 2 groups.

Overall Response to Treatment

The median follow-up was 9 years. At the last follow-up, the median serum PRL was 12 µg/L, with a median decrease in PRL of 99% from diagnosis ($P < .001$). Forty-six patients (55%) had normalized PRL, and 54 (64%) had a PRL level $< 2 \times \text{ULN}$ with no difference between sexes. At the last follow-up, the median maximum tumor diameter had decreased to 22 mm, with a median tumor diameter reduction of 50% ($P < .001$). Tumor response was reported in 58 patients (69%), of whom 16 had complete tumor regression on MRI. Tumor enlargement was in 1 patient. A combined response occurred in 36 patients (43%).

In 49 patients with VFD at diagnosis and available data, an improvement was observed in 82% (n = 40), no change in 14% (n = 7), deterioration in 4% (n = 2).

Among 33 patients with reduced visual acuity at diagnosis, the percentages were 73% (n = 24), 21% (n = 7), and 6% (n = 2).

At the last follow-up, 74% (59/80) had gonadotropin deficiency. At the last, gonadal function recovered in 11 (17%), all in patients were treated with DA monotherapy. Hypogonadism developed in 4 initially eugonadal patients, 2 were treated with surgery and 2 with DA monotherapy.

Forty-six men with hypogonadism received testosterone replacement after diagnosis. After initiating **testosterone** replacement, the serum **PRL increased** in 3 patients. Two of them required a higher DA dose, anastrozole was added in 1, these treatments led to a decrease in PRL in all 3. Two women with hypogonadism (age at diagnosis of 23 and 35 years) received **estrogen** replacement after diagnosis, and in both patients their serum PRL remained **unchanged**.

Table 2. Treatment outcomes at the last follow-up in the whole cohort and in subgroups of patients with DA) monotherapy vs multimodal treatment

	Entire cohort (n = 84)	DA monotherapy (n = 61)	Multimodal treatment (n = 23)	<i>P</i> -value*
Follow-up time (years)	9 (4-15)	9 (4-15)	8 (5-17)	.90
Final PRL ($\mu\text{g/L}$)	12 (4-126)	8 (4-52)	128 (8-1002)	.01
PRL normalization (%)	46 (55)	38 (62)	8 (35)	.02
PRL <2 \times ULN (%)	54 (64)	44 (72)	10 (43)	.02
Tumor max diameter (mm)	22 (3-40)	16 (2-37)	31 (2-43)	.24
Tumor disappearance (%)	16 (19)	12 (20)	4 (17)	1.0
Tumor response (incl disappearance) (%)	58 (69)	41 (67)	17 (74)	.55
Tumor enlargement (%)	1 (1)	0	1 (4)	.27
Combined response (PRL normal and tumor response) (%)	36 (43)	29 (48)	7 (30)	.16
Visual fields defects				
Improved (%)	40/49 (82)	25/30 (83)	15/19 (79)	.70
Deteriorated (%)	2/49 (4)	0/30	2/19 (11)	.15
Pituitary insufficiency				
Gonadotrophin (%)	59/80 (74)	39/58 (67)	20/22 (91)	.03
TSH (%)	36/83 (43)	20/60 (33)	16 (70)	.003
ACTH (%)	19/82 (23)	8/59 (14)	11 (48)	.001
ADH (%)	3/83 (4)	0/60	3 (13)	.02

DA Monotherapy

In 61 patients treated with DA monotherapy, the median serum PRL level decreased from 6274 $\mu\text{g/L}$ to 8 $\mu\text{g/L}$ at the last follow-up ($P < .001$) and tumor diameter decreased from 45 mm to 16 mm ($P < .001$). The combined response was 48% ($n = 29$).

Thirty-nine patients treated with DA monotherapy were on CAB at last follow-up; among them PRL normalized in 56% ($n = 22$). In this group, the median weekly dose of CAB was 1.5 mg compared to 3.0 mg in the patients with nonnormalized PRL ($n = 17$) ($P = .15$).

