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Real-World Outcomes of Cabergoline Treatment in Non-Functioning Pituitary Adenomas: An Insight into Dose Responsiveness and Radiological Follow-Up at a UK Tertiary Centre

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Abstract

Introduction: Evidence on the use of dopamine agonists (DAs) for managing residual or recurrent non-functioning pituitary adenomas (NFPAs) is limited. We aim to evaluate the use of cabergoline (CAB) for NFPAs. **Methods:** A retrospective cohort study was conducted at a single UK centre, between November 2011 and December 2025. Twenty-six patients were identified. Ten patients were excluded due to CAB intolerance or discontinuation (n = 5), insufficient data (n = 4), or invalid scan due to patient movement (n = 1). The remaining 16 patients (mean age 68.9 ± 4 years (range 42–89 years old), 7/16 females) were included. CAB was initiated in cases where surgery or radiotherapy were not appropriate (e.g., due to age and/or comorbidities, or patient choice). Radiological response was assessed using at least two scans separated by a minimum interval of six months. Tumour shrinkage was defined as a reduction in volume of 20% or more, growth as an increase of 20% or more, and stabilisation as interval change of less than 20%. **Results:** Overall, tumour shrinkage was observed in 7/16 (43.8%) patients, stabilisation in the remaining 9/16 (56.3%) patients, over 503 ± 51 days (range of 117–934 days) (from the date of CAB initiation to latest MRI scan). There was a statistically significant reduction in tumour volume (p = 0.0335). In five patients with documented tumour growth prior to CAB initiation, growth rates retarded or reversed post-CAB initiation. **Conclusions:** Our findings in this small cohort potentially suggests that cabergoline can retard, arrest, or even reverse tumour growth in selected patients with NFPAs. Our review also highlights ongoing uncertainty regarding optimal dosing, approaches to dose up-titration, follow-up imaging intervals, and objective criteria for defining radiological response. Our results may provide a proof of concept for future, larger-scale prospective studies and controlled trials to validate the conclusions drawn.

Keywords: dopamine agonists; pituitary neoplasms; cabergoline; adenoma; retrospective studies

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1. Introduction

Non-functioning pituitary adenomas (NFPAs) are benign tumours characterised by the absence of clinical or biochemical evidence of pituitary hormonal hypersecretion, aside from associated hyperprolactinaemia due to pituitary stalk deviation [1]. Due to their non-secretory nature, NFPAs are often discovered incidentally on imaging or remain clinically silent until significant tumour growth leads to compressive symptoms, particularly visual loss and hypopituitarism [2]. NFPAs have an annual reported incidence of 20.3 cases per 1 million [3], and they are further classified according to their pituitary hormone and transcription factor profile, as defined by the 2017 World Health Organization (WHO) classification for endocrine tumours [4].

The mainstay of treatment for symptomatic NFPAs is transsphenoidal surgery (TSS). However, complete resection is often not feasible due to factors such as large tumour size, local invasion of adjacent structures, or unfavourable tumour consistency [5]. Long-term follow-up is therefore essential, and further intervention is often required in cases with significant residual tumour, particularly where the visual apparatus is at risk or where post-operative tumour growth occurs.

For those with progressive residual tumours, multimodal treatment strategies, including repeat surgery and adjuvant fractionated stereotactic radiotherapy or radiosurgery, may be employed to achieve prolonged disease control [6]. This is especially important given that, over a mean of 6.1 years, untreated residual tumour tissue is associated with a reported progression rate of 34.8% [7].

In cases where surgery or radiotherapy is not possible—due to frailty, comorbidities, or tumour location, or when patients decline these options—dopamine agonists (DAs) may be considered. DAs have been used in such cases to provide a non-invasive treatment alternative, particularly when tumour progression threatens to compromise visual function [8–24].

This retrospective cohort study examines the efficacy of cabergoline (CAB), a dopamine agonist, in the management of NFPAs, aiming to better understand its role in this challenging clinical context.

2. Materials and Methods

2.1. Study Design

A retrospective study was conducted from a single centre, which looked at the management of NFPAs using dopamine agonists. Our methods and results were reported according to the STROBE guidelines [25].

2.2. Setting

A search on our electronic outpatient letters database (electronic document template) was carried out using the keywords “non-functioning”, “incidentaloma”, “cabergoline”, “quinagolide”, “bromocriptine” and “dopamine agonist”.

2.3. Outcomes

Radiological response was based on one or two follow-up (FU) scans with an interval of at least six months. Tumour shrinkage was defined as a reduction in volume of 20% or more, growth as an increase in volume of 20% or more, and stabilisation as a variability in volume of less than 20%. Tumour volume was calculated based on the maximum x, y, and z diameters measured on sagittal and coronal images. Assuming a spherical volume, the formula $4/3\ \pi r^3$ would then be used for volume calculation, with r being the mean of the x, y, and z radii.

