Effect of cabergoline on tumor remnant after surgery in nonfunctioning pituitary adenoma

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Abstract

Background. In recent years, dopamine agonists (DAs) have become an attractive therapeutic option to prevent both tumor growth and post-surgical tumor remnant growth in clinically non-functioning pituitary adenoma (NFPA).

Aim. To analyze our experience on the effect of cabergoline (CAB) on tumor remnant after initial surgery in NFPA patients.

Patients and Methods. A retrospective and multicenter study of NFPA patients with tumor remnant after surgery treated with CAB was performed.

Results. From a total of 142 NFPA patients (79 men, 55.2%; mean age 57.2 ± 14.2 year) who underwent surgery, we selected 62/142 (43.7%) patients (32 men, 51.6%; mean age 59.3 ± 13.9 year) with tumor persistence (TP) after surgery. In 22/62 (35.5%) TP patients CAB was used (CAB group), while the rest of the patients (40/62, 64.5%) underwent active surveillance [observation (OBS) group)]. The maximum diameter of the tumor remnant did not change significantly in either the CAB group [11.5 (6.0-16.9) mm vs. 12.0 (7.0–15.0) mm, p = 0.85) or

the OBS group [8.5 (6.0-13.7) mm vs. 9.0 (6.2–14.0) mm, p = 0.064) at the end of the follow-up [13 (10.5–17) vs. 77.5 (50.2-107.2) months, CAB vs. OBS group; p < 0.001]. At the end of the treatment period with CAB most of the patients (n = 20/22, 90.9%) showed no progression of the tumor remnant [stable disease, SD (n = 17/22, 77.2%) and partial response, PR (n = 3/22, 13.6%)], while 2/22 patients (9.1%) exhibited progression. Similar response rates were observed in the OBS group [SD (n = 32/40, 80%), PR (n = 2/40, 5%), and progression (n = 6/40, 15%)]. Although no statistically significant differences (p = 0.42) were found in these responses, the percentage of progression was 1.65 times higher in the OBS group compared to the CAB group. On the contrary, the percentage of PR was 2.72 times higher in the CAB group compared to the OBS group, despite a significantly shorter follow-up period in the CAB group.

Conclusión. Although the present study showed no significant differences in the type of tumor response between the CAB and OBS groups of patients, the percentage of PR was higher and that of progression lower in the CAB group compared to the OBS group. This finding does not rule out a potential therapeutic benefit of CAB in the management of tumor remnant in patients with NFPA undergoing surgery.

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Introduction

Pituitary adenoma (PA) is the third most frequent type of intracranial tumor, after meningioma and glioma [1]. With imaging studies, its prevalence has increased to 22% in some series, with a wide range varying from 1 to 40% [2,3,4,5].

PAs can be both functioning and non-functioning (NF). NFPA, usually ≥ 10 mm (macroadenoma), is common in adults (around the sixth decade of life) without predominance by sex [6]. Clinically, NFPAs in adult patients are frequently associated with compressive symptoms resulting from local involvement of neighboring structures with neuro-ophthalmologic symptoms and/or hypopituitarism.

Initial treatment of NFPAs depends on tumor size, symptoms, invasion of adjacent tissues, neuro-ophthalmologic involvement and pituitary hormone function. Although a high percentage may be followed initially by active surveillance with imaging tests, surgery is the initial treatment of choice in symptomatic tumors and in those showing tumor growth during follow-up. Transsphenoidal surgery is usually accompanied by

significant reduction in tumor size and improvement in visual and pituitary function [7]. Because these tumors are usually large and often invasive, the presence of tumor remnant after initial surgery is common. The prevalence of residual tumor growth is up to 50% at 10 years of follow-up, leading to a second surgery, radiotherapy or both [8].

Post-surgical radiotherapy may be considered in cases of remnant tumor growth after initial surgery or tumor recurrence. In those cases with invasive post-surgical tumor remnant with high rates of cell proliferation radiotherapy is an appropriate therapeutic option [9]. However, and despite its proven efficacy as an antiproliferative treatment, the absence of randomized controlled clinical trials, the arbitrary criteria for its indication, the generally benign nature of NFPAs, the potential side effects and the possibility of using radiotherapy at later stages are arguments against its routine use in the management of tumor remnant after initial surgery.