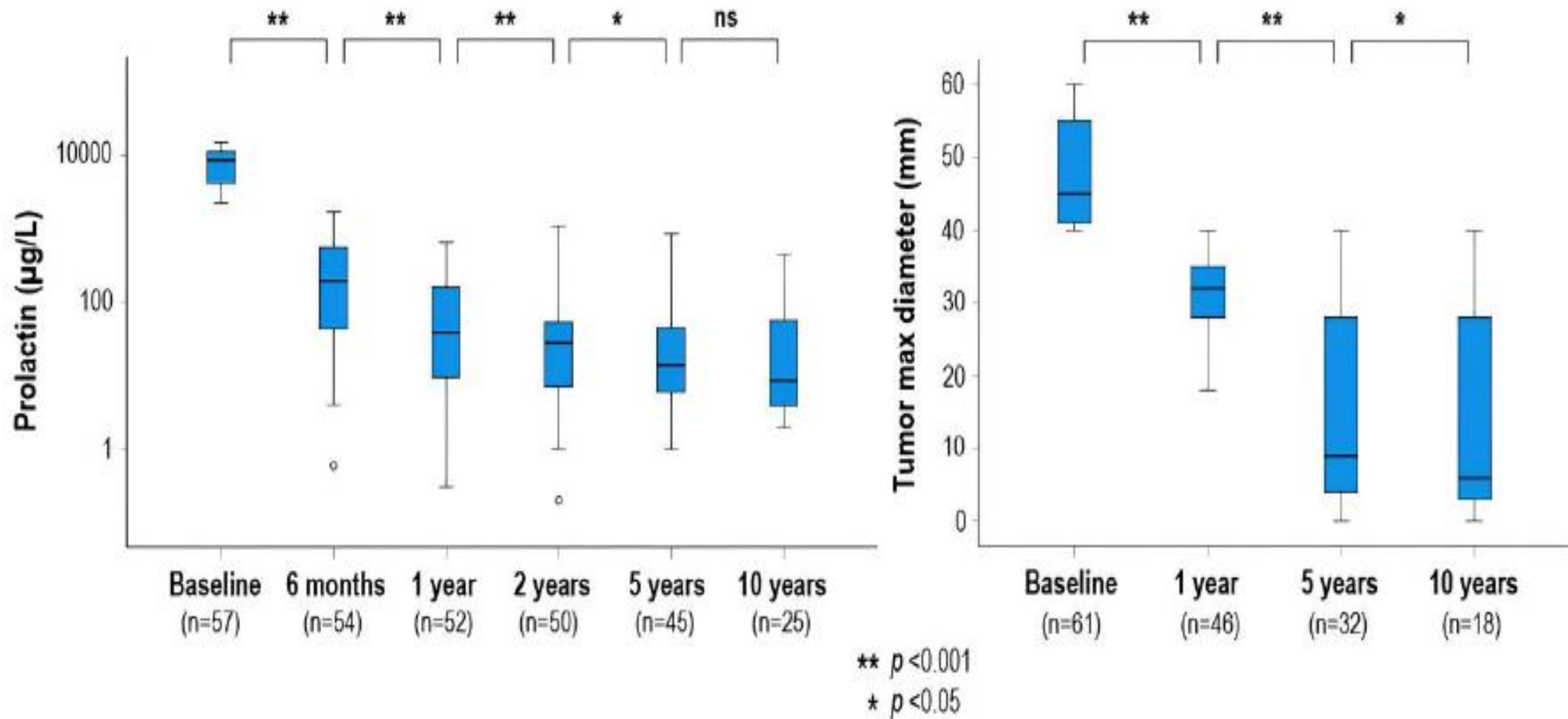


Figure 3. PRL and maximum tumor diameter over time in 61 patients with giant prolactinoma treated with dopamine agonist monotherapy, excluding 4 patients with serum PRL >5000 µg/L at baseline but with no information on the exact value. Abbreviations: PRL, prolactin.

Among patients who received a CAB, 36% (n = 12) were DA responders (normalized PRL with CAB <2 mg/week), 30% (n = 10) had partial DA resistance (normalized PRL with CAB \geq 2.0 mg/week), and 33% (n = 11) had **DA resistance** (elevated PRL despite CAB \geq 2.0 mg/week).