2.4. Data Measurement

Data collection included tumour size before initial surgery (in patients who underwent TSS), tumour size on diagnosis when intervention with CAB was considered, and on post-treatment with CAB, along with the dosing schedule of CAB for individual patients. All MRI scans were interpreted independently by two radiologists. Demographic data including patient age at diagnosis, gender, baseline visual fields, prolactin levels and cabergoline dosage were also collected. All eligible patients were systematically included from the database search. The pre-CAB scan was defined as the last pituitary MRI scan prior to CAB initiation. The 1st FU scan was the first scan post-CAB initiation. The 2nd FU scan was the second scan post-CAB initiation. The latest MRI scan was the latest scan in patients who had two FU scans. The treatment interval was calculated in days, from the date of recommendation of cabergoline (based on the outpatient clinic or advice letter) to the date of the scan, excluding the end date from the calculation. The interval between scans was calculated in days, between the actual imaging, excluding the end date from the calculation.

2.5. Statistical Analysis

Statistics were performed using the IBM SPSS Statistics Software Version 29.0.2.0. The normality of tumour volume changes between pre- and post-treatment with CAB were assessed with Kolmogorov–Smirnov and Shapiro–Wilk tests ($p \leq 0.05$). Descriptive statistics such as means and standard deviations were used to summarise the normally distributed data, whilst medians and interquartile ranges were used to summarise the data that were not normally distributed.

The Wilcoxon signed-rank test was utilised to evaluate the significance of tumour volume changes between the pre-CAB and the latest MRI scans. This paired non-parametric test was utilised due to the non-parametric distribution of tumour volumes. For patients with more than one FU scan, the latest scan was used for analysis. A within-patient paired comparison was used, where each patient's tumour volume pre-CAB initiation was compared with their own latest FU scan post-CAB initiation.

Growth rate changes between pre- and post-treatment with cabergoline were assessed using a paired *t*-test. Spearman's rank correlation was performed to assess the relationship between CAB dose and tumour volume change between the pre-CAB and the latest MRI scans, as well as between treatment interval and tumour volume change between the pre-CAB and the latest MRI scans.

Using our keywords, a total of 26 patients were identified under the Endocrine Department from November 2011–December 2025. Our study included 16 patients in total after applying the exclusion criterion (Figure 1).

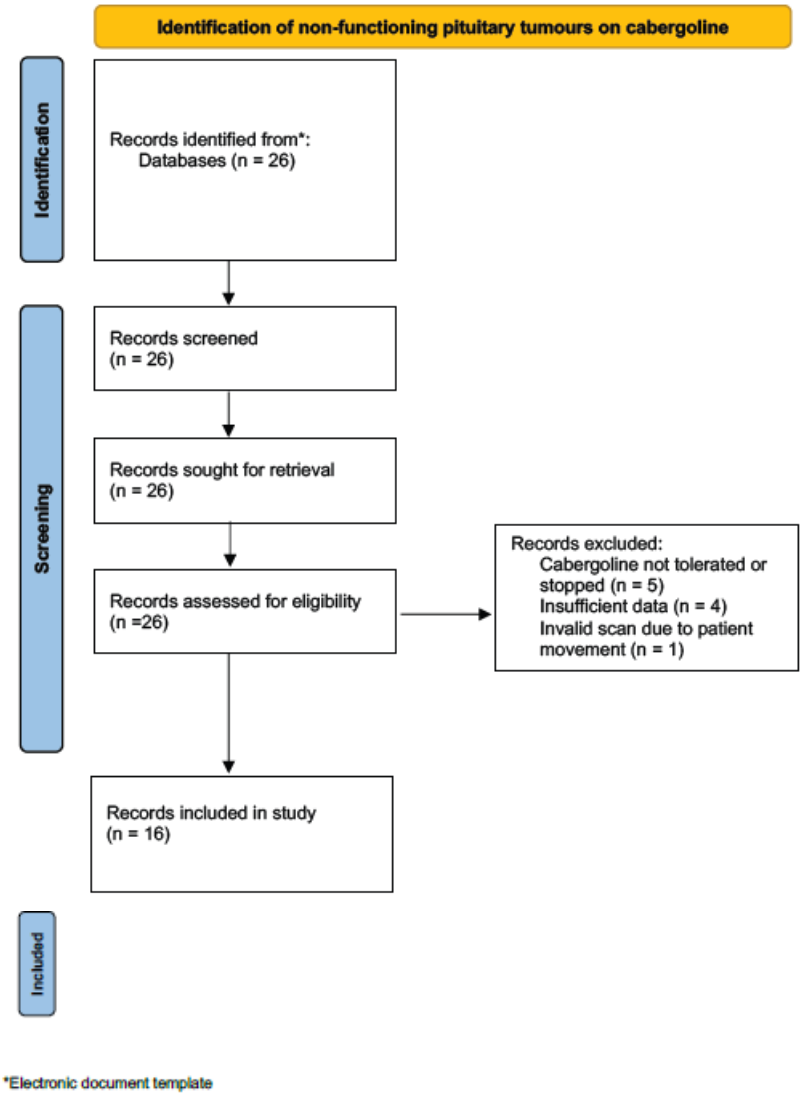

Figure 1. PRISMA flow diagram illustrating the selection process of patients.

3. Results

3.1. Patient and Sample Characteristics

The 16 analysed subjects had a mean age of 68.9 ± 4 years (range 42–89 years old) and 7/16 (43.8%) were females. All 16 patients were offered CAB as the dopamine agonist of choice. Out of the 16, six patients were offered CAB post-surgery (Table 1).

