ADDITIONAL EFFECTS OF RADIOTHERAPY TO DOPAMINE AGONISTS IN THE TREATMENT OF MACROPROLACTINOMAS

M. Coculescu*[,1,2], Rodica Anghel[3], C.Badiu[1,2], Andra Caragheorgheopol[1,2], D.Hortopan[2], Anda Dumitrascu[2], Ioana Virtej[1], Raluca Trifanescu[1], Cristina Capatana[2], Daniela Voicu[1]

[1] Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[2] "C.I.Parhon" Institute of Endocrinology, Bucharest, Romania

[3] "N. Trestioreanu" Institute of Oncology, Bucharest, Romania

INTRODUCTION: The aim of our study was to evaluate the cure rate of macroprolactinomas treated for a long term (> 4 years) or a short term (<4 years) with dopamine agonists (DA) alone or combined with radiotherapy (RT). Sometimes pituitary surgery was performed.

MATERIAL AND METHODS: We performed a retrospective study in 111 patients with macroprolactinomas, hospitalized in the Institute of Endocrinology, Bucharest, between 1978-2005. There were two groups, according to the length of DA therapy: group A =41 patients, treated more than 4 years and group B =70 patients, treated less than 4 years. Overall, 25 patients underwent additional radiotherapy, 13 in group A and 12 in group B. 28 patients were submitted to pituitary surgery, 9 in group A and 19 in group B.

RESULTS: The cure rate (i.e. normalization of prolactin=PRL level and absence or minimal residual tumor mass, stable minimum 2 years after DA withdrawal) was 5/41 (12.1%) in group A and none in group B. 48 out of 111 patients achieved significant improvement (serum prolactin level less than 20 ng/ml and tumor shrinkage more than 50%) during DA therapy, but not after DA withdrawal: 17/41patients (41.5%) in group A and in 31/70 patients (44.3%) in group B, p=NS. Radiotherapy produced an additional improvement: in serum PRL levels only in group A, in 4/13 patients- 2/8 patients responsive to DA therapy and 2/5 patients resistant to DA therapy. In group B, the 3 patients resistant to DA submitted to radiotherapy were evaluated before the interval necessary for maximal effect of radiotherapy, but in 4/9 patients responsive to DA, we noticed further reduction in tumor volume, 2/4 progressing from mild to significant tumor shrinkage and ¼ progressing from no shrinkage to mild shrinkage. After radiotherapy, the medium prolactin level was 5.1 ng/ml in 10 patients from both groups on low bromocriptine (BRC) dose (7.5 mg/day), significantly less than in patients without radiotherapy, i.e. than in 19 patients from group A

*Correspondence to: Mihail Gr. Coculescu, Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, 34-36 Bd. Aviatorilor, Code 011863, Bucharest, Tel/Fax: + 4021 3198718, e-mail: m.coculescu@uni-davila.ro

Acta Endocrinologica (Buc), vol. I, no. 1, p 41-57, 2005

(serum PRL 49.5 ng/ml, p=0.02) and in 29 patients from group B (serum PRL 30.3 ng/ml, p=0.01). So, the daily BRC dose could safely decrease from 30 mg/day to 7.5 mg/day in those patients previously submitted to radiotherapy.

Among 23 patients resistant to initial DA treatment, only 8 patients were submitted to radiotherapy, 2 became responsive to DA thereafter and 2 others obtained a significant decrease of prolactin levels.

CONCLUSIONS: The overall cure rate is quite low in prolactinomas and it was noticed only after long-term treatment with dopamine agonists; it was improved up to 12.1% by the additional high voltage radiotherapy, useful even in DA resistant cases. The addition of radiotherapy is indicated for the cure of most prolactinomas.

Key words: prolactinoma, radiotherapy, cure, dopamine agonists.

INTRODUCTION

There is a large agreement about the efficacy of dopamine agonist administration as primary treatment for the majority of macroprolactinomas, being successful in 75% of cases, reducing tumor size and restoring normal serum prolactin levels (1, 2). The evaluation of withdrawal effect is often disappointing (1) even with rapid reexpansion of tumor mass (3). A number of macroprolactinomas are resistant to all dopamine agonists, even when using cabergoline (CAB) instead of bromocriptine (BRC) (4), or using very high doses of dopamine agonists. Additional surgery or radiotherapy could be necessary for improving the cure rate of prolactinomas**.**

The aim of our study was to evaluate the cure rate of macroprolactinomas treated with dopamine agonists (DA) therapy alone or in association with radiotherapy. DA treatment duration was either long (over 4 years), or short (below 4 years). In addition, we assessed the effects of the high dose BRC as compared with the low dose. The effect of high voltage radiotherapy upon the resistance to dopamine agonists was also evaluated. Pituitary surgery did not produce additional improvement in our series.

SUBJECTS AND METHODS

A retrospective study was performed in 111 patients with macroprolactinomas, hospitalized in "C.I.Parhon" Institute of Endocrinology, Department of Neuroendocrinology, between March 1978 and March 2005 (27 years). The studied subjects (N=111) were divided in two groups, according to dopamine agonists treatment duration: 41 patients treated more than 4 years (Group A) and 70 patients treated less than 4 years (Group B) as shown in Table 1.

In Group A (N= 41 patients) there are 30 women, aged 14-57 years (38.8 ± 2.59 years) and 11 men, aged 33-73 years (40.4 ± 4.31 years).

In Group B (N= 70 patients) there are 38 women, aged 18-59 years (38.3 ± 2.14 years) and 32 men, aged 15-72 years (38.9 ± 2.4 years).

Table 1. Characteristics of cases in groups A and B

		Group A (N=41)		**Group B (N=70)**	
	Sex ratio F/M	30/11		58/12	
	Parameter	Mean ±SEM	Range	Mean±SEM	Range
	Age	39.5±2.3	16-73	38.9±1.6	17-72
DA± surgery Gr. A:N=28 Gr. B:N=58	Initial PRL (ng/ml)	1203.9±393.9	71-9328	1637.6±360	42-16000
	Therapy duration (months)	99.9 ±13	19-264	21.4 ± 1.5	3-48
	Follow-up (months)	127.3±14.6	48- 264	28.3±1.9	9-48
RT+DA ±surgery Gr. A: N=13 Gr. B: N=12	InitialPRL (ng/ml)	1468.4±708.6	90-9790	744.9±197.4	157-2330
	Therapy duration (months)	133.2±21	56-259	23.3±3.2	7-44
	Follow -up (months)	140.5±25.7	60-276	28±4.2	12-60

The diagnosis of macroprolactinoma (tumor diameter > 10 mm) was established according to Melmed (2). Clinical history, physical examination, serum PRL, other pituitary hormone assessments, visual field testing and tumor size evaluation by pituitary CT or MRI scan were recorded in all patients.