In 2 patients achieving PRL normalization and complete tumor regression after a total treatment period of 3 and 21 years, respectively, DA (BRC and CAB, respectively) was discontinued. At the last follow-up, 6 and 36 months after DA withdrawal, PRL remained normal.

DA Monotherapy vs Multimodal Treatment

The patients who received multimodal treatment (n = 23) had higher median PRL ($P = .01$) and lower rates of PRL normalization ($P = .02$) at the last follow-up than the patients with DA monotherapy (n = 61).

Patients who received multimodal treatment had higher rates of pituitary deficiencies [hypogonadism ($P = .03$), hypothyroidism ($P = .003$), hypocortisolism ($P = .001$), diabetes insipidus ($P = .02$)] at the last follow-up.

Immunohistochemistry and Ki-67 Index

Immunohistochemical analysis of the tumors was available in 16/19 patients who underwent surgery.

PRL immunoreactivity was demonstrated in 15 tumors (1 was not analyzed due to technical problems). The median value of Ki-67 was 4.5%. The highest value at 40%, and the second highest value was 15% in 2 patients. Eight tumors had $Ki-67 > 3\%$, 4 had $Ki-67 \geq 10\%$. There was no difference in the median maximum tumor diameter at diagnosis in the tumors with $Ki-67 > 3\%$ compared to the tumors with $Ki-67 \leq 3\%$ [54 mm vs 58 mm, ($P = .74$)]. **None** of the 8 patients with **$Ki-67 > 3\%$** achieved a **combined response** at the last follow-up, whereas 4 of the 6 patients (67%) with tumor $Ki67 \leq 3\%$ did ($P = .02$). Three patients fulfill the definition for aggressive pituitary tumors [invasiveness and rapid growth despite standard treatment (DA, surgery, radiotherapy)].

Prediction of Treatment Response

In patients treated primarily with DA (n = 79), reduction of serum **PRL to <2×ULN** or reduction of the maximum tumor diameter by **20%** after the **first year** of treatment were both associated with a combined response at the last follow-up [both univariate and multivariate analyses].

Age, sex, VFD at diagnosis, and multimodal treatment were not associated with a combined response. PRL levels, maximum tumor diameters at diagnosis, and multimodal treatment did not predict combined response at the last follow-up.

Table 3. Multivariate analysis of the variables associated with combined biochemical and tumor response at the last follow-up in patients with primary dopamine agonist treatment (n = 79)

	OR (95% CI)	<i>P</i> -value
Initial serum PRL	1.00 (1.00-1.00)	.66
Initial max tumor diameter	0.98 (0.89-1.1)	.62
Multimodal treatment	0.21 (0.02-1.9)	.16
PRL <2xULN at year 1	30.5 (4.9-189.8)	<.001
Reduction of max tumor diameter \geq 20% at year 1	14.8 (1.8-122.9)	.012

Abbreviations: CI, confidence interval; OR, odds ratio; PRL, prolactin; ULN, upper level of normal.

Discussion

Giant prolactinomas are rare, and treatment can be a challenge in some patients. In this study of 84 patients, most of the patients had a good outcome of treatment, with long-term normalization of PRL achieved in over half of the patients and a significant tumor response in almost 70%. The largest decrease in PRL levels occurred during the first year of DA treatment, and the long-term combined response was predicted by the effect after the first year of treatment.

Most of the patients were treated with DA monotherapy, but approximately **1 in 4** needed **additional therapy**, mainly pituitary surgery.

A large majority of the patients in the current study were men, and the most frequent symptoms at diagnosis were related to the mass effects of the tumor, such as **visual problems** and **headache**, and these results are in line with the findings in smaller cohorts of giant prolactinomas.

In our study, 1 out of 10 patients were discovered incidentally on a brain CT/MRI that was undertaken for other reasons. Similar rates of incidentally diagnosed giant prolactinomas were observed in other studies, indicating slow growth of the tumors over many years.

In patients with prolactinomas, there is a correlation between PRL levels and tumor size at diagnosis, an association that seems **less evident** in **giant prolactinomas** ($r = 0.24-0.63$).