The median tumour volume pre-CAB initiation was 3073.3 mm^3 (IQR 1477.5–4387.3 mm^3) (Table 1).

Mean tumour diameter pre-CAB initiation (measured as the longest diameter in the axial plane) [26] was 20.6 ± 1.3 mm (range of 12.2–31.9 mm) (Table 1).

At the time of CAB initiation, in the non-operated group (ten patients), 9/10 had normal visual fields on direct confrontation, and one had bitemporal superior quadrantanopia on Goldmann perimetry. In the operated group (six patients), while there was evidence of visual field compromise pre-surgery (bitemporal hemianopia on Goldmann perimetry) in all patients, there was complete resolution post-surgery and at the time of CAB initiation. In the operated group, 5/6 (83.3%) patients (IDs 6, 10, 13, 15, 16) of the operated group had normal visual fields on confrontation at the time CAB initiation, whilst 1/6 (16.7%) patients (ID 7) had a pre-existing blind right eye due to glaucoma at the time of CAB initiation (Table 1).

Table 1. Patient characteristics.

ID	Gender	Age	Pre or Post-Surgery	Pre-CAB Maximal Diameter of Tumour (mm)	Pre-CAB Tumour Volume (mm^3)	Baseline Visual Fields (on Initiation of Cabergoline)	Indication for Starting Cabergoline: (1) Surgery Not Possible Due to Patient Age/Comorbidities, or (2) Surgery Declined by the Patient, (3) Enlarging Tumour, (4) Substantial Tumour Remnant Post-Surgery	Cabergoline Titrating Schedule	Final Weekly Cabergoline Dosage (mcg)
1	Female	44	Pre	17.9	1618.4	Normal	2 + 3	250 mcg once weekly	250
2	Male	49	Pre	23.9	5012.5	Normal	2	500 mcg twice weekly	1000
3	Male	76	Pre	14.6	703.3	Normal	1 + 3	500 mcg thrice weekly	1500
4	Female	72	Pre	14.8	1014.5	Normal	1	500 mcg once weekly	500
5	Male	86	Pre	19.9	3648.4	Normal	1	250 mcg once weekly	250
6	Male	55	Post	20.3	3535.0	Normal (bitemporal hemianopia pre-surgery which resolved afterwards)	2 + 3 + 4	250 mcg thrice weekly	750
7	Female	42	Post	18.7	2239.9	Blind right eye post-surgery (due to glaucoma)	2 + 4	250 mcg twice weekly	500
8	Male	89	Pre	28.1	7513.1	Normal	1 + 3	250 mcg once daily	1750
9	Male	85	Pre	23.6	3902.4	Normal	1 + 3	250 mcg once weekly for 9 months, then increased to 1000 mcg once weekly for 6 months, then increased to 1000 mcg twice weekly for 2 months, then increased to 1000 mcg thrice weekly	3000
10	Female	49	Post	31.9	11,453.0	Normal (bitemporal hemianopia pre-surgery which resolved afterwards)	2 + 4	500 mcg once weekly for 7 weeks, then increased to 1000 mcg once weekly for 3 weeks, then increased to 1500 mcg once weekly for 3 weeks, then increased to 2000 mcg once weekly for 3 weeks, then increased to 2500 mcg once weekly for 3 weeks, then increased to 3000 mcg once weekly	3000
11	Male	83	Pre	21.5	4872.2	Normal	1	500 mcg twice weekly	1000
12	Male	86	Pre	20.5	2648.8	Normal	1	500 mcg twice weekly	1000
13	Female	63	Post	26.0	3497.7	Normal	1 + 2 + 4	1000 mcg thrice weekly	3000
14	Female	80	Pre	21.0	2424.1	Bitemporal superior quadrantanopia	1 + 2	500 mcg once daily	3500
15	Female	75	Post	15.0	1336.6	Normal	1 + 3	500 mcg once weekly for 6 weeks, then increased to 500 mcg twice weekly for 6 weeks, then increased to 500 mcg thrice weekly	1500
16	Male	69	Post	12.2	653.5	Normal	1 + 3	500 mcg thrice weekly	1500

3.2. Histopathology of Post-Surgical Patients

Three patients had gonadotroph adenomas, one had a corticotroph adenoma, one had a plurihormonal adenoma with mixed corticotroph and gonadotrophin lineage, and histopathology was not available for the remaining one patient.

3.3. Prolactin Concentrations

The median prolactin concentrations prior CAB initiation were 241 mIU/L (IQR 151.8–535.3 mIU/L) (normal range of 40–530 mIU/L).

3.4. Other Pituitary Hormonal Profile Concentrations

Full pituitary hormonal profiles were also performed prior to CAB initiation and during follow-up, including thyroid, adrenal, growth hormone and gonadotroph axes. Three patients had pre-existing hypothyroidism and remained on levothyroxine pre and post-CAB initiation. There were no significant changes to their levothyroxine dose following CAB initiation. In the remaining patients, all were eupituitary prior to treatment, and no new endocrine dysfunction was observed following CAB treatment.

3.5. Cabergoline Dosing and Monitoring:

The median CAB dosage was 1250 mcg weekly (IQR 625–2375 mcg weekly), with variable titrating schedules to achieve maximal dosing (Table 1).

