Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients

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*(L Vroonen, M-L Jaffrain-Rea and P Petrossians contributed equally to this work)

Abstract

Background: Dopamine agonist resistance in prolactinoma is an infrequent phenomenon. Doses of cabergoline (CAB) of up to 2.0 mg/week are usually effective in controlling prolactin (PRL) secretion and reducing tumor size in prolactinomas. The clinical presentation, management, and outcome of patients that are not well controlled by such commonly used doses of CAB-resistant patients are poorly understood.

Design and methods: A multicenter retrospective study was designed to collect a large series of resistant prolactinoma patients, defined by uncontrolled hyperprolactinemia on CAB R 2.0 mg weekly.

Results: Ninety-two patients (50 F, 42 M) were analyzed. At diagnosis, most had macroprolactinomas (82.6%); males were significantly older than females (P=0.0003) and presented with a more aggressive disease. A genetic basis was identified in 12 patients. Thirty-six patients (39.1%) received only medical therapy, most underwent surgery (60.9%, including multiple interventions in 10.9%), and 14.1% received postoperative radiotherapy. Eight patients developed late CAB resistance (8.7%). The median maximal weekly dose of CAB (CABmax/w) was 3.5 mg (2.0–10.5). Despite a higher CABmax/w in patients treated with multimodal therapy (P=0.003 vs exclusive pharmacological treatment), a debulking effect of surgery was shown in 14 patients, with a higher rate of PRL control (P=0.006) and a significant reduction in CABmax/w (P=0.001) postoperatively. At last follow-up (median 88 months), PRL normalization and tumor disappearance were achieved in 28 and 19.9% of the patients respectively, with no significant sex-related difference observed in CABmax/w or disease control. Mortality was 4.8%, with four patients developing aggressive tumors (4.3%) and three a pituitary carcinoma (3.3%).

Conclusion: CAB-resistant prolactinomas remain a serious concern. Surgical debulking, newer therapeutic strategies, and early diagnosis of genetic forms could help to improve their outcome.

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Introduction

The clinical prevalence of pituitary adenomas (PAs) is ~1:1000 of the general population (1). Prolactinomas account for 40–60% of all PA; they occur usually in females aged 20–50 years old and up to 80% present as microadenomas (2). Although they are usually sporadic, up to 5% of PA overall may present in a familial or genetic setting such as multiple endocrine neoplasia type 1 (MEN1) and familial isolated PAs (FIPAs) (3, 4, 5). Dopamine agonists (DA) are first-line therapy for prolactinomas as they are effective in controlling clinical symptoms, prolactin (PRL) levels and tumor volume, while being well tolerated (2, 6). Because of its
high D2 receptor (D2R) affinity and its long half-life, cabergoline (CAB) has become the DA of choice in the last 15 years. It has proved to be more effective and better tolerated than bromocriptine, permitting PRL normalization in 90% of prolactinoma patients with microadenomas and in 80% with macroadenomas at a median weekly dose of ~1.0 mg (7, 8). Significant tumor shrinkage also occurs in up to 70–90% of patients over a 12–24 months period of CAB treatment, with complete tumor disappearance in about 40 and 10% of micro- and macroadenomas respectively (8).

A minority of patients do not respond satisfactorily to pharmacological treatment. Although no consensus has yet been reached about the definition of pharmacological resistance to DA drugs, the most widely accepted criterion is a failure to normalize PRL levels (2, 6, 9), which can be associated with a lesser degree of tumor shrinkage. In a large study on dose–response relationships in prolactinoma patients with macroadenomas receiving CAB as first-line treatment, disease control was obtained by a weekly dose of <1.5 mg in most patients (>80%) (10).

Most studies to date have dealt with populations that are responsive to CAB therapy, and there have been relatively few on prolactinoma patients who are resistant to DA therapy. To better understand this population, we performed a multicenter, retrospective study to characterize the clinical presentation and evolution of a large group of patients with prolactinomas who did not experience PRL normalization despite treatment with CAB using at least the maximum dose used in the placebo and active controlled trials of CAB during its registration, which led to the usual maximal labeled dose of 2.0 mg/week (11, 12). We aimed to better define the practical clinical characteristics of such cases and to evaluate their evolution and prognosis in order to provide insights on improved clinical management.