This is consistent with our study where a weak correlation between PRL levels and baseline maximum tumor diameters ($r = 0.35$). When a patient presents with very high PRL levels, the diagnosis of a prolactinoma is evident.

A discrepancy between tumor size and PRL levels warrants serial dilutions of PRL to exclude the “**hook effect**”. This was reported in 2/84 patients in our study, which is similar to other studies that reported the hook effect in 1/71 and 2/34 patients with giant prolactinomas, respectively.

The overall **treatment goals** for prolactinomas are normalized PRL levels; recovery of gonadal, pituitary, and visual functions; and reduction of tumor size. In some patients with prolactinomas, these goals are not possible to reach, and the primary focus should be on tumor control and relieving compressive symptoms.

In our cohort, PRL normalized in 55% of the patients, and a tumor response was seen in 69% of the patients. Accordingly, the normalization rate of PRL in giant prolactinomas treated with multimodal therapy in other studies was 44% to 65%.

DAs are recommended as primary treatment in prolactinomas, even for giant tumors with compressive symptoms. This is due to the potent effects of DAs, which in many cases can induce tumor shrinkage and relieve neurological symptoms within a few days. In addition, complete surgical resection is rare.

A complication of DA treatment is **CSF leakage** due to rapid tumor shrinkage. In our cohort, 4 patients (5%) developed CSF leakage during treatment with DAs, which led to additional treatment with temporary or permanent withdrawal of DAs. Other studies of giant prolactinomas have reported CSF leakage in 0% to 10% of patients.

In the current study, a reduction in PRL to $<2 \times \text{ULN}$ or tumor size by 20% in the first year of follow-up predicted a combined response at the last follow-up. This adds to the findings of a previous study where PRL reduction at the **first month of BRC** treatment significantly correlated with the nadir PRL at long-term follow-up.

Our result of the response to DA treatment is of clinical value. Thus, if a reduction in PRL or tumor size **has not been obtained 1 year after initiation** of DA treatment, a further decrease in PRL and/or tumor size may be protracted and/or insufficient, and in these patients a more thorough follow-up or multimodal treatment is warranted.

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In our patients treated with DA monotherapy, PRL normalized in 62% of the patients, and there was a significant tumor response in 67%. In a review of 13 studies including 97 patients with giant prolactinomas primarily treated with DA, 60% had normalized PRL levels (ranging from 17% to 100% in different studies) and 74% had a significant tumor response.

The responsiveness to DA appears to be similar in men and women, and in concordance we did not observe any differences between sexes. In our study, 20% of the patients treated with DA monotherapy had no visible tumor on MRI at the last follow-up. This is in line with one study that reported tumor disappearance in 25% of 38 patients treated with DA monotherapy

The duration of DA treatment in patients with giant prolactinomas is expected to be **life-long** due to the potential risk of rapid tumor regrowth if therapy is discontinued.

In a case series, a successful withdrawal of DA was reported in 1 patient with a giant prolactinoma treated with DA monotherapy; the patient had an elevated ACTH level and possibly a mixed tumor. In 1 study, 2 out of 71 patients with giant prolactinomas maintained normal PRL and tumor response after DA withdrawal, but it's unclear these patients had received DA monotherapy or multimodal therapy. Two patients in the current study could discontinue DA treatment with maintained normoprolactinaemia.

Withdrawal of DA treatment in patients with giant prolactinomas should be an exception, and discontinuation of DA necessitates close surveillance of PRL and tumor size.

DA resistance is failure to normalize PRL levels with CAB doses from ≥ 2.0 mg per week and, in macroprolactinoma, failure to achieve tumor size reduction of 30% to 50%.

Resistance to CAB is more frequent in macro compared to microprolactinomas (15-20% vs $<10\%$). In our cohort, was one-third of the patients. In a review of patients with giant prolactinomas with primary DA, 24% (18/76) were resistant to DA (**daily dose of ≥ 15 mg BRC or a weekly dose of ≥ 2 mg CAB**) ; was similar to our study.