No incidence of CAB-related hormonal disturbance or visual disturbance occurred during follow-up for all of our patients.

3.6. Radiotherapy

In total, 2/16 (12.5%) patients (ID 6, 7) received radiotherapy treatment prior to CAB initiation.

4. Radiological Response Following Cabergoline Initiation

4.1. First FU Scan

After CAB initiation, there was a variable interval to the first FU scan (from the date of CAB initiation) (90–612 days) with a mean interval of 275 ± 36 days (Table 2).

Table 2. Tumour volumes in the pre-CAB scan to 1st FU scan.

ID	Pre-CAB Volume (mm^3)	1st FU Volume (mm^3)	Pre-CAB vs. 1st	Time Between Pre-CAB Scan to 1st FU Scan (Days)	Duration of CAB Treatment (CAB Initiation—1st FU Scan) (Days)	Result Pre-CAB vs. 1st FU
1	1618.4	1177.1	0.73	918	358	Shrinkage
2	5012.5	1674.6	0.33	266	214	Shrinkage
3	703.3	690.6	0.98	436	315	Stable
4	1014.5	1064.1	1.05	335	326	Stable
5	3648.4	3942.5	1.08	181	153	Stable
6	3535.0	2919.9	0.83	245	139	Stable
7	2239.9	2395.1	1.07	350	90	Stable
8	7513.1	6124.6	0.82	273	200	Stable
9	3902.4	4599.5	1.18	482	187	Stable
10	11,453.0	13,215.5	1.15	445	225	Stable
11	4872.2	3279.5	0.67	378	117	Shrinkage
12	2648.8	2158.1	0.81	398	357	Stable
13	3497.7	3591.4	1.03	464	346	Stable
14	2424.1	2572.4	1.06	611	501	Stable
15	1336.6	943.0	0.71	315	181	Shrinkage
16	653.5	722.6	1.11	698	612	Stable

Out of the 16 patients, tumour shrinkage was demonstrated in 4/16 (25%) patients (IDs 1, 2, 11, 15) (including one post-surgery patient, ID 15) while the remaining 12/16 (75%) patients (IDs 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 16) demonstrated tumour stability (including five post-surgery patients; IDs 6, 7, 10, 13, 16) (Table 2). Whilst there was still absolute

tumour growth in 8/16 (50%) patients (IDs 4, 5, 7, 9, 10, 13, 14, 16), they were classified as stabilisation, as the volume increase remained below the >20% threshold for growth.

4.2. Second FU Scan

Out of the 16 patients, a second FU scan was performed in 11/16 (68.8%) patients at the time of undertaking the data collection.

Post-CAB initiation, there was a variable interval to the second FU scan (from the date of CAB initiation) (247–934 days) with a mean interval of 561 ± 56 days (Table 3).

Table 3. Tumour volumes in the pre-CAB scan to 2nd FU scan.

ID	Pre-CAB Volume (mm^3)	2nd FU Volume (mm^3)	Pre-CAB vs. 2nd FU	Time Between Pre-CAB Scan to 2nd FU Scan (Days)	Duration of CAB Treatment (CAB Initiation- 2nd FU Scan) (Days)	Result Pre-CAB vs. 2nd FU
2	5012.5	518.4	0.10	510	458	Shrinkage
3	703.3	796.3	1.13	1055	934	Stable
4	1014.5	974.3	0.96	701	692	Stable
5	3648.4	1814.7	0.50	538	510	Shrinkage
6	3535.0	2726.7	0.77	419	313	Shrinkage
7	2239.9	1887.6	0.84	507	247	Stable
8	7513.1	4711.8	0.63	623	550	Shrinkage
9	3902.4	4134.6	1.06	817	551	Stable
10	11,453.0	13,215.5	1.15	899	679	Stable
13	3497.7	2887.1	1.03	774	656	Stable
15	1336.6	943.0	0.71	704	570	Shrinkage

Out of the 11, five (45.5%) patients (IDs 2, 5, 6 (post-surgery patient), 8, 15 (post-surgery patient)) demonstrated shrinkage while the remaining (54.5%) patients (IDs 3, 4, 7 (post-surgery patient), 9, 10 (post-surgery patient), 13 (post-surgery patient)) demonstrated tumour stability (Table 3). Whilst there was still absolute tumour growth in 3/11 (27.3%) patients (IDs 3, 9, 10), they were classified as stabilisation, as the volume increase remained below the >20% threshold for growth.

4.3. Combining Both First and Second FU Scans

Overall, combining the first and second FU scans (using the latest scan in patients who had two scans), 7/16 (43.8%) patients demonstrated tumour shrinkage (IDs 1, 2, 5, 6 (post-surgery and radiotherapy patient), 8, 11, 15 (post-surgery patient)) and the remaining (56.3%) patients demonstrated stabilisation (IDs 3, 4, 7 (post-surgery and radiotherapy patient), 9, 10 (post-surgery patient), 12, 13 (post-surgery patient), 14, 16 (post-surgery patient)). Whilst there was still absolute tumour growth in 6/16 (37.5%) patients (IDs 3, 9, 10, 13, 14, 16), they were classified as stable, given that the overall volume increase remained less than 20%.