Materials and methods

Clinical data

Prolactinomas patients with non-normalized PRL secretion and with associated insufficient clinical symptom/sign control on a minimal weekly CAB dose of 2.0 mg were identified at 12 centers (CHU Liège, Belgium; Assistance Publique-Hopitaux de Paris CHU Kremlin-Bicêtre, France; Neuromed Institute, Pozzilli, Italy; Federal University of Recife, Brazil; CHU de Lyon, France; Federal University of Brasilia, Brazil; CHU La Timone Marseille, France; CHU Bordeaux, France; CHU Reims, France; Ospedale Valdese, Turin, Italy; Ospedale Maggiore Milano, Italy; CHU Larrey Toulouse, France). Such patients were designated as being ‘resistant’ to the hormone-lowering effects of CAB. Late resistance was defined by an escape of pharmacological treatment after initial PRL normalization in compliant patients. Anonymized patient information was collected via a questionnaire that included epidemiological, clinical, hormonal, and radiological data on the patient, the tumor characteristics, and the responses to therapy. PRL levels were determined by commercial assays at each center but were unavailable at diagnosis in five patients because of emergency surgery and/or due to an unrecognized hook effect. Macroprolactin was assessed in all patients and was not found to be the cause of elevated PRL in any of the cases. PAs were classified into micro- and macroadenomas according to their maximal diameter, and a classification of giant adenomas (≥40 mm) was also included. Invasion of adjacent structures (cavernous sinus, sphenoid sinus, and bone) was defined macroscopically according to neuroradiological imaging and/or intra-operative findings. Compliance with prescribed therapy was assessed by direct patient interview.

A total of 92 prolactinoma patients treated with CAB met the criteria for the study. Although the first diagnosis of prolactinoma was made over the period 1973–2010 (median: 1999), CAB began to be used from late 1997 to early 1998. CAB was therefore given as first-line treatment in 31 patients, whereas 54 patients had received previous DA drugs either alone (n=41) or in combination with either surgery (n=7) or surgery followed by radiotherapy (n=6). A further seven patients had undergone previous initial surgery. Median duration of follow-up from diagnosis was 88.5 months (range 8–408).

As this was a retrospective study, no systematic genetic analysis was performed. However, information on genetic or familial diagnosis was systematically sought from patient files (MEN1, Carney complex, FIPA, or McCune–Albright syndrome).

Statistical analysis

Statistical analysis was performed using the Statview 5.1 Software for PC (SAS Institute, Cary, NC, USA). Nonparametric tests were used for comparison of continuous values, using the Mann–Whitney and Wilcoxon rank tests for unpaired and paired two-group analysis respectively, and the Kruskall–Wallis test for multiple subgroups analysis. The χ²-test was used to compare percentages values. P values <0.05 were considered significant.

Results

Characteristics at diagnosis

Prolactinomas that were hormonally resistant to control up to a dose of 2.0 mg/week of CAB had a mean prevalence of 3.4% of prolactinoma patients across the study centers. Among the 92 resistant prolactinoma patients, 50 were female and 42 were male. The mean age at diagnosis was 32.0 ± 16.1 years.
Most patients (82.6%) had a macroadenoma and of these, 15 patients had giant adenomas. The majority of tumors were invasive at diagnosis (51.7%), and among macroadenomas, invasion occurred in 60.8% of cases. Neurological symptoms were frequent (54.9%). Endocrine symptoms were very common (93.4%) but complete hypopituitarism was rare (10.9%). Details are summarized in Table 1.

Significant gender-related differences were noticed. Men were older than women ($P = 0.0003$) and had significantly higher PRL levels at diagnosis ($P < 0.0001$; Fig. 1). Macroadenomas were significantly more frequent in men than women ($P < 0.0001$); four men (9.5%) presented as acute medical emergencies due to hydrocephalus/raised intracranial pressure ($n = 3$) or pituitary apoplexy ($n = 1$). Complete hypopituitarism at diagnosis was significantly more frequent in men (19.0 vs 4.0% in women, $P = 0.021$).

### Pharmacological treatment with CAB

CAB was given as a first-line treatment in 31 patients (33.7%), whereas the majority had received previous therapeutic approaches (predominantly other DA) (Table 1). A significant evolution in the choice of first-line treatment was observed over time ($P < 0.0001$), with an increasing use of first-line DA, mainly represented by CAB over the last decade (Fig. 2).