The use of dopamine agonists (DAs) in the management of NFPAs has become an attractive therapeutic option in recent years with the aim of preventing the growth of both the tumor and the post-surgical tumor remnant. In some studies this treatment has been associated with a stabilization or reduction in the size of the post-surgical tumor remnant, reducing the need for radiotherapy and second surgery in these patients [10,11,12,13,14,15,16]. Although different DAs have been used, it appears that cabergoline (CAB) is the DA that is associated with the highest probability of tumor size reduction [17]. At present, there is no consensus on the medical treatment of NFPAs [8], and more studies are needed to gain a more precise understanding of the therapeutic role of DAs in these patients. Given the paucity of information, we considered to analyze in more detail our experience on the role of DAs, in particular CAB, in the therapeutic management of NFPAs.

Patients and methods

We retrospectively studied a group of NFPA patients followed up in seven pituitary reference centers in Spain. Adult patients (> 18 years) diagnosed with PA with absence of hyperfunction of the anterior pituitary gland [acromegaly, Cushing's disease or macroprolactinoma (PRL > 100 ng/ml) [18]] at the time of the adenoma diagnosis and pathological demonstration of PA after surgery were included.

Clinical and analytical data, as well as imaging tests obtained during their clinical visits to the different medical and surgical specialties both at the clinical diagnosis of NFPA

and after surgery were recorded. In every patient the following parameters were analyzed: sex, age at diagnosis, clinical manifestations at diagnosis, tumor features, therapies used, surgical complications, and therapeutic outcomes.

Type and number of pituitary hormone deficiencies were also registered. Hypopituitarism was defined as partial or complete deficiency in one or more of the hormones produced by the anterior pituitary gland (ACTH, TSH, FSH, LH, GH, prolactin) or posterior pituitary (vasopressin or antidiuretic hormone, ADH) diagnosed by criteria of routine clinical practice. The diagnosis of hypopituitarism was made based on the baseline hormonal values [thyrotropin, TSH; free thyroxine, FT4; follicle stimulating hormone, FSH; luteinizing hormone, LH; testosterone (men), 17-beta-estradiol (women); ACTH; cortisol; insulin-like growth factor type 1, (IGF 1) and PRL]. Panhypopituitarism was defined as deficiency of all pituitary hormones of the anterior pituitary gland with or without deficiency of ADH secretion by the neurohypophysis. Hormonal measurements were performed in each laboratory using standard immunoradiometric assay or enzymoimmunometric assay methods, with their respective reference ranges. Hormonal status was evaluated at diagnosis, up to 3–6 months after surgery, and again at their last clinical visit.

We considered 1) complete resection (CR) and tumor persistence (TP) in the absence or presence, respectively, of tumor remnant in the pituitary MRI performed in the first 3–6 months after surgery. According to tumor response, we considered (1) partial response (PR) (reduction in maximum tumor diameter ≥ 2 mm), (2) stable disease (SD) (change in maximum tumor diameter < 2 mm), and (3) progression (increase in maximum tumor diameter ≥ 2 mm) [15].

The responses obtained were compared with the results of the different studies published to date in which the response to CAB in primary prevention in NFPA patients after surgery was analyzed [12,13,14,15,16,19]. A pooled analysis of the type of response to CAB in the 164 reported patients [8] was performed together with that obtained in our patients.

After surgery, patients with TP were treated with CAB according to the clinical criteria of each responsible physician at each of the centers that participated in the study. Patient's data were obtained under the standard medical care conditions. The patient's confidential information was protected according to national law and the study was approved by the local ethics committee of the hospital Universitario Puerta de Hierro Majadahonda, Madrid. Spain (Protocol code: ADAHNF Study, approval date February 8, 2021).