CT scans or MRI evaluated the tumor size during the follow-up period. Before 1982, in 28 patients, the initial radiographic evaluation was made by fractionated pneumoencephalotomography.

Radioimmunoassay, rapid fluoroimmunoassay with Europium or immunochemiluminescence, was used for assessment of serum prolactin level. A similar schedule was used in all patients, consisting of serum PRL measurement at baseline, one month after starting therapy and then every six months. For any given clinical end point, the most recent values of serum PRL level and pituitary tumor volume were reported.

Visual field was evaluated by Goldman perimetry and computerized. Abnormalities were noted initially in 31 out of 111 study subjects (20 men/11 women).

During DA therapy, 13 women became pregnant. The medical therapy was usually continued along the whole gestation period as was communicated elsewhere (5).

The methods of antitumoral therapy are shown in Table 2.

Table 2. Modalities of therapies in groups A and B

Therapy	Group A	Group B
DA	28(3)	58(0)
DA+RT	13(2)	12(0)
Total	41(5)	70(0)

Incomplete pituitary surgery was performed in several cases of each subgroup; the number of cured patients are in parenthesis.

Medical therapy

Dopamine agonists used for the medical treatment of prolactinomas were Bromocriptine (Parlodel-Sandoz, Bromocriptine - ICCF Romania, or Bromocriptine- Biofarm) and Cabergoline (Dostinex- Pharmacia & Upjohn). 101 patients received only Bromocriptine and 10 patients received also Cabergoline, between 1 mg/week and 7 mg/week.

In 92 patients, the dose of BRC administered was initially 30 mg/day and in 19 patients 7.5 mg/day, for at least 6 months each one. In order to compare the efficacy of high dose BRC with low dose in 48 patients responsive to DA, the alternative BRC dose was administered at least 2 times along two years.

Radiotherapy

High voltage conventional radiation therapy was applied to 16 patients, 6 in group A and 10 in Group B, using a linear accelerator of 180 MeV.

The total dose administered to the defined treatment volume was 50Gy (54Gy for masses larger than 2cm), in daily fractions of 1.8-2 Gy.

Most often, a three portal arrangement has been used, but, in some cases, the technique included two fixed parallel-opposed fields, which yields to poor isodose distribution.

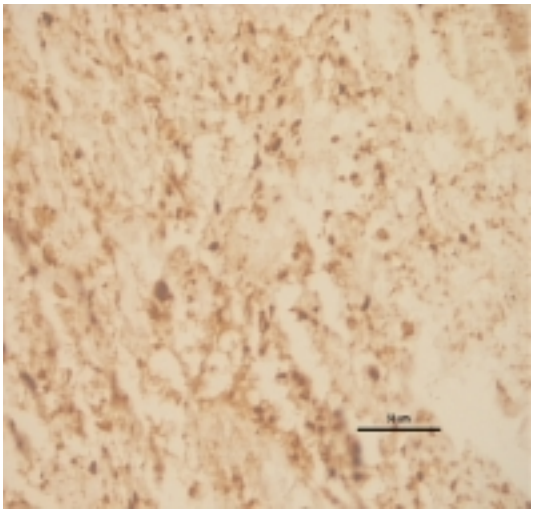
The treated volume included the pituitary fossa and adjacent tissues, as determined by evaluation of the adenoma extension by CT. Special care was taken to avoid irradiation of the optic pathways. Accuracy increased even more for the cases treated between March 2003 and March 2005, when conformal 3D treatment based on CT simulation has been used.

Conventional low voltage roentgen therapy was performed in 9 patients: 7 from group A and 2 from group B.

Surgery

Surgery was indicated in 28 cases, applied in 8 cases via transsphenoidal approach, in 17 cases via transfrontal route and 5 patients were submitted to reiterative intervention. A number of 26 patients were diagnosed as prolactinomas after pituitary surgery, were not cured and therefore started the DA treatment after surgery. In patients submitted to surgery the diagnosis was confirmed by immunocytochemistry (Fig. 1), using avidin-biotin method, as described elsewhere (6).

Figure 1. Immunocytochemistry positive for PRL; ×400. Tumor fragment from a macroprolactinoma in a 28 year-old male.



Criteria of efficiency

Previously published criteria of efficacy (7) were used, i.e.: a) cured - serum PRL<20ng/ml after DA withdrawal and absence or a minimal residual tumor mass stable for minimum 2 years; b) significant improvement - serum PRL<20ng/ml during DA therapy and tumor shrinkage =50%; c) mild improvement- cases with normoprolactinemia (less than 20 ng/ml) during DA therapy and the tumor mass reduced only with 20%-50%; d) resistance to DA therapy - was considered the lack of PRL normalization after a minimum of 6 months of treatment with high dose of DA, 30 mg/day bromocriptine or 3 mg/week cabergoline, with or without significant tumor shrinkage (>50%).

Statistical analysis

Data are presented as the mean ± SEM. Chi^2 test and Student's t test were performed where appropriate, with $P < 0.05$ considered significant.

RESULTS

In group A (N=41), 32 patients responded to BRC therapy and 9 were resistant to bromocriptine (7 resistant also to cabergoline). Significant improvement (including cured patients) was obtained in 22/32 patients (68.8%), under combined therapeutical methods and mild improvement in 6/32 patients (18.8%), as are shown in Figs. 2, 3 and Table 3.

The tumor mass has disappeared in 6 patients of group A on CT and MRI and 5 of them have been cured, with normal PRL level after 24-84 months of DA withdrawal. In two cases, post-therapeutical CT assessment was unavailable.

Table 4 shows the characteristics of patients resistant to DA (BRC or CAB), using the highest dose (up to 30 mg/d BRC and up to 3 mg/wk CAB) at least 6 months. Resistance was noticed in 9 patients in group A, 9/41 (22%), similar to the rate in group B, in which were 14/70 (20%), p=NS.