The DA dose escalation was at the treating physicians' discretion, it cannot be excluded that use of higher DA doses might have reduced the number of patients resistant to DA. In this study, it was not possible to evaluate resistance to BRC due to a switch to CAB in more than half of the patients.

The main hormonal consequence of hyperprolactinaemia is hypogonadotropic hypogonadism. In our study most of the patients had hypogonadotropic hypogonadism at diagnosis, but only 17% had recovered their gonadal axis at the last follow-up. This is similar to data reported in other studies of giant prolactinomas but differs from a small study in which a recovery of gonadal function was reported in 67% (8/12).

Persistent hypogonadism despite a normalization of PRL obtained with DA may be the **result of suppression of gonadotropins by longstanding hyperprolactinemia** in combination with the **mass effect** of the tumor on normal pituitary tissue.

In the current study, 85% of the males had testosterone replacement, which continued throughout the follow-up. Since withdrawal of testosterone replacement in general was not attempted, we cannot exclude that resumption of gonadal function had occurred in some men.

Testosterone aromatizes to estradiol, which might lead to **lactotroph hyperplasia** with an entailing increase in PRL and tumor size. In our cohort, an increase in PRL was seen in 3 men after initiation of testosterone replacement and was addressed by an increased DA dose and/or by addition of the antiestrogen anastrozole. The initiation of replacement with sex hormones should be done with caution while **monitoring PRL**.

Pituitary surgery in giant prolactinomas is considered for the subset of patients with acute compressive symptoms due to pituitary apoplexy, progressive tumor growth, or visual deterioration not controlled with DA, as well as intolerance to DA treatment.

In the present cohort, surgery was performed in 6% of the patients as primary treatment and in 17% after the initial DA treatment. In the literature, the rates of surgery in giant prolactinomas vary considerably, between 13% and 62%.

In our cohort, none of the patients who underwent surgery had normalized PRL postoperatively, and all needed additional treatment. In a study of 42 patients with giant prolactinomas, 48% (13/27) of the patients treated with BRC as primary treatment normalized PRL levels, in contrast to none who were primarily treated with surgery (n = 14).

At surgery, tissue for immunohistochemical analyses becomes available. In 2 studies of giant prolactinomas, the median Ki-67 was 2% and 5%.

Six patients in our cohort received radiotherapy: 4 patients after surgery and 2 after DA. Three of these patients needed additional medical therapy after radiation. The risk of developing **pituitary insufficiencies** after radiotherapy and the **long duration** until a full effect is achieved are the disadvantages of radiotherapy. Radiotherapy is an option due to its effect in controlling tumor growth.

In our cohort, other adjuvant medical treatments were used in 6 patients (anastrozole, temozolomide (TMZ), lomustine, and pasireotide).

TMZ is an **oral alkylating agent**, that has been recommended in the last decade as the first-line chemotherapy in the treatment of locally aggressive or malignant prolactinomas.

In a study of 171 aggressive pituitary tumors and pituitary carcinomas, including 54 prolactinomas, tumor shrinkage was reported in 40% of 156 patients treated with TMZ.

In patients with giant prolactinomas not responding to DA, and additional treatment should be discussed in a multidisciplinary team.

The **limitations** of the study are the retrospective design and the inborn issues, such as not having a predefined study protocol and missing data. On the other hand, our study reflects a real-life setting for this patient group. Other limitations are the use of different biochemical assays and lack of uniform re-evaluations of pituitary function.

The **strengths** of our study are the large sample size, unselected nationwide cohort, long follow-up time, and detailed evaluation of each patient by experienced endocrinologists.

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Conclusion

In this study of a large cohort of patients with giant prolactinomas followed for a median of 9 years, treatment with DAs was effective and sufficient as monotherapy in most patients, and DAs could be withdrawn in 2 patients.

A quarter of the patients needed additional treatment, mainly surgery, and 2 of 84 had an aggressive tumor course requiring chemotherapy. The decrease in PRL and tumor size after the first year of treatment predicted the long-term combined response.

The study emphasizes the heterogeneity of these tumors and suggests that treatment response after 1 year can be useful for identifying patients who need a more careful follow-up and, in some cases, additional treatment.

THANKS FOR YOUR ATTENTION