Using the 20% threshold for defining growth, none of the patients demonstrated interval growth post-CAB initiation, at a mean interval (from the date of CAB initiation) of 503 ± 51 days (117–934 days) (Table 4).

Table 4. Tumour volumes in pre-CAB scan, and tumour volumes when combining the 1st and 2nd FU scans (using the latest scan in patients who had two scans).

ID	Pre-CAB Volume (mm^3)	Latest FU Volume (mm^3)	Pre-CAB vs. Latest FU	Time Between Pre-CAB Scan to Latest FU Scan (Days)	Duration of CAB Treatment (CAB Initiation—Latest FU Scan) (Days)	Result Pre-CAB vs. Latest FU
1	1618.4	1177.1	0.73	918	358	Shrinkage
2	5012.5	518.4	0.10	510	458	Shrinkage
3	703.3	796.3	1.13	1055	934	Stable
4	1014.5	974.3	0.96	701	692	Stable
5	3648.4	1814.7	0.50	538	510	Shrinkage
6	3535.0	2726.7	0.77	419	313	Shrinkage
7	2239.9	1887.6	0.84	507	247	Stable
8	7513.1	4711.8	0.63	623	550	Shrinkage
9	3902.4	4134.6	1.06	817	551	Stable
10	11,453.0	13,215.5	1.15	899	679	Stable
11	4872.2	3279.5	0.67	378	117	Shrinkage
12	2648.8	2158.1	0.81	398	357	Stable
13	3497.7	2887.1	1.03	774	656	Stable
14	2424.1	2572.4	1.06	611	501	Stable
15	1336.6	943.0	0.71	704	570	Shrinkage
16	653.5	722.6	1.11	698	612	Stable

4.4. Tumour Volume

The median tumour volume pre-CAB initiation was 3073.3 mm^3 (IQR 1477.5–4387.3 mm^3).

The median tumour volume post-CAB initiation at the first FU scan was 2483.8 mm^3 (IQR 1120.6–3767.0 mm^3).

The median tumour volume post-CAB initiation at the second FU scan was 1887.6 mm^3 (IQR 943.0–4134.6 mm^3).

Overall (using the latest scan for those that received two scans), the median tumour volume post-CAB initiation at the latest MRI scan was 2022.9 mm^3 (IQR 958.7–3083.3 mm^3).

Overall, there was a statistically significant reduction in tumour volume between the pre-CAB scan and the latest MRI scan ($p = 0.0335$) (Wilcoxon signed-rank test). For patients with more than one FU scan, the latest scan was used for analysis here.

4.5. Maximal Tumour Diameter

The mean tumour diameter pre-CAB initiation (measured as the longest diameter in the axial plane) [26] was 20.6 $\pm$ 1.3 mm (range of 12.2–31.9 mm).

The median tumour diameter on the first FU scan was 19.8 mm (IQR 16.3–23 mm).

The median tumour diameter on the second FU scan (for 11 patients) was 19.2 mm (IQR 14.5–22.6 mm).

4.6. Correlation Between CAB Dose and Radiological Response

Overall, there was a moderate positive correlation ($r_s = 0.53$, $p = 0.036$) (Spearman's rank correlation) between CAB dosage and tumour volume change from the pre-CAB MRI scan to the latest MRI scan, as well as a moderate positive correlation ($r_s = 0.50$, $p = 0.061$) (Spearman's rank correlation) between the CAB treatment interval and tumour volume change from the pre-CAB MRI scan to the latest MRI scan. However, this was not statistically significant ($p = 0.061$).

4.7. Five Patients with Documented Absolute Tumour Growth Prior to CAB Initiation

In five patients (IDs 1, 3, 6, 8, 9), additional MRI scans prior to CAB initiation were available. All five patients had positive growth rates before CAB treatment, of which 3/5 (60%) (IDs 3, 6, 9) experienced tumour growth whilst the remaining two (IDs 1, 8) experienced tumour stabilisation between the additional MRI prior to CAB initiation and the pre-CAB scan (Table 5). Patient ID 6 had a large tumour remnant post-surgery with evidence of post-surgical interval growth. Absolute tumour growth occurred in two patients (IDs 1, 8) but they were classified as stabilisation as the volume increase remained below the >20% threshold for growth.

Table 5. Positive growth rates of patients with enlarging tumours.

ID	Additional MRI Prior to CAB Initiation Volume (mm^3)	Pre-CAB Volume (mm^3)	Additional MRI vs. Pre-CAB	Growth Rate from Additional MRI to Pre-CAB (mm^3/days)
1	1574.3	1618.4	1.03	+0.04
3	523.6	703.3	1.34	+0.38
6	1838.8	3535.0	1.92	+1.62
8	5937.6	7513.1	1.27	+2.01
9	3671.3	3902.4	1.06	+1.96

4.8. Growth Rate

The data for growth rates pre- and post-CAB initiation were only available for five patients (IDs 1, 3, 6, 8, 9). Due to a variable time period between the additional MRI scan performed prior to CAB initiation and the pre-CAB scan between patients, the growth rate was calculated from the absolute tumour volume change (pre-CAB scan volume–additional MRI prior to CAB-initiation volume) divided by the number of days elapsed between the scans, excluding the end date from the calculation.