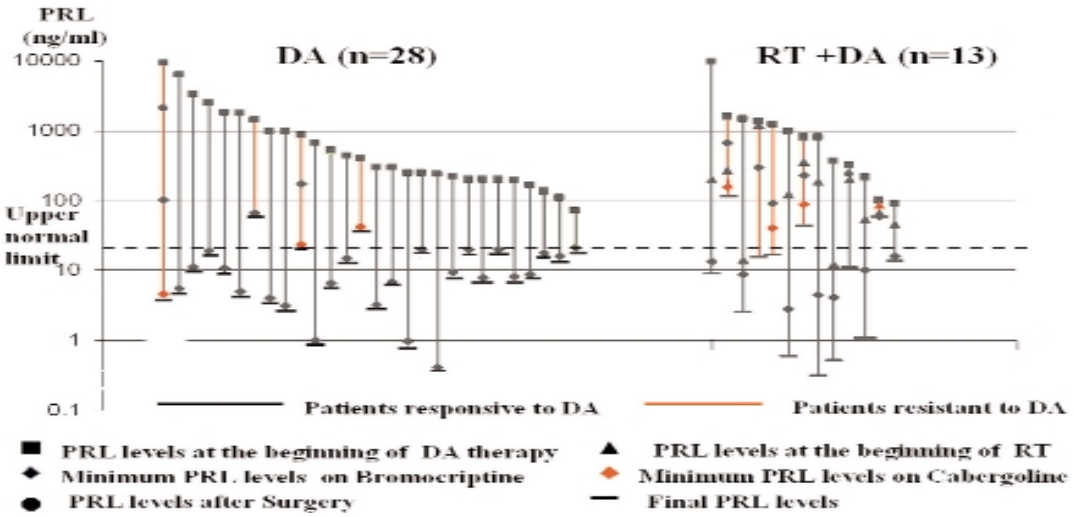


Figure 2. PRL levels under combined therapy in group A
(follow-up and treatment lasting more than 4 years).

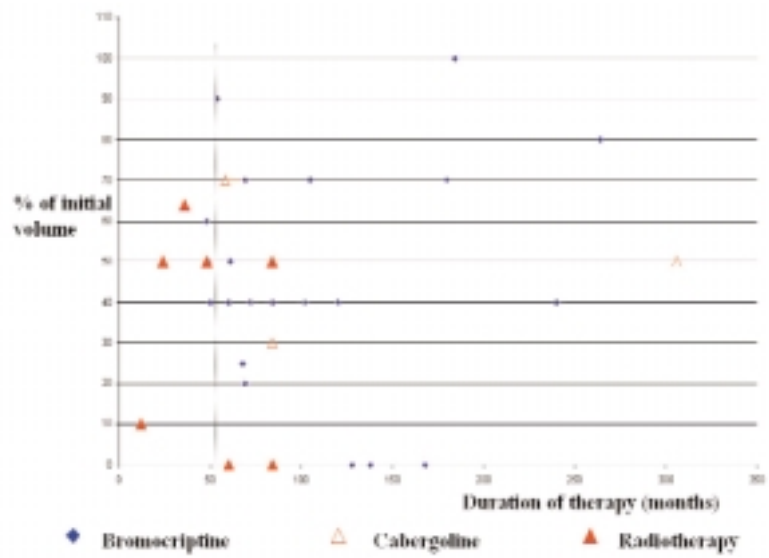


Figure 3. Tumor shrinkage in group A (there are 32 responsive patients to long lasting DA therapy; the effect of additional radiotherapy is shown by full red triangles).

Table 3. Tumor shrinkage after BRC as compared to BRC+RT in DA responsive patients

	Group A N=32 responsive patients		**Group B** N=56 responsive patients	
Tumor shrinkage	DA	DA + RT	DA	DA + RT
Cured	3	2	0	0
Significant improvement	13	4	28	3
Mild improvement	5	1	9	4
No shrinkage	2	0	9	1
No data	1	1	1	1
Total	24	8	47	9

Table 4. Characteristics of DA resistant patients (n=23)

Parameter	**Group A** N=9 resistant patients		**Group B** N=14 resistant patients	
Sex ratio (F/M)	7/2		9/5	
Parameter	Mean ±SEM	Range	Mean±SD	Range
Age (years)	31.7 ± 4.4	16-59	30.6 ± 3.8	17-64
Baseline PRL (ng/ml)	1964.1 ± 1009.4	200-9328	2218.6 ± 1160.4	42-16000
Follow-up (months)	156.3 ± 40.2	60-378	21.3 ± 3.2	6-48

* All these patients were resistant to both bromocriptine and cabergoline, except two from group A, responsive to cabergoline.

A shrinkage of the tumor mass occurred, despite the high PRL level, in 5/9 cases on high BRC dose, with two additional patients, when BRC was replaced with high CAB dose (4mg/wk). The correction of the resistance with the decrease up to normal of PRL level was accomplished in 4/9 cases: i.e. in two after CAB and in other two after radiotherapy.

In group A, 13 patients were submitted to additional radiotherapy, with the following results: 2 out of 8 patients responsive to DA treatment were cured. In 5 DA resistant cases, radiotherapy normalized PRL levels in 2 patients, as shown before, significantly decreased PRL level in another one and further reduced tumor volume in 3 patients (without changing the class of improvement).

In group B (N=70), there were 56 responsive cases. Among them, 31 out of 56 patients (55.3%) achieved significant improvement and 13/56 patients (23.2%) achieved mild improvement, as shown in Figs. 4, 5 and Table 3. None of these 70 patients with macroprolactinomas was cured.

Only in 1 patient, the tumor shrank completely, but it grew again, when CAB was withdrawn (N.L., 33-year-old male). In 2 cases, the comparative results of CT evaluation were unavailable.

In the 14 DA resistant cases, a significant tumor shrinkage occurred in 4/14 patients, although PRL level failed to normalize. Using different approaches to obtain PRL normalization, 1 patient responded after combined treatment with CAB 5mg/w and surgery (C.M., 29-year-old female).

Radiotherapy was added in group B in 12 patients (9 responsive and 3 resistant to DA treatment). PRL remained above normal levels in all of these cases, although in one DA resistant patient PRL level significantly decreased. From 9 patients responsive to DA, further reduction in tumor volume was noticed in 4 patients after radiotherapy, 2/4 progressing from mild to significant tumor shrinkage and 1/4 progressing from no shrinkage to mild shrinkage (Table 3 and Fig. 5).