The mean maximal weekly dose of CAB ($CAB_{\text{max}}/w$) was $4.1 \pm 1.7$ mg (median 3.5, range 2.0–10.5) and was similar in men and women (data not shown). Although median pre-CAB PRL values were higher in patients who received CAB as a first-line option than in other patients (741.7 vs 155.0 ng/ml respectively, $P = 0.0034$), the median $CAB_{\text{max}}/w$ was similar in both groups (3.5 mg).

Eight patients (8.7%) developed late resistance following an initial response to CAB ($n = 1$) or other DA ($n = 7$). Most had macroadenomas ($7/8$), half were invasive, and none had received prior radiotherapy.

### Table 1 Clinical characteristics of 92 patients with resistant prolactinomas.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male (M)</th>
<th>Female (F)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>92</td>
<td>42</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Mean age at diagnosis (years; range)</td>
<td>32.0 ± 16.1 (9–86)</td>
<td>38.8 ± 17.6 (9–86)</td>
<td>26.6 ± 12.2 (11–65)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age ≥ 50 years (%)</td>
<td>14 (15.2%)</td>
<td>11 (26.2%)</td>
<td>3 (6.0%)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Pubertal delay/1 amenorrhea</td>
<td>85/91 (93.4%)</td>
<td>36/41 (87.8%)</td>
<td>49/50 (98.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary hypogonadism</td>
<td>69 (75.8%)</td>
<td>29 (69.0%)</td>
<td>40 (80.0%)</td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism$^\text{C}$</td>
<td>21 (23.1%)</td>
<td>15 (35.7%)</td>
<td>6 (12.0%)</td>
<td>0.020</td>
</tr>
<tr>
<td>MPHD</td>
<td>10 (11.4%)</td>
<td>8 (19.0%)</td>
<td>2 (4.0%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Neurological symptoms$^a$</td>
<td>50/91 (54.9%)</td>
<td>36/41 (87.8%)</td>
<td>14/50 (28.0%)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>14</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Visual defects</td>
<td>14</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ocular nerve palsy</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tumor characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro/macrogiant</td>
<td>15/62/15</td>
<td>1/29/12</td>
<td>14/33/3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Invasive$^b$</td>
<td>46/89 (51.7%)</td>
<td>30/42 (68.2%)</td>
<td>16/47 (36.4%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Median PRL levels at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ng/ml) (range)</td>
<td>755.0 (n = 87)</td>
<td>1990.0 (n = 40)</td>
<td>363.0 (n = 47)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Median PRL levels before CAB$^c$</td>
<td></td>
<td></td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>(ng/ml) (range)</td>
<td>369.0 (n = 83)</td>
<td>771.0 (n = 40)</td>
<td>193.0 (n = 43)</td>
<td>(6.0–7862.0)</td>
</tr>
<tr>
<td>First-line CAB treatment</td>
<td>31 (33.7%)</td>
<td>12 (28.6%)</td>
<td>19 (38.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment received before CAB</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>DA alone</td>
<td>41 (44.6%)</td>
<td>21 (50.0%)</td>
<td>20 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>7 (7.7%)</td>
<td>4 (9.5%)</td>
<td>3 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>Surgery + DA</td>
<td>7 (7.7%)</td>
<td>4 (9.5%)</td>
<td>3 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>Surgery + DA + RTx</td>
<td>6 (6.5%)</td>
<td>1 (2.4%)</td>
<td>5 (10.0%)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Unavailable in one patient; $^b$Galactorrhea was associated with menstrual abnormalities in all patients; $^c$Hypopituitarism refers to at least one pituitary dysfunction other than hypogonadism; ED, erectile dysfunction; MPHD, multiple pituitary hormone deficiency; DA, dopamine agonist; RTx, radiotherapy.
Late resistance was not significantly more frequent in men (11.9 vs 6.0% in women, \( P=NS \)), and patients were similar to those affected by primary resistance in terms of age, PRL, and tumor characteristics at diagnosis (data not shown). Median CAB\( ^{\text{max/w}} \) was 3.5 mg regardless of early/late resistance.

**Surgery in resistant prolactinomas**

Fifty-six patients (60.9%) were operated on during the study period (48 macro- and eight microadenomas), including 15 patients undergoing first-line surgery (16.3%). Initial characteristics of patients who underwent first-line surgery were similar to those who did not (data not shown) and none of those treated surgically as first-line treatment was controlled postoperatively. Overall, 74 surgical interventions were performed (one surgery, \( n=46 \) patients; two surgeries, \( n=5 \) patients; three surgeries, \( n=3 \) patients; four surgeries, \( n=1 \) patients; and five surgeries, \( n=1 \) patients), including spinal surgery for dural metastasis in a patient with a malignant prolactinoma (see below). Median PRL values decreased significantly from 540 ng/ml (range: 15.6–12 672) before surgery to 161 ng/ml (range: 0.0–10 850) after surgery (\( P<0.0001 \)). However, the rate of postoperative PRL normalization was low overall (7.8%).