Growth rates prior to CAB initiation ranged from +0.04 mm^3/day (ID 1) to +2.01 mm^3/day (ID 8), with a mean growth rate of +1.20 ± 0.41 mm^3/day (Table 5).

Post-CAB initiation, tumour growth rates either retarded or reversed in all five patients at the first FU scan, over 245–918 days (mean time of 471 ± 121 days). By the first FU scan, the mean growth rate dropped to −1.87 ± 0.93 mm^3/day (range of −0.17–−5.09 mm^3/day). Patient 8 had the largest reduction, transitioning from +2.01 mm^3/day pre-treatment to −5.09 mm^3/day after initiation of CAB (Table 6).

Table 6. Growth rate of tumours, between the additional MRI prior to CAB initiation to pre-CAB scan, between pre-CAB scan to 1st FU scan, and between the pre-CAB scan to 2nd FU scan.

ID	Additional MRI Prior to CAB Initiation Volume (mm^3)	Pre-CAB Volume (mm^3)	1st FU Volume (mm^3)	2nd FU Volume (mm^3)	Additional MRI vs. Pre-CAB	Growth Rate from Additional MRI to Pre-CAB (mm^3/days)	Pre-CAB vs. 1st FU Scan	Growth Rate from Pre-CAB to 1st FU (mm^3/days)	Pre-CAB vs. 2nd FU Scan	Growth Rate from Pre-CAB to 2nd FU (mm^3/days)	Result Additional MRI vs. Pre-CAB	Result Pre-CAB vs. 1st FU	Result Pre-CAB vs. 2nd FU
1	1574.3	1618.4	1177.1	N/A	1.03	+0.04	0.73	−0.17	N/A	N/A	Stable	Shrinkage	N/A
3	523.6	703.3	690.6	796.3	1.34	+0.38	0.98	−0.03	1.13	+0.09	Increase	Stable	Stable
6	1838.8	3535.0	2919.9	2726.7	1.92	+1.62	0.83	−2.51	0.77	−1.93	Increase	Stable	Shrinkage
8	5937.6	7513.1	6124.6	4711.8	1.27	+2.01	0.82	−5.09	0.63	−4.50	Increase	Stable	Shrinkage
9	3671.3	3902.4	4599.5	4134.6	1.06	+1.96	1.18	−1.54	1.06	+0.28	Stable	Stable	Stable

By the second FU scan, patients 6 and 8 demonstrated sustained reductions in tumour volume whilst patients 3 and 9 demonstrated stability in 419–918 days (mean time of 644 ± 141 days). The mean growth rate was −1.52 ± 1.11 mm^3/day (range of −4.50–+0.28 mm^3/day) (Table 6). A second scan for patient 1 was not available.

The analysis of the tumour growth rates before and after CAB initiation (from pre-CAB to first FU scan) demonstrated a mean reduction of 3.070 ± 1.281 mm^3/day in 245–918 days

(mean time of 471 ± 121 days) (one-tailed p-value = 0.037, paired t-test); 95% CI: −0.486 to +6.626 mm^3/day. Cohen's d was 1.072 (>0.8).

5. Discussion

5.1. Principal Findings

Our study has shown that the use of cabergoline in patients with NFPAs is associated with a statistically significant shrinkage or stabilisation of tumour volume.

When comparing responses in all 16 patients by their latest scan (mean interval of 503 ± 51 days), 7/16 (43.8%) demonstrated tumour shrinkage and the remaining 9/16 (56.3%) patients demonstrated stabilisation. An overall statistically significant reduction in tumour volume was also observed (p = 0.0335).

Out of 16 patients in our cohort, 4/16 (25%) demonstrated shrinkage on the first FU scan at a mean time of 275 ± 36 days. The second FU scan, which was undertaken at an extended interval in comparison on 11/16 (68.8%) patients, demonstrated tumour reduction in 5/11 (45.5%) of patients at a mean time of 561 ± 56 days. Three patients (IDs 5, 6, 8) had initially shown stability on the first FU scan and subsequently demonstrated shrinkage on the second FU scan.

Out of five patients (IDs 1, 3, 6, 8, 9) who had data on pre- and post-treatment growth rates, a mean reduction of 3.070 ± 1.281 mm^3/day was observed at a mean time of 471 ± 121 days (one-tailed p-value = 0.037), demonstrating evidence of retarded growth post-cabergoline initiation.

5.2. Comparison with Related Literature

The current main treatment option for vision threatening or enlarging NFPAs is surgery. In untreated, surgery-naïve NFPAs, the risk of tumour growth has been reported to be 27% by 4 years [27] and 51% by 5 years [28].

Following TSS, some patients may still have residual tumours. The rates of achieving complete resection (leaving no residual tumour) [29] have been reported to range between 43 and 90% for endoscopic and 40 and 65% for microscopic TSS [30]. In residual disease, where there is an obvious tumour remnant [29], regrowth has been reported at 34.8% [7] and 36.2% at five years after partial excision [31]. In particular, patients with extrasellar remnants had lower recurrence-free survival rates than those with intrasellar remnants (23.1% and 58.3% respectively) at ten years [32]. Complete resection is associated with higher progression-free survival rates compared with residual disease (92.4% vs. 72.1% at five years) [33], supporting the notion that tumour remnants carry a risk of regrowth if left unchecked.