Statistical analysis

Qualitative data are presented as the number of patients and the percentage in parenthesis or the number of patients with the feature / total number of patients with available information and relevant percentage in parenthesis. Quantitative data are expressed as mean ± SD for normally distributed data or as median (interquartile range) for nonparametric data. Kolmogorov- Smirnov test was used to check the normal distribution of the quantitative variables. The Student t-test was used for mean comparisons between two groups of subjects for normally distributed data, and the Mann-Whitney test was employed for nonparametric data. For ratio comparisons the χ^2 test was used. The presence of statistical significance was considered for values of $p < 0.05$.

Results

Study population

Out of a total of 279 NFPA patients we selected a group of 142 (50.9%) patients (79 men, 55.6%; mean age 57.1 ± 14.2 year) who underwent surgery due to symptomatology and/or associated tumor growth during follow-up.

At 3–6 months after surgery, CR was achieved in 80/142 (56.3%) patients, while the rest (62/142, 43.7%) showed TP on pituitary MRI. In 22/62 (35.5%) TP patients CAB was used (CAB group), while the rest of the patients (40/63, 64.5%) underwent active surveillance (observation group). The clinical characteristics of both groups of patients are summarized in Table 1.

Tumors of patients belonging to the CAB group were more symptomatic at diagnosis than patients in the observation group. Tumors were incidentally discovered less frequently (13.6% vs. 47.5%, $p = 0.007$), and presented a higher likelihood of hypopituitarism (81.8% vs. 52.5%, $p = 0.02$), especially gonadotropin deficiency (81% vs. 46.2%, $p = 0.009$). In addition, patients treated with DAs showed a higher percentage of tumors with cavernous sinus invasion (90.5% vs. 65%), although this difference did not reach statistical significance ($p = 0.065$).

The percentage distribution of NFPAs according to immunohistochemical staining in the CAB group was as follows: gonadotroph adenoma [12 (54.5%)], null cell adenoma [3 (13.6%)], plurihormomal adenoma [3 (13.6%)], corticotroph adenoma [2 (9.1%)],

somatotroph adenoma [1 (4.5%)] and lactotroph adenoma [1 (4.5%)]. Although in the OBS group (35/40 (87.5%) the most common tumor type was null cell adenoma [18/35 (51.4%)] followed by gonadotroph adenoma [12/35 (34.3%)], corticotroph adenoma [2/35 (5.7%)], plurihormomal adenoma [2/35 (5.7%)] and somatotroph adenoma [1/35 (2.9%)], no significant differences were found ($p = 0.093$).

We also found no statistically significant differences in the Ki-67 index value between the CAB group [n = 19/22, 2% (1–3)] and the OBS group [n = 34/40, 2% (1–2)] ($p = 0.35$).

Time on CAB treatment was significantly shorter than the follow-up time of the OBS group [13 (10.5–17) vs. 77.5 (50.2-107.2) months, $p < 0.001$]. CAB dose ranged from 0.5 to 1.5 mg/week with a mean cumulative dose of 102.0 ± 93.4 mg.

Effects of cabergoline therapy

The maximum diameter of the tumor remnant did not change significantly in either the CAB group [11.5 (6.0-16.9) mm vs. 12.0 (7.0–15.0) mm, after surgery vs. last visit with CAB therapy, $p = 0.85$)] or the OBS group [8.5 (6.0-13.7) mm vs. 9.0 (6.2–14.0) mm, after surgery vs. last visit under active surveillance, $p = 0.064$)] at the end of the follow-up period (Fig. 1). Neither were there significant differences in the maximum diameter of the tumor remnant between the two groups at the end of follow-up ($p = 0.3$).

At the end of the treatment period with CAB most of the patients (n = 20/22, 90.9%) showed no progression of the tumor remnant [SD (n = 17/22, 77.2%) and PR (n = 3/22, 13.6%)], while 2/22 patients (9.1%) exhibited progression (Figs. 1 and 2). Similar response rates were observed in the OBS group [SD (n = 32/40, 80%), PR (n = 2/40, 5%), and progression (n = 6/40, 15%)]. Although no statistically significant differences (chi-square 1.71, $p = 0.42$) were found in these responses, the percentage of PR was 2.72 times higher in the CAB group compared to the OBS group and progression was 1.65 times higher in the OBS group compared to the CAB group, with similar percentages of SD in both groups of patients (Fig. 2).