We therefore wished to further evaluate the contribution of surgery in subsequent disease control. Excluding patients who received previous radiotherapy, a significant effect of surgical debulking could be shown in 14 patients who received CAB before and after noncurative surgery. As shown in Fig. 3, median PRL levels significantly decreased on preoperative CAB treatment (\( P=0.002 \) vs PRL at diagnosis). After surgery, significantly lower PRL values were obtained (\( P=0.0012 \) vs PRL at diagnosis and \( P=0.006 \) vs preoperative PRL respectively) at significantly lower weekly CAB dose (\( P=0.001 \) vs preoperative). Excluding one patient with uncontrolled disease requiring further surgery and radiotherapy, median PRL levels at last follow-up were further decreased (\( P=0.006 \) vs postoperative values), with three patients reaching normal PRL values, and CAB\( ^{\text{max/w}} \) was further reduced as compared with the postoperative values (\( P=0.028 \)).

**Long-term follow-up**

The outcome of resistant prolactinomas was evaluated at last follow-up in terms of PRL normalization and tumor evolution, and results were analyzed according to patients’ characteristics, follow-up, and treatment schedule. Overall, DA was used exclusively in 36 patients (39.1%) or as part of multimodal treatment including surgery in 43 patients (46.7%) or surgery followed by radiotherapy in 13 patients (14.1%). Median follow-up duration was significantly shorter in patients treated by an exclusive pharmacological approach as compared with multimodal treatment (60 vs 120 months respectively, \( P=0.0007 \)) but was similar in irradiated and nonirradiated operated patients. The mean CAB\( ^{\text{max/w}} \) significantly increased with treatment complexity \((3.4\pm1.2 \text{ mg in patients treated by DA only, } 4.3\pm1.8 \text{ mg in patients with surgery and DA, and } 5.5\pm2.0 \text{ mg in patients with DA, surgery, and postoperative radiotherapy } (P=0.003))\). Details on the evolution of macroprolactinomas are provided in Table 2.

Overall, 26/92 patients reached normal PRL levels (28.3%). These include 8/36 patients treated by exclusive DA therapy (22.2%) and 18/56 patients...
who received multimodal therapy (32.1%, \( P = \text{NS} \)) compared to exclusive DA. Although median PRL at diagnosis was significantly lower in patients who normalized at last follow-up than in those who did not (356.5 vs 915.0 ng/ml, \( P = 0.001 \)), the rate of PRL normalization was not significantly influenced by patients' gender, tumor volume, primary/secondary resistance, \( \text{CAB}_{\text{max/w}} \), or follow-up duration (data not shown). Among patients with uncontrolled PRL at last follow-up and available PRL at diagnosis (61 out of 66), a \( \geq 50\% \) PRL decrease was obtained in most cases (72.1%), whereas 14.7% had a PRL decrease < 50% and 13.1% a further PRL increase.

Tumor disappearance was reported in 16/87 cases (19%) and residual micro- and macroadenomas were present at last imaging in 26.7 and 53.3% of the cases respectively. Tumor disappearance tended to be more frequent in microprolactinomas (35.7 vs 15.1% in macroadeninomas, \( P = 0.07 \)) and in women (25 vs 10.2% in men, \( P = 0.08 \)). Overall, 16/73 macroadenomas shrank to microadenomas (21.9%), one microadenoma progressed into a macroadenoma after pregnancy, and six tumors were still in progression at last follow-up (6.9%).

We finally analyzed the modifications of \( \text{CAB} \) schedule throughout follow-up. In patients who reached normal PRL, the mean weekly \( \text{CAB} \) dose could be progressively reduced from 4.5 ± 1.9 mg (median 3.5 mg) to 1.8 ± 1.8 mg (median 1.25 mg) at last follow-up (\( P < 0.0001 \)), with complete drug withdrawal in seven patients (26.9%). The use of multimodal therapy allowed a significant reduction in \( \text{CAB} \) requirement (Fig. 4).