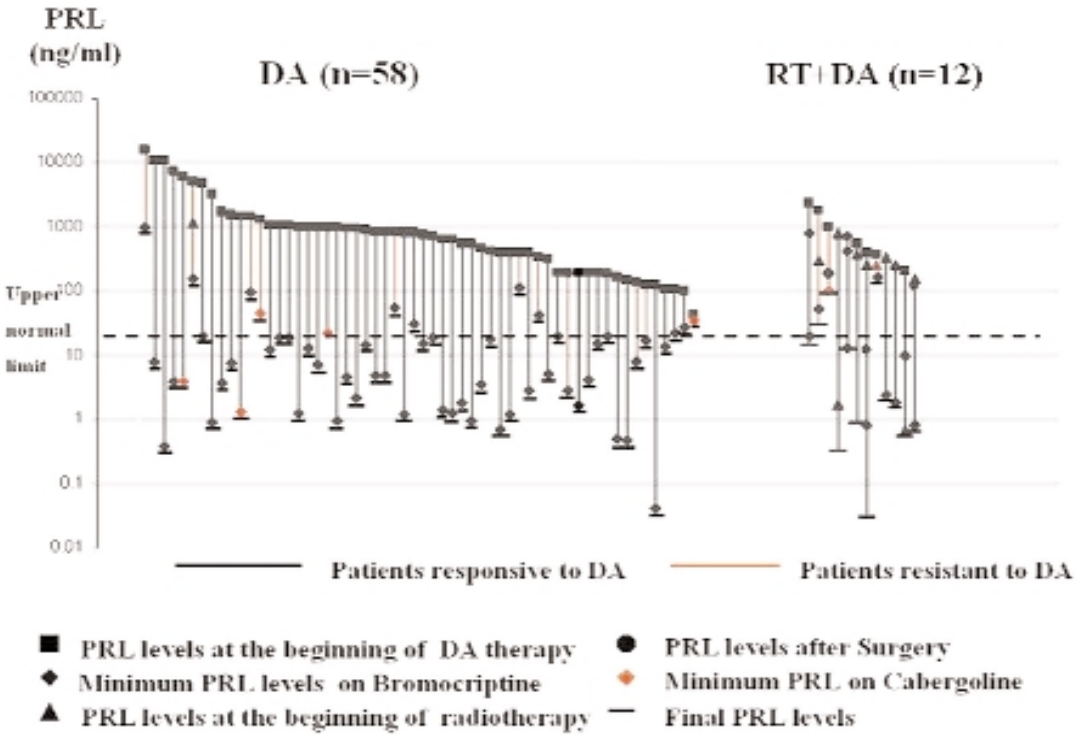


Figure 4. PRL levels under therapy in group B (follow-up therapy less than 4 years).

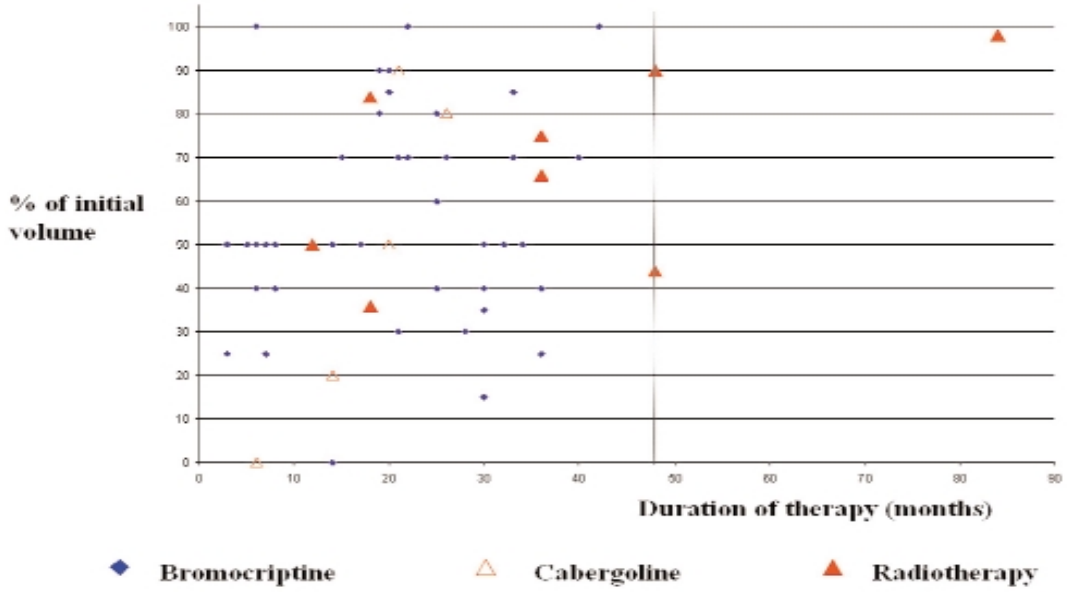


Figure 5. The shrinkage of the tumor mass in macroprolactinomas of group B, under complex treatment with duration and follow-up less than 4 years.

Visual field abnormalities were noted initially in 31 out of 111 study subjects (20 men/11 women). With reduction of tumor size, visual field improvement

occurred in 18 of 31 (58%) cases, while in 12 of 31 (38.7%) patients there were no changes and 1 of 31 (3.22%) cases worsened.

Hypopituitarism after RT was noted in 10 out of 25 cases (40%) after 59 months mean follow-up period, but 5 out of these 10 cases had also pituitary surgery.

As already mentioned, there are some discrepancies between the shrinkage of the tumor mass and PRL level. There are tumors in the subgroup of responsive cases which failed to shrink despite PRL normalization (Fig. 6), as there are so-called resistant prolactinomas, in which PRL level always remains above upper limit of normal, but the tumor volume significantly decreased (Fig. 7), even up to a non-detectable mass on CT and MRI, but with serum PRL 60.7 ng/ml (Fig. 8).

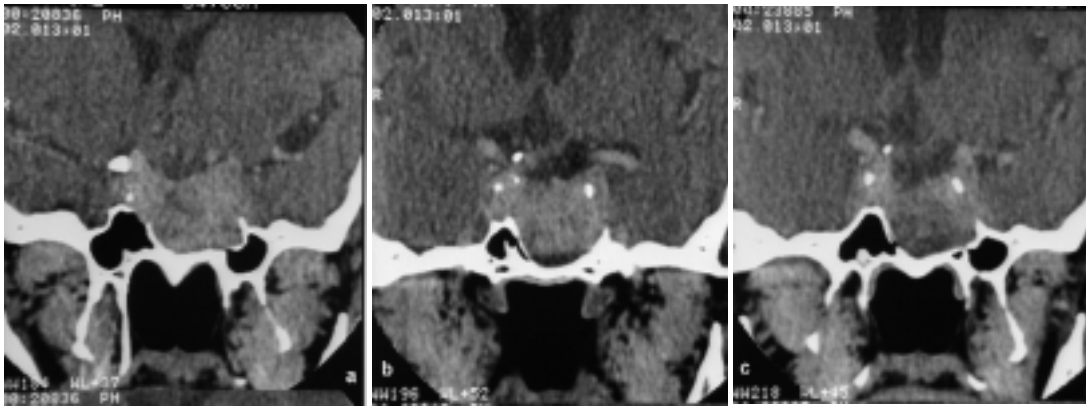


Figure 6. CT scan of a macroprolactinoma before the beginning of DA therapy (a); six months later, after treatment with BRC 30 mg/day- no shrinkage (b); after other 6 months of therapy with BRC 7.5 mg/day - minimal shrinkage (c).