Of the 2 patients who progressed with CAB, one of them was treated with radiotherapy and the other was a candidate for surgery but was discarded due to age and comorbidity (ischemic heart disease). Of the 6 patients who progressed in the observation group, only one of them was considered for surgery, which was rejected due to the patient's age.

CAB treatment was well tolerated and no clinically significant valvular heart disease, DA-induced impulse control disorders or severe psychiatric disorders were observed. CAB was discontinued in three (13.6%) patients due to mild symptomatology related to gastric discomfort, dizziness and mood alterations, respectively.

Pooled analysis of all NFPA patients with residual tumor after surgery treated with DAs [8], including our patients ($n = 164 + 22 = 186$) in primary prevention showed tumor shrinkage, stability and growth in 65 (34.9%), 101 (54.3%) and 20 (10.7%) cases, respectively, while in the observation group ($n = 117 + 40 = 157$) these responses were observed in 8 (5.1%), 102 (65%) and 47 (29.9%), respectively (chi-square 53.32; $p < 0.00001$) (Fig. 3).

Discussion

The present study shows our experience regarding the effect of treatment with CAB on the growth of the tumor remnant after initial surgery in NFPAs. After a median treatment period of 13 months, tumor responses did not reach a statistical difference compared to the OBS group, since both groups showed high percentages of stable disease (80–90%). However, CAB group showed more than double PR, and almost half of tumor progression.

The analysis of non-operated NFPAs followed by active surveillance after diagnosis has shown that the adenoma size is positively associated with the likelihood of tumor growth. In this regard, macroadenomas (≥ 10 mm) are more likely to grow (34% vs. 12%; $p < 0.01$) and to develop pituitary apoplexy (5% vs. < 1%; $p = 0.01$) than microadenomas (< 10 mm) [20]. Regardless of size at diagnosis, 11% of these NFPA patients undergo surgery during follow-up [20,21,22].

The treatment of choice for symptomatic (headache and/or visual disturbances) NFPAs is transsphenoidal surgery with or without adjuvant radiotherapy in cases of persistent or recurrent disease [6]. Although surgery controls tumor size and improves visual disturbances, complete cure is unusual. In our study, approximately half of the patients (142/279, 50.9%) with an initial clinical diagnosis of clinically NFPA had surgical indication. Of all the patients who underwent surgery, more than half (56.3%) achieved complete tumor resection, while 43.7% presented TP.

The usual clinical practice in the follow-up when there is a tumor remnant and, depending on its evolution is active surveillance, surgical reintervention and/or radiotherapy [23].

Recently DA, have been postulated as an interesting therapeutic alternative Dopamine receptors (DRs) are expressed in both normal and adenomatous pituitary cells. NFPAs also express DRs, mainly the DR2 type [12, 24,25,26]. CAB, a DA of the DR2 receptor, is the first-line treatment of choice in the management of prolactinoma, accompanied by a normalization of serum prolactin levels and a significant reduction in tumor size. This DR2 expression in NFPAs suggests a possible therapeutic role of DAs in these tumors, mainly to control tumor remnant growth after initial surgery [12]. In fact, CAB is able to inhibit also cell viability in NFPAs via DR2 by inhibiting vascular endothelial growth factor secretion [27]. However, despite the positive expression of DR2 in NFPAs, no clinical correlation between DA response and DR2 expression has been demonstrated in these patients [15,28].

A multicenter analysis evaluating the recurrence rate (RR) of postoperative tumor remnant in patients with NFPAs showed that it differed according to the status of the postoperative tumor remnant. In patients without detectable residual tumor, the RR was 12%, while the tumor growth-free survival rate (TGFSR) at 5 and 10 years was 96% and 82%, respectively. On the other hand, when patients with detectable residual tumor were considered, the RR was 46%, while the 5- and 10-year TGFSR was 56% and 40%, respectively [29]. In the same study, the mean time to doubling of residual tumor volume was 3.4 years.