If regrowth of the tumour remnant occurs, the options at present are further surgery or radiotherapy. In patients that were offered post-operative radiotherapy, 85–95% achieved tumour control at five to ten years post-operatively [34]. Its routine use, however, is limited due to the association with a high rate of complications, including a 13.62% risk of developing hypopituitarism and 2.55% risk of panhypopituitarism [35]. Repeated surgery is necessary in cases of impending or definite visual compromise but carries an additional risk of post-operative hypopituitarism, cerebrospinal fluid leak, meningitis, cranial nerve damage, and visual compromise, along with a mortality rate of 0.3–0.5% [36]. Subsequent surgery and radiotherapy also carries an increased risk of corticotropic and thyrotropic deficiency rates (38% and 59% after second or third surgical operation, and 40% and 73% after radiotherapy, respectively) [37].

Treatment with DAs, in particular cabergoline, have been evaluated for their potential clinical use in managing NFPAs in the past [8–18,21,22,24,38]. In addition to this, NFPAs express dopamine receptors (DR) [23], primarily dopamine receptor 2 (DR2) [39]. Based

on this, DAs have been the most studied, providing a potential therapeutic benefit in managing NFPAs. Overall, dopamine agonists like bromocriptine, quinagolide, and notably cabergoline (1–3 mg/week over 6–12 months) in the above studies demonstrate significant potential in reducing residual tumour growth post-surgery.

Role of Dopamine Agonists in Management of NFPAs

Most NFPAs have dopamine receptors and predominantly comprise DR2 [39]. DAs can reduce gonadotropin secretion [24] and inhibit thymidine incorporation in vitro [38], providing a potential therapeutic benefit in NFPAs. However, the variable DR expression in NFPAs suggests that some patients are more likely to respond to DA therapy than others, warranting further investigation into the selection criteria for treatment [23]. Emerging evidence also suggests that NFPA behaviour is based on a complex interplay of multiple lineages, further warranting future research to focus on lineage-specific mapping, which may further refine patient selection for DA therapy in the future [40].

Most of the literature surrounding the use of cabergoline have been retrospective studies [3,7,10–12,14–16,18,19,21,22,27–29,31–33,36,37]. More recently, a meta-analysis reported that cabergoline treatment resulted in tumour shrinkage in 19% of patients and prevented tumour progression in around half of the treated patients, supporting a potential therapeutic role of dopamine agonists in select NFPA patients [41]. A historical cohort analysis across two centres spanning 8.8 ± 6.5 years, with different standard practices for post-TSS NFPA management (bromocriptine and cabergoline) therapy vs. conservative follow-up, demonstrated that 21/55 (38.2%) patients who received DAs had tumour shrinkage (defined as at least a 2 mm change in diameter), whereas none in the conservative follow-up group exhibited tumour shrinkage [12]. Another retrospective study with the same definitions for tumour size change showed that 5/25 (20%) had tumour reduction, 12/25 (48%) demonstrated stabilisation, whilst 8/25 (32%) demonstrated growth over a follow-up period of 4.6 ± 3.4 years whilst treated with cabergoline, with at least 1 mg/week [19]. Another retrospective study with the same definitions for tumour shrinkage as our study (20% or more) found that tumour shrinkage was documented in 29 patients (66%), whereas in 11 (25%) the tumour increased in size and in four (9%), it remained stable [42], which was comparable to our findings. A longer-term study spanning 4.6 ± 3.4 years, however, found less-promising results, where five tumours (20%) decreased in size (mean decrease of 5.0 ± 3.0 mm), 12 tumours (48%) remained stable, and eight (32%) increased in size (mean growth of 5.0 ± 3.3 mm) with cabergoline treatment [19].

There was, however, a randomised clinical trial spanning over two years, demonstrating that in patients with remnant NFPAs post-TSS, out of those who received cabergoline, tumour shrinkage was exhibited in 28.8%, stabilisation in 66.1%, and growth in 5.1% of patients, as opposed to the observation group, which had corresponding figures of 10.5% for shrinkage, 73.7% for stabilisation, and 15.8% for growth [22].

The effectiveness of short-term treatment and the optimal dosing strategy with cabergoline has also been investigated. In one study spanning six months, cabergoline of 2 mg/week showed >25% tumour shrinkage in 6/19 (31.6%) patients, >10% shrinkage in 9/19 (47.4%) patients, and growth in 4/19 (21.1%) patients [15]. Further supporting this, in another trial, 5/9 (55.6%) patients experienced a >25% tumour shrinkage after one year, at a dose of 1–3 mg/week of cabergoline post-TSS [10]. The potential efficacy of cabergoline is further reinforced by minor shrinkage (>10%) in 7/13 (53.8%) patients after treatment for one year, with an initial dosage of 0.25 mg/week, increased by 0.25 mg increments to a maximum of 1 mg/week [11]. Furthermore, another study in 2022 showed that 20/22 (90.9%) patients with residual tumours post-TSS who were treated with cabergoline for a mean time of 13 months (range of 10.5–17 months) exhibited no tumour progression,

compared with the higher progression rates in the observation group, reinforcing the potential role of cabergoline in managing NFPAs [21]. A recent review also suggested that cabergoline doses of 1.5–3 mg/week may be effective in actively growing remnants and high-risk pituitary adenomas [16].