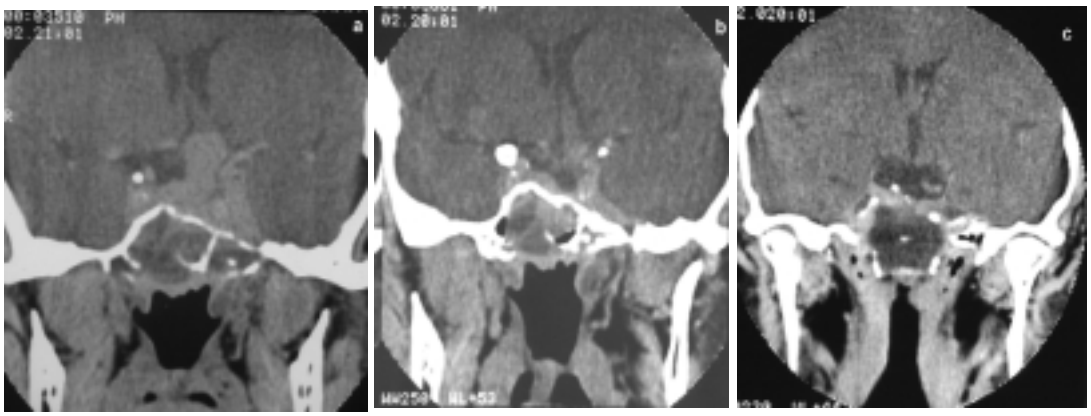


Figure 7. CT scan of a resistant macroprolactinoma before the beginning of DA therapy (a); two years later, after treatment with BRC 30 mg/day+CAB 7mg/w- shrinkage 30% (b); two years after radiotherapy and under BRC 30 mg/day - tumor remnants with necrotic changes (c).

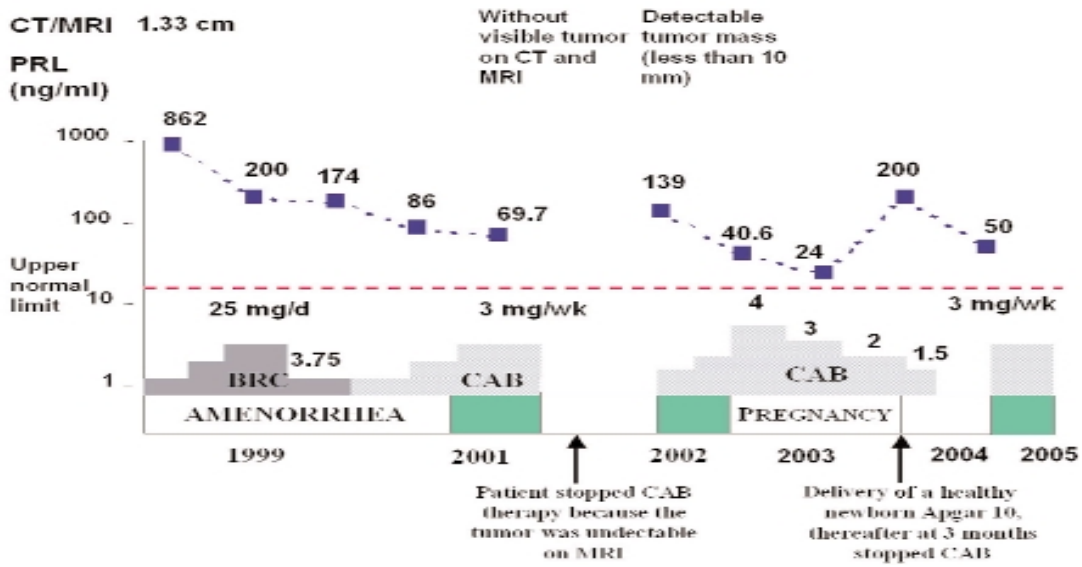


Figure 8. S.M, female, 26 years, macroprolactinoma with high serum PRL, resistant to bromocriptine and cabergoline, but with surprising regression of tumor mass up to undetectable on CT and MRI. After withdrawal of CAB the tumor mass grew once again and as well PRL levels. Starting again CAB therapy at 4 mg/wk she became pregnant and continued CAB along the whole gestation period. The newborn was in good health.

Comparing the effect of high BRC dose (i.e. 30 mg/d) with that of the low BRC dose (i.e. 7.5 mg/d), we noticed a better effect of the high dose concerning the PRL serum level and the cure rate. In 48 patients responsive to the high dose of BRC, the average serum levels of PRL were 7.5 ± 1.1 ng/ml after high dose BRC and 37.9 ± 9.2 ng/ml after BRC low dose (p=0.001). Changing to low BRC dose after a long term therapy with high BRC dose, PRL levels increased over 20 ng/ml in 6/19 patients (31.6%) in group A and in 9/29 patients (31%) in group B.

After radiotherapy, medium prolactin level after a median 3 years follow-up period was significantly lower (p=0.02 and 0.01 respectively) in 10 patients from both groups on low BRC dose (5.1 ng/ml), than in 19 patients from group A (49.5 ng/ml) and in 29 patients from group B (30.3 ng/ml) who were not submitted to radiotherapy. So, the daily BRC dose could be safely decreased from 30 mg/day to 7.5 mg/day in patients previously submitted to radiotherapy (Fig. 9). In 9 patients, we are able to compare the tumor shrinkage after DA only and after DA+RT; further improvement in tumor shrinkage was noticed in 8/9 and 2 patients from group B progressed from mild to significant tumor shrinkage.

Comparing the effects of high and low dose BRC on tumor shrinkage, in patients submitted to high BRC dose there are more cases with a significant improvement than with a mild improvement (p=0.03).

Overall, the cure rate was quite low, 5/111 patients (4.5%), registered only in group A (patients treated for more than 4 years), even if we considered only the

percent of patients responsive to DA therapy and submitted to high dose DA therapy for more than 4 years (5/32=15.6%). Three cured cases were treated with BRC only and two with combined BRC and RT.