Given the low probability of recurrence in the group of patients with no residual tumor after surgery, prophylactic radiotherapy after surgery seems to be unnecessary, and active surveillance would be more appropriate. However, in the case of tumor remnant, given the high probability of growth, the optimal treatment strategy is today a challenge. In these cases, both surgical reintervention and/or radiotherapy are possible therapeutic options. However, both measures are not free of complications. Although infrequent, surgical complications include hypopituitarism, diabetes insipidus, cerebrospinal fluid leak, and meningitis [6,30]. On the other hand, although radiotherapy is very effective in the long term in controlling tumor growth (a local tumor control rate of $> 90\%$ for > 10 years), the development of complications such as hypopituitarism, cognitive impairment, and cerebrovascular disease are common [31,32,33]. In recent years the possibility of using medical treatment that is effective and safe in controlling the growth of the tumor remnant in NFPAs, avoiding the complications associated with surgery and/or radiotherapy, has been considered [8].

The experience to date with DAs in NFPAs comes from small series of patients suggesting beneficial effects with tumor shrinkage in some cases [8,23]. Most studies have evaluated the effect of CAB on NFPAs in small groups of patients, usually less than 20. [11,12,13,14,15]. Its effect has been assessed both in primary prevention (prevention of residual tumor growth after surgery) and in secondary prevention (prevention of residual tumor that has already grown after the initial surgery) [10,11,12,13,14,15,16]. A pooled analysis of NFPA patients with residual tumor after surgery treated with DAs (n = 164) in primary prevention showed tumor shrinkage, stability and growth in 62 (37.8%), 84 (51.2%) and 18 (11%), respectively, while in the observation group (n = 117) these responses were 0.05%, 59.8% and 35%, respectively [8]. These results appear to demonstrate some degree of efficacy of CAB in controlling tumor remnant growth in a considerable proportion of patients with NFPA.

In our cohort of NFPA patients treated with DA in primary prevention, the response rates were similar to those published recently [8].

The majority of our patients (90.9% vs. 89%) showed no progression of tumor remnant, while the percentage of patients who showed progression was also similar to that previously described (9.1% vs. 11%). However, in our study the percentage of SD and PR was higher (77.2% vs. 51.2%) and lower (13.6% vs. 37.8%), respectively compared to recently published literature data [8].The differences in these responses are not entirely clear although they could be explained, at least in part, by different causes, such as differences in the histopathological characteristics of the tumor, the size of the tumor remnant, the different clinical response criteria used, the dose and type of DA, and the time on pharmacological treatment.

It is noteworthy that in our study, the analysis of clinical responses showed no significant differences between the DA treated group and the observation group, probably due to the small sample size of the subgroups analyzed. SD was similar in both groups (77.2% vs. 80%); however, the percentage of patients with PR was more than double (13.6% vs. 5%; 2.7-fold) in the DA treated group compared to the observation group, while the percentage of patients showing progression was almost double (15% vs. 9.1%; 1.6-fold) in the observation group versus the DA treated group, despite the fact that the DA treatment time was significantly shorter than the follow-up time of the observation group [13 (10.5–17) vs. 77.5 (50.2-107.2) months, $p < 0.001$]. We must consider that the two study groups were not entirely comparable, as evidenced by the findings in Table 1. This may be due to the fact that clinicians tend to consider treatment with CAB in patients with potentially

more aggressive tumors. In fact, those patients treated with CAB were more symptomatic at diagnosis and 90.5% of the tumors were invasive, compared to 65% of the tumors belonging to the observation group, probably indicating greater aggressiveness, although the Ki-67 index value was similar in both groups.

On the other hand, it is also unclear why the OBS group of our study behaves differently compared with the pooled data form the literature [8]. In this sense, our patients showed a higher percentage of SD (80% vs. 59.8%) and PR (5% vs. 0.05%) with a lower percentage of progression (15% vs. 35%), in the absence of treatment with post-surgery radiotherapy. It is possible that factors such as, histological type of tumor, Ki-67 index, and the size of the remnant may have influenced these differences.