Other dopamine agonists were also studied in the management of NFPAs. Placebo-controlled trials, using a variation in drug protocols, such as bromocriptine (2.5–60 mg/day), quinagolide (300–600 mg/day) and cabergoline (1–3 µg/week), demonstrated that the cumulative evidence for tumour shrinkage after DA therapy in 199 patients was 27.6% [8].

Bromocriptine also shows potential therapeutic benefit. In 32 post-TSS patients with residual NFPAs, after six months of treatment, 11/32 (34.3%) showed tumour reduction, 13/32 (40.6%) showed stabilisation, whilst 8/32 (25%) showed growth. After two years, 10/32 (31.3%) demonstrated further tumour shrinkage, showing that bromocriptine could play a role in managing NFPAs post-TSS [18]. Tumour shrinkage was also demonstrated in a patient treated by another DA (CV 205–502), with two others reporting an improvement in visual field defects [24].

In another trial, when patients were treated with either cabergoline or quinagolide, 11/18 (61.1%) patients demonstrated tumour shrinkage over 89.7 months [9]. This is similar to our findings, where 6/12 (50%) demonstrated shrinkage but over a shorter mean interval of around 14 months.

Overall, DAs such as bromocriptine, quinagolide and cabergoline show promising results, as they have also been found to reduce residual tumour growth post-operatively, when they were given even before any tumour growth was detected [14]. Out of all the various dopamine agonists used, cabergoline at 1–3 mg/week, spanning 6–12 months, was associated with the highest likelihood of tumour shrinkage and was superior to expectant follow-up protocols [9–11,15,16].

6. Strengths and Limitations

Our study has several strengths. The use of pre-defined radiological criteria ensures a consistent and objective evaluation of treatment response. Additionally, the inclusion of an MRI-based volumetric analysis performed by experienced radiologists enhances the reliability of tumour measurements. Our retrospective design reflects real-world practice, capturing the heterogeneity of patient characteristics, treatment protocols, and outcomes, enhancing the clinical relevance of the findings. Beyond binary outcomes like shrinkage or stabilisation, tumour growth rates before and after treatment were calculated, which shows promising results and supports the potential clinical value of cabergoline.

However, there are limitations to our study. The small sample size (n = 16) limits statistical power. This is compounded by the retrospective nature of the study, which introduces selection bias. The variability in follow-up intervals and heterogeneity in cabergoline dosing, as well as a lack of a control group with randomisation, limits the ability to contextualise the efficacy of cabergoline relative to standard care. There is also a timing discrepancy between the pre-CAB scan and the date of cabergoline initiation, and additionally, the outpatient letter date may not reflect the actual cabergoline start date, introducing potential over or underestimation of cabergoline's effect. Other potential confounders such as dopamine receptor expression levels, baseline health and comorbidities of the patients were also not accounted for, as well as the inclusion of patients who had received radiotherapy previously.

7. Conclusions

In this single-centre retrospective study on our limited cohort of patients with NFPAs, the use of cabergoline was associated with either tumour shrinkage or stabilisation in all

patients with NFPAs, as well as the retardation or reversal of growth rates in five patients. A total of 43.8% (7/16) of the cohort demonstrated tumour shrinkage at a mean follow-up of 503 ± 51 days, with a statistically significant reduction in tumour volume ($p = 0.0335$). The growth rate analysis of five patients demonstrated a deceleration in tumour growth (reduction of 3.070 ± 1.281 mm^3/day, $p = 0.037$) post-treatment, over 471 ± 121 days.

Importantly, our review does not seek to redefine the role of cabergoline in the management of NFPAs but highlights a lack of clarity on optimal dosing and approaches to dose up-titration, along with no recommended interval for FU imaging for assessing dose responsiveness. In addition, the objective criteria for defining the radiological response to treatment is also lacking, with variation across published evidence so far. Using real-world data from our centre, we demonstrated a moderate dose–response association ($r_s = 0.53$, $p = 0.036$) (Spearman's rank correlation) between cabergoline exposure and tumour volume reduction, alongside highlighting the limited value in early imaging (<12 months) for assessing response, post-initiation of cabergoline in NFPAs.

While encouraging, these findings should be interpreted with caution given the small sample size, retrospective design, lack of a control group and heterogeneity in treatment dosing and duration. Our study provides a possible proof of concept that cabergoline may have a role in selected patients where surgery or radiotherapy is not feasible.

8. Recommendations and Going Forward

Surgical resection remains the standard treatment for symptomatic NFPAs, particularly in the presence of visual compromise or mass effect. However, cabergoline may be considered in selected patients, such as those unsuitable or declining surgical intervention, and those with slowly progressive disease or residual tumour following surgery. Larger prospective studies are required to better define its role and establish clearer treatment pathways.

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Informed Consent Statement: For retrospective, observational research and secondary analysis of medical records, a project that analyzes something that has already happened or uses previously collected data (e.g., most surveys; or examining the outcomes of surgery at a hospital, where the researchers did not have any role in deciding who was operated on), informed consent is usually not required.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article, Further inquiries can be directed to the corresponding author.

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