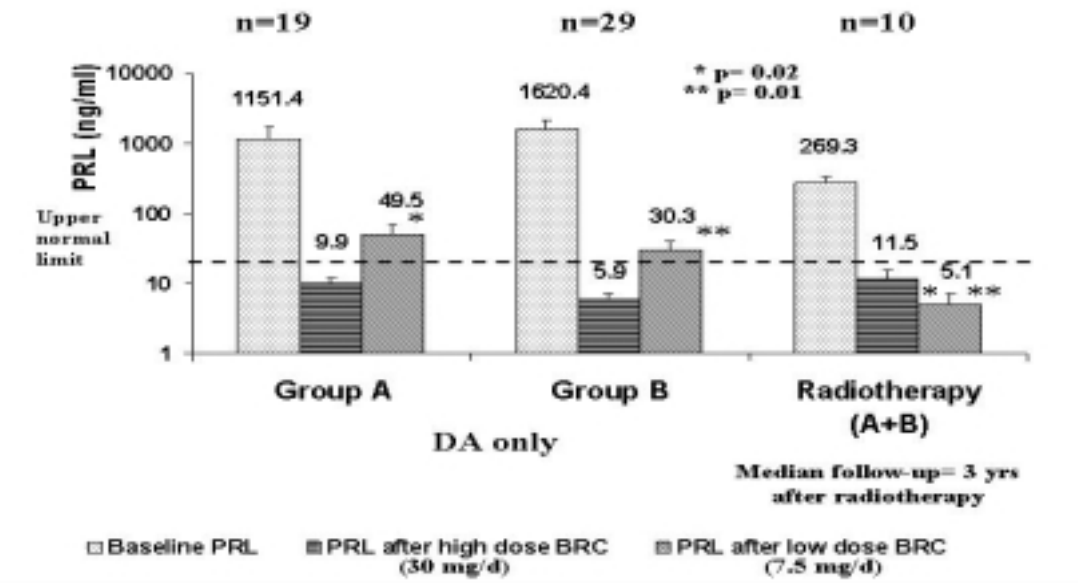


Figure 9. Escape phenomenon by decreasing bromocriptine daily dose is prevented by radiotherapy.

DISCUSSION

There is a large agreement that the prolactinomas are responding to medical anti-tumor therapy much better than other pituitary secreting- or nonfunctioning adenomas. This is due to the specific anti-lactotroph effects of bromocriptine and of other chemically related compounds (cabergoline, quinagolide, pergolide), called dopamine agonists (DA) therapy (7). The primary treatment for prolactinomas has been the medical treatment with DA drugs for the past 15 years. The largest series were reported up to now using bromocriptine (2) and the best results were reported using cabergoline (8). Normalization of PRL serum levels and a significant shrinkage of the tumor mass is the rule during DA administration. These results represent about 75% cases with bromocriptine treatment calculated by metaanalysis (9); in our series, PRL normalization occurred in 79% (88/111 cases) and volume shrinkage in 64% (72/111 cases) after 24 months of DA therapy; in other series similar figures were reported: 66% PRL normalization and 64% volume shrinkage at 1 year (10), or 46.4% for PRL and 46.4 % for volume shrinkage at 2 years for BRC and an improved figure for CAB treatment (11).

The cure rate is still low in all series, as proved after withdrawal of DA medication for one year. In our series, it was 4.5% (5 out of all 111 patients) or 15.6% (5 out of 32 with similar therapy), i.e. using only bromocriptine in high dose

(30 mg/day) for a long period (over 4 years). A better cure rate of 48% was recently reported for Cabergoline, i.e. 34 out of 70 macroprolactinomas treated only with CAB (0.5-1.5 mg/week for 2-6 years) (8).

Surgery is the primary treatment for all the other pituitary tumors, excepting prolactinomas. This has included acromegaly produced by adenoma cells secreting GH and PRL (2, 7). However, the efficacy of surgery for macroprolactinomas was much smaller than with DA medical treatment in all published series, with less than 20% PRL normalization (9, 12-13). In our series among the 28 patients submitted to pituitary surgery, 26 came in the Institute of Endocrinology "C.I Parhon" after transfrontal or transsphenoidal surgery, presenting large tumor remnant mass over 1 cm in maximal diameter and serum PRL much over normal levels (Table 2).

The medical treatment for macroprolactinomas is often indicated for life long. This is due to the good results of DA administration in the majority of patients, but with the recurrence of clinical signs and symptoms, after the withdrawal of bromocriptine or cabergoline, with an increase of serum PRL and tumor mass (2-3, 7-8, 14-15).

As an alternative, we used in our series several strategies for improving the cure rate, i.e.:

A. The administration of high daily dose (dd) of bromocriptine, 30 mg/day instead of low dd 7.5 mg/day;

B. The long term DA therapy, lasting for more than 4 years;

C. The replacement of bromocriptine with cabergoline;

D. Additional external high voltage radiotherapy.

A. The first case reports about the tumor mass shrinkage of macroprolactinoma under bromocriptine therapy were published by Sobrinho (16), followed by Scanlon group (17). The last used high dose BRC, i.e. 30 mg/day first evaluated after three months. Our group started the therapy with a high daily dose of Bromocriptine (30 mg/day) also in 1978 and noticed a spectacular shrinkage of the tumor mass after six months (1). Similar shrinkage was produced in another patient with low dose BRC and in a very short period (7.5 mg/day for 3 weeks) (3) (5 mg/day for 4 weeks) (18). Some authors claim now that the effects of high or low dose BRC are quasi equal (9), in contrast to others and our opinion that a low BRC daily dose is usually anti-secretory for PRL and that the high BRC dose is, as a rule, both anti-secretory and anti-tumor for the lactotroph cell (7) probably by an antimitotic or cytonecrotic mechanism (19).

In our present series of 111 patients the high daily doses of BRC showed better antitumoral effects than the low ones:

A.1. The few patients cured only by medical therapy were all on high BRC dd and on long time administration (Table 3) (cases N.P., female, 32 yrs; T.J.M., female, 21 yrs; D.E., female, 28 yrs). However, we noticed seldom cases that showed significant improvement of macroprolactinomas after a small daily dose of bromocriptine or cabergoline, but for bromocriptine, these are rare cases and the shrinkage effects are slow and late occurring. For this reason in patients with

suprasellar extension of prolactinoma, we recommend to start with a high dose of bromocriptine (gradually increasing the daily dose). In one patient with chiasm optic syndrome (N.I, male, aged 50), we noticed the first sign on improvement of the visual field and visual acuity after ten days of treatment with 30 mg/day BRC.