The results of the pooled analysis of all patients treated with CAB to date along with our patients demonstrate some degree of efficacy of CAB in controlling tumor remnant growth after the first surgery in a substantial proportion of patients with NFPA.

Although alterations in cardiac valves have been reported in patients receiving high doses of DAs for prolonged periods in patients with Parkinson's disease, a recent analysis performed in a large number of patients with prolactinoma (n = 646) treated with CAB (median weekly dose 2.1 mg for > 6 months) did not detect any association between the use of this drug and the development of clinically significant valvular heart disease [34]. We also did not detect clinically significant valvulopathies, severe psychiatric syndromes or impulse disturbances associated with CAB use in our population. Although the drug had to be withdrawn in three patients (13.6%) due to mild symptomatology, associated with low doses of CAB (< 2 mg/week).

The main limitations of our study derive from its retrospective nature, the lack of uniformity in the clinical criteria for the initiation of medical treatment with CAB, the short treatment period, the lack of homogeneity between the CAB group and the OBS group, with a higher disease burden in the former and a longer follow-up period in the latter, and the absence of analysis of DR2. Among the strengths are the fact that it is a multicenter study, the number of patients evaluated (second largest retrospective study analyzed in primary prevention) and the knowledge of the histological study of tumor together with the value of the Ki-67 index.

In conclusion, although our study showed no significant differences in the type of tumor response between the two groups of patients, most likely due to the small sample size, the percentages of PR and progression were higher in the CAB and OBS groups, respectively. These results could indicate a possible therapeutic benefit of CAB in the management of

tumor remnant in patients with NFPAs. Further randomized controlled studies conducted in a larger number of patients are needed to definitively demonstrate the therapeutic effect of CAB in preventing tumor remnant growth after initial surgery in NFPA patients.

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Table 1 Clinical data at diagnosis of 62 patients with NFPA with tumor remnant after surgery treated (n = 22) and not treated (n = 40) with cabergoline

	CAB group	OBS group	Total
Number of patients, n (%)	22 (35.5)	40 (64.5)	62 (100)
Sex (male), n (%)	9 (40.9)	23 (57.5)	32 (51.6)
Age (mean ± SD)	58.6 ± 14.0	59.6 ± 14.0	59.3 ± 13.9
Incidental finding on imaging study, n (%)	3 (13.6)	19 (47.5)***	22 (35.5)
Headache, n (%)	11 (50.0)	22 (55.0)	33 (53.2)
Visual disturbances, n (%)	13 (59.1)	19 (47.5)	32 (51.6)
Hypopituitarism, n (%)	18 (81.8)	21 (52.5)*	39 (62.9)
ACTH deficiency	7 (31.8)	12 (30.0)	19 (30.6)
TSH deficiency	6 (27.3)	12 (30.0)	18 (29.0)
Gonadotropin deficiency	17/21 (81.0)	18/39 (46.2)**	35/60 (58.3)
GH deficiency	8/20 (40.0)	9/39 (23.1)	17/59 (28.8)
Diabetes insipidus	1 (4.5)	1 (2.5)	2 (3.2)
Panhypopituitarism, n (%)	4/21 (19.0)	7/31 (22.6)	11/52 (21.2)
Maximum tumor diameter (mm), median (IQR)	27.5 (16.0-34.5)	25.5 (18.2–32.0)	25.5 (17.7–34.0)
Maximum tumor diameter (mm) of the tumor remnant after surgery, median (IQR)	11.5 (6.0-16.9)	8.5 (6.0-13.7)	9.5 (6.0–14.0)
Chiasmatic compression, n (%)	15 (68.2)	27 (67.5)	42 (67.6)
Cavernous sinus invasión, n (%)	19/21 (90.5)	26 (65.0)	45/61 (73.8)
Ki-67 (%)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	2 (1.0-2.5)
Type of surgery, n (%)			
EETS	21 (95.5)	36 (90.0)	57 (91.9)

Table 1 Clinical data at diagnosis of 62 patients with NFPA with tumor remnant after surgery treated (n = 22) and not treated (n = 40) with cabergoline

	CAB group	OBS group	Total
MTS	1 (4.5)	4 (10.0)	5 (8.1)
TC	0	0	0

Abbreviations: CAB, cabergoline; **EETS**, endoscopic endonasal transsphenoidal surgery; **IQR**, interquartile range; **MTS**, microscopic transsphenoidal surgery; **OBS**, observation; **TC**, transcranial surgery. *p = 0.02; **p = 0.009; ***p = 0.007

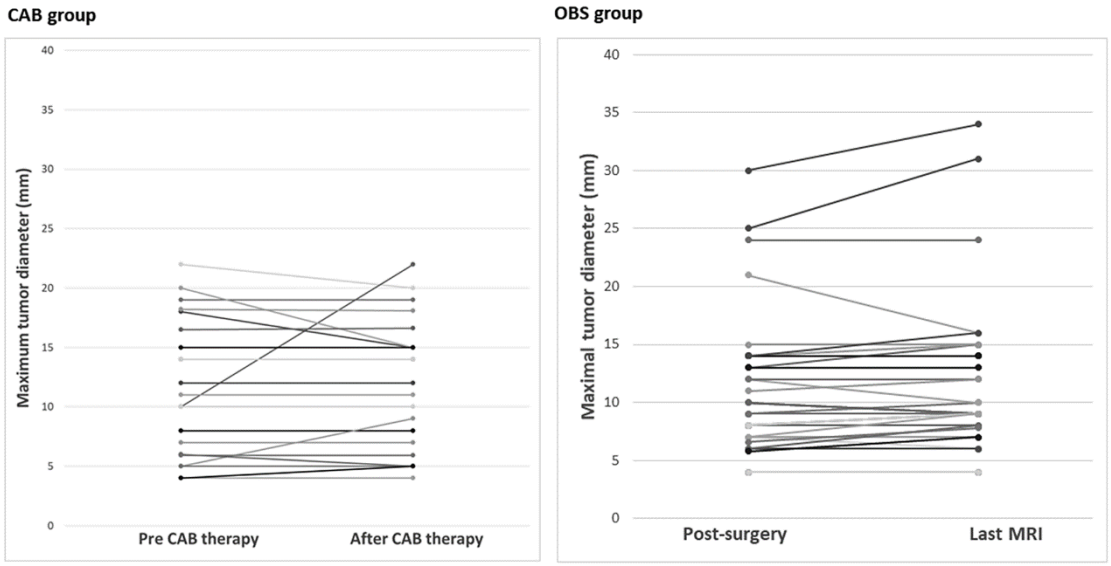

Fig. 1 Individual evolution of the maximum tumor diameter of the tumor remnant after surgery until the last revision in 20 patients treated with cabergoline (left) and in 40 patients under active surveillance (right)