A.2. In the subgroup of 48 macroprolactinomas who alternatively received either high or low dd BRC every 6 months, for each patient, the medium serum level of PRL has increased under low dd BRC, above the normal limits except in cases previously submitted to radiotherapy (Fig. 9).

B. The duration of therapy is important for the cure rate, but it is not decisive.

B.1. All five macroprolactinomas cured were from group A with DA therapy lasting and follow-up more than 4 years (Table 3).

B.2. The significant improvement rate was similar in group A and in group B: 17/41patients (41.5%) in group A and in 31/70 patients (44.3%) in group B, p=NS (Table 3). The same figure of significant improvement is if considering only responsive cases receiving DA as single therapy 16/24 (66.7%) patients in group A and 28/47 (59.6%) patients in group B, p= NS.

The ratio between significant improvement and mild improvement is significantly higher in group A, under long lasting therapy, than in group B (P= 0.03, χ^2 test). The number of cases showing resistance to DA therapy is a bit smaller in group A, i.e. 9 *versus* 14 (group B), without statistical significance.

There are several patterns of response to DA therapy in prolactinomas as a function of time: rapid regression during therapy and rapid reexpansion by withdrawal of medication (3, 18); slowly progressive improvement under DA and recurrence by DA withdrawal (majority cases of our series); initial normalization of PRL levels under DA lasting about 2 years, and thereafter a huge increase of serum PRL during continuous DA therapy (in one case of our series, F.A., female, 32 yrs, up to 251.8 ng/ml). Another case was reported by Bevan et al (14). Another pattern is an initial shrinkage of tumor mass with improvement of visual field defect, but still with high serum PRL, and further developing resistance to DA therapy (case S.M., female, 31yrs). All these data revealed an important difference of prolactinomas cells between patients, and suggests that there are many kinds of lactotroph cells in the same prolactinomas, explaining the peculiar responses to the same DA therapy.

Two case histories are indirect but suggestive for the presence of at least two kinds of lactotroph cells in the same prolactinoma. One case belongs to group A (S.P., female, 26 yrs, Fig. 8), one to group B (case N.L, male, 33 yrs). In both patients the macroprolactinomas shrank and became undetectable on MRI under DA therapy, but withdrawal of DA revealed remnant and resistant tumor cells with the recurrence of the tumor mass. The patient S.P., treated over 4 years, responded only to CAB, but not to BRC (30 mg dd). CAB corrected amenorrhoea and induced menstrual cycles at 3mg/week dose and induced ovulation followed by pregnancy increasing up to 4 mg/week. However, PRL serum levels never decreased to normal levels, although the tumor mass decreased from 13 mm diameter to undetectable

tumor on MRI. Recurrences were twice proved by withdrawal of Cabergoline: once before pregnancy, once at three months post-delivery of a normal child (Fig. 8). The demonstration of resistant lactotroph cells to DA therapy coexisting with low sensitive cells is indirect, but suggestive. Only the prolonged therapy can reveal such prolactinomas with pluri-sensitive differentiated lactotroph cells.

C. The replacement of bromocriptine with cabergoline, recommended by literature (10, 20-22), was done in 10 patients of our series, 8 with DA-resistance. Cabergoline was able to break the resistance to bromocriptine in only two cases. However, this was not able to improve the cure rate after withdrawal of medication.

D. Additive radiotherapy is efficient, but not spectacular, in improving the cure rate of macroprolactinomas. The following effects of high voltage radiotherapy were noticed: 2 additional cases were cured (D.E., female, 27 yrs, N.F., female, female, 19 yrs), as proved by withdrawal of DA therapy for more than one year, both cases belong to group A; the decrease of BRC dose from 30 mg to 7.5 mg dd, with the maintenance of a normal PRL level, was achieved after radiotherapy in a subgroup of 48 macroprolactinomas in which without radiotherapy PRL serum levels increased over normal limits; radiotherapy improved serum PRL levels in 4 out of 8 cases with DA resistance (2 up to normal level). All these data indicate radiotherapy as a complementary method to be added to DA therapy of macroprolactinomas.

The mechanism of action of BRC and CAB upon lactotroph tumor cells is partially clarified and is largely attributed to their agonistic effects to dopamine, a neurohormone that inhibits pituitary prolactin production (7).

However, this does not explain the specific shrinkage of the tumor mass of prolactinomas only, with more than 50% of the initial volume. Regarding the nucleo-cytoplasmic ratio within each cell, this shrinkage can be achieved only by decreasing the nuclear volume. This is an antimitotic effect. It is not clear yet why this antimitotic effect of BRC and CAB is not sufficient to cure the prolactinoma, after a time necessary to destroy the tumor cells. Radiotherapy shows the same antimitotic effects but it is nonspecific for lactotroph cells.

The study of the mechanisms of resistance to DA therapy could clarify the problem of the low cure rate of prolactinomas. The number of DA-resistant cases is high enough- 23 out of 111 in our series (Table 4), as reported also by others (8-9, 21-23). Recent data revealed that in many pituitary adenomas including prolactinomas there are a low percent of multihormonal expressing cells (with mute hormones) and with multi functional PRL-secreting cells (24-26). Such cells were also revealed in nontumoral pituitary gland in mammals (27). Other mechanisms of DA resistance are under study, regarding the sensitivity of lactotrophs, expression of D2 receptors (28-29), of somatostatin receptors (30) or subunits of G protein (31). If in the same prolactinoma there are cells with different characteristics, this fact could show different responses to DA therapy and could be selected in time.

It was reported that prolactinoma shrinkage under cabergoline is greater in naive patients than in patients previously treated with bromocriptine or other DA

(20). If certain prolactinomas are multiclonal, it is tempting to believe that the number of patients with resistance to DA therapy will increase if only the DA therapy is used. Understanding the mechanisms of DA resistance will improve the cure rate even in resistant prolactinomas, which are still difficult to treat (32).

In conclusion, because the mechanisms of recurrence of prolactinomas and of their resistance to DA therapy have not been clarified yet, and the cure rate of prolactinomas is low under long lasting medical therapy with dopamine agonists, it is tempting to suggest that common factors are involved in these three processes and limit the efficacy of DA therapy. Therefore, radiotherapy is strongly recommended for the treatment of DA resistant prolactinomas, as well as for majority of cases with recurrence after withdrawal of DA therapy.