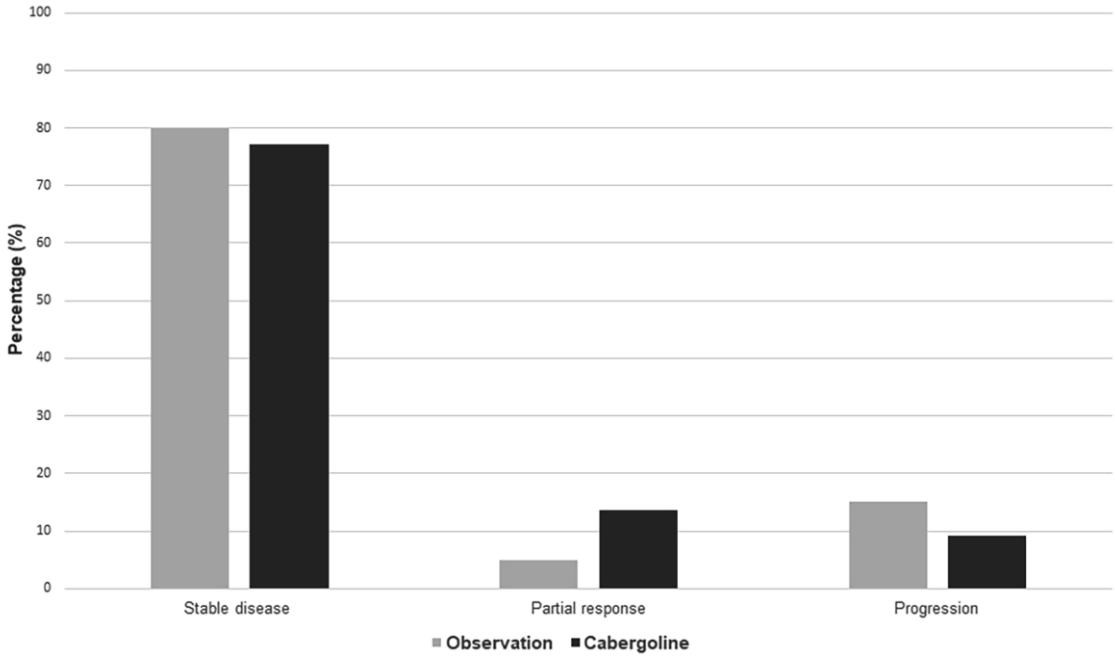

Fig. 2. Clinical response rates (stable disease, partial response, and progression) of tumor remnant after surgery in patients treated with cabergoline (CAB group, n = 22) and patients followed with active surveillance (OBS group, n = 40) (chi-square 1.71, p = 0.42)

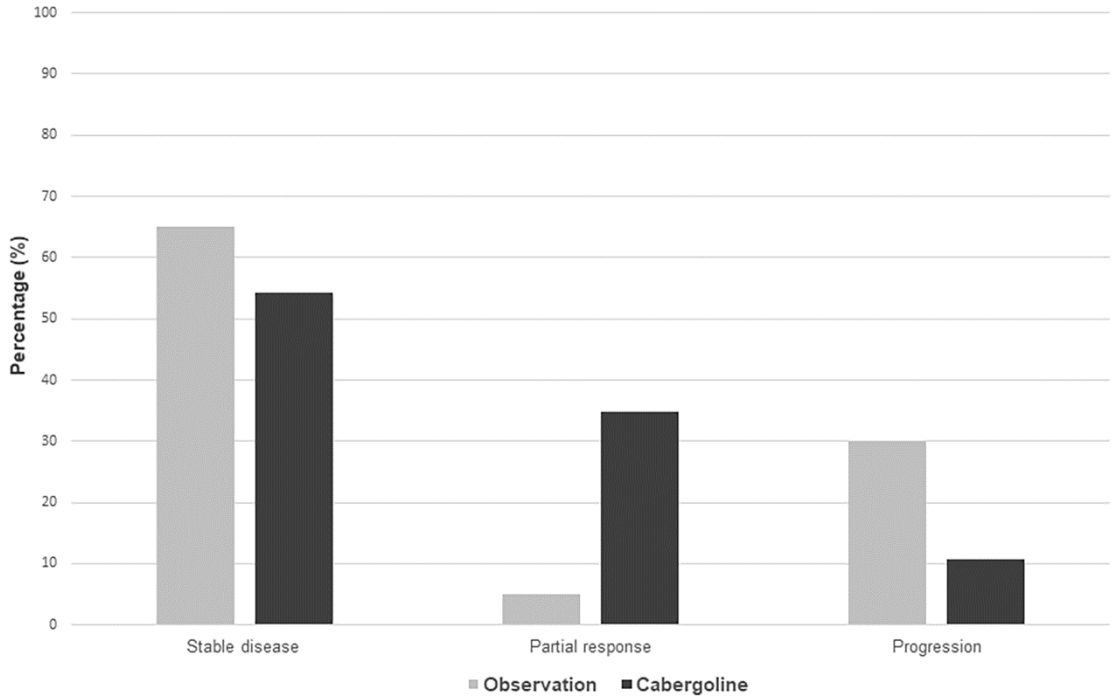

Fig. 3. Clinical response rates (stable disease, partial response, and progression) of tumor remnant after surgery in patients treated with CAB (n = 186) and patients followed with active surveillance (OBS group, n = 157) obtained from literature data [8] together with those of our patients (chi-square 53.32, $p < 0.00001$)