References

1. Coculescu M, Simionescu N, Oprescu M, Alessandrescu D. Bromocriptine treatment of pituitary adenomas. Evaluation of withdrawal effect. Revue Roumaine Med Endocrinol 1982; 21:157-168.

2. Molitch M. Prolactinoma. In: Melmed S, editor. The pituitary. Toronto, New York: Blackwell Publishing, 2002: 455-495.

3. Thorner MO, Perryman RL, Rogol AD, Conway BP, MacLeod RM, Login IS et al. Rapid changes of prolactinoma volume after withdrawal and reinstitution of bromocriptine. J Clin Endocrinol Metab 1981; 53(3):480-483.

4. Colao A, di Sarno A, Landi ML, Cirillo S, Sarnacchiaro F, Facciolli G et al. Long-term and low-dose treatment with cabergoline induces macroprolactinoma shrinkage. J Clin Endocrinol Metab 1997; 82(11):3574-3579.

5. Coculescu M, Hudita D, Gussi I, Gheorghiu M, Hortopan D, Caragheorgheopol A. Tumor size changes in prolactinomas treated with minimum bromocriptine throughout gestation. Gynecological Endocrinology 2000; 14(suppl 2).

6. Badiu C, Ham J, Carnu R, Coculescu M. TRH synthesis in “mute” thyrotropinomas: cause-effect or coincidence? J Cell Mol Med 2001; 5(1):88-91.

7. Coculescu M. Neuroendocrinologie clinica. Bucuresti: Editura Stiintifica si Enciclopedica, 1986.

8. Colao A, di Sarno A, Cappabianca P, di Somma C, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med 2003; 349(21):2023-2033.

9. Molitch ME. Dopamine resistance of prolactinomas. Pituitary 2003; 6(1):19-27.

10. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. Pituitary 2002; 5(2):55-65.

11. di Sarno A, Landi ML, Cappabianca P, Di Salle F, Rossi FW, Pivonello R et al. Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. J Clin Endocrinol Metab 2001; 86(11):5256-5261.

12. Losa M, Mortini P, Barzaghi R, Gioia L, Giovanelli M. Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome. J Clin Endocrinol Metab 2002; 87(7):3180-3186.

13. Acquati S, Pizzocaro A, Tomei G, Giovanelli M, Libe R, Faglia G et al. A comparative evaluation of effectiveness of medical and surgical therapy in patients with macroprolactinoma. J Neurosurg Sci 2001; 45(2):65-69.
14. Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonists and pituitary tumor shrinkage. Endocr Rev 1992; 13(2):220-240.
15. Passos VQ, Souza JJ, Musolino NR, Bronstein MD. Long-term follow-up of prolactinomas: normoprolactinemia after bromocriptine withdrawal. J Clin Endocrinol Metab 2002; 87(8):3578-3582.
16. Sobrinho LG, Nunes MC, Santos MA, Mauricio JC. Radiological evidence for regression of prolactinoma after treatment with bromocriptine. Lancet 1978; 2(8083):257-258.
17. McGregor AM, Scanlon MF, Hall K, Cook DB, Hall R. Reduction in size of a pituitary tumor by bromocriptine therapy. N Engl J Med 1979; 300(6):291-293.
18. Orrego JJ, Chandler WF, Barkan AL. Rapid re-expansion of a macroprolactinoma after early discontinuation of bromocriptine. Pituitary 2000; 3(3):189-192.
19. Gen M, Uozumi T, Ohta M, Ito A, Kajiwara H, Mori S. Necrotic changes in prolactinomas after long term administration of bromocriptine. J Clin Endocrinol Metab 1984; 59(3):463-470.
20. Colao A, di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R et al. Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. J Clin Endocrinol Metab 2000; 85(6):2247-2252.
21. Delgrange E, Maiter D, Donckier J. Effects of the dopamine agonist cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine. Eur J Endocrinol 1996; 134(4):454-456.
22. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994; 331(14):904-909.
23. Colao A, di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B et al. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab 1997; 82(3):876-883.
24. Saveanu A, Morange-Ramos I, Gunz G, Dufour H, Enjalbert A, Jaquet P. A luteinizing hormone-alpha-subunit- and prolactin-secreting pituitary adenoma responsive to somatostatin analogs: in vivo and in vitro studies. Eur J Endocrinol 2001; 145(1):35-41.
25. Ma W, Ikeda H, Yoshimoto T. Clinicopathologic study of 123 cases of prolactin-secreting pituitary adenomas with special reference to multihormone production and clonality of the adenomas. Cancer 2002; 95(2):258-266.
26. Senovilla L, Nunez L, de Campos JM, de Luis DA, Romero E, Sanchez A et al. Multifunctional cells in human pituitary adenomas: implications for paradoxical secretion and tumorigenesis. J Clin Endocrinol Metab 2004; 89(9):4545-4552.
27. Mignot M, Skinner DC. Colocalization of GH, TSH and prolactin, but not ACTH, with betaLH-immunoreactivity: evidence for pluripotential cells in the ovine pituitary. Cell Tissue Res 2005; 319(3):413-421.
28. Pellegrini I, Rasolonjanahary R, Gunz G, Bertrand P, Delivet S, Jedynak CP et al. Resistance to bromocriptine in prolactinomas. J Clin Endocrinol Metab 1989; 69(3):500-509.
29. Trouillas J, Chevallier P, Remy C, Rajas F, Cohen R, Calle A et al. Differential actions of the dopamine agonist bromocriptine on growth of SMtTW tumors exhibiting a prolactin and/or a

somatotroph cell phenotype: relation to dopamine D2 receptor expression. Endocrinology 1999; 140(1):13-21.

30. Jaquet P, Ouafik L, Saveanu A, Gunz G, Fina F, Dufour H et al. Quantitative and functional expression of somatostatin receptor subtypes in human prolactinomas. J Clin Endocrinol Metab 1999; 84(9):3268-3276.

31. Caccavelli L, Morange-Ramos I, Kordon C, Jaquet P, Enjalbert A. Alteration of G alpha subunits mRNA levels in bromocriptine resistant prolactinomas. J Neuroendocrinol 1996; 8(10):737-746.

32. Trifanescu R, Karavitaki N, Coculescu M, Turner HE, Wass JAH. What is the final outcome in patients with macroprolactinoma resistant to dopamine agonists? 24th Joint Meeting of the British Endocrine Societies, 4-6 April 2005, Harrogate, U.K, Endocrine Abstracts, Vol. 9, P98, published by BioScientifica.