**High-dose \( \text{CAB} \) regimen**

In order to evaluate the efficacy of exclusive high-dose \( \text{CAB} \) regimen, a subgroup of 19 patients receiving at least daily 0.5 mg \( \text{CAB} \) therapy (\( \text{CAB} \geq 3.5 \text{ mg/week} \)) was analyzed separately. PRL normalization was achieved in 5/19 patients (26.3%), with some degree of tumor shrinkage in 10/19 (52.6%). None had complete tumor disappearance and none had tumor progression. Three patients (15.8%) had reduced weekly \( \text{CAB} \) at last follow-up.

**Locally aggressive and malignant prolactinomas**

The mortality rate was 4.3%, due to pituitary carcinomas (\( n = 2 \)) or neurological complications of a rapidly growing pituitary tumor (\( n = 2 \)). Overall, three patients developed a pituitary carcinoma and four had locally aggressive tumors (Table 3). All patients had macroadenomas at diagnosis and required surgery (up to five times) and radiotherapy (up to four times). High \( \text{CAB}_{\text{max/w}} \) were used: 7.0 mg in all carcinoma patients, 5.4 ± 2.5 mg in those with aggressive tumors. Temozolomide (TMZ) induced a significant hormonal and tumor response in two carcinoma patients (Table 3, patients 2 and 3): the first was partially controlled but died of disease progression 1 year after TMZ withdrawal because of severe drug intolerance. In the second patient (who had MEN1), PRL near-normalization was obtained, which remained stable after TMZ withdrawal. TMZ was also successfully used in another MEN1 patient (Table 3, patient 5), leading to PRL normalization, significant tumor shrinkage, and progressive reduction in tumor volume.

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**Figure 3** The debulking effect of transphenoidal surgery in 15 patients with resistant PRL-secreting macroadenomas. (A) PRL values, (B) \( \text{CAB} \) weekly dose. \( T_0 \), PRL at diagnosis; \( T_1 \), minimum preoperative PRL; \( T_2 \), postoperative PRL; \( T_3 \), minimum PRL at last follow-up.
of CAB from 8.0 to 1.5 mg weekly. Other chemotherapy regimens induced only partial and transient responses in three patients. Rapid tumor progression in patient 6 was accompanied by PRL normalization during the last follow-up period, suggesting tumor de-differentiation.

**Genetic aspects**

Five patients presented with clinical MEN1 disease and three had FIPA. Germline MEN1 mutations were found in 4/5 clinical MEN1 patients and an AIP mutation in 1/3 FIPA patients. AIP sequencing was also performed in 22 of the sporadic patients aged 9–60 years old at diagnosis, with three AIP mutations and one variant of uncertain significance being found – all were young patients (<20 years old) with invasive macroadenomas. Overall, a genetic/familial background was recognized in 12 patients. All had macroadenomas and, as compared with other patients, they were significantly younger at diagnosis (23.2 ± 13.7 vs 33.3 ± 16.1 years old, \( P = 0.021 \)), received a significantly higher CAB\(^{\text{max/\text{week}}} \) (5.1 ± 1.9 vs 3.9 ± 1.7 mg, \( P = 0.013 \)), and radiotherapy was used more frequently (33.3 vs 11.2%, \( P = 0.04 \)).

**Discussion**

The concept of pharmacological resistance in prolactinomas, empirically defined as a failure to normalize PRL levels and/or reduce tumor volume by at least 50% (9), has been refined in recent years, thanks to studies focused on CAB-treated patients. Because of its greater efficacy and tolerance, CAB has reduced the number of patients unable to achieve PRL normalization because of side effects that limit tolerance and compliance to treatment (7, 8, 13). In addition, discrepancies between the hormonal and tumor responses have led to tumor shrinkage being considered unsuitable to define pharmacological resistance (8). Based on a recent dose–response study on PRL-secreting macroadenomas (14) and on current labeling dose ranges for CAB in clinical practice (11, 12), we focused our attention on patients who failed to normalize PRL at the upper end of the labeled titration range for CAB in prolactinoma treatment, namely 2.0 mg/week.

The first aim was to define the epidemiology of such patients and the following characteristics were observed: i) a large majority had macroadenomas (>80%) and/or invasive tumors (>50%), indicating that hormonal resistance is generally associated with larger/more aggressive tumors. ii) An unusually high proportion of patients were males and this gender

### Table 2 Outcome of patients with prolactin-secreting macroadenomas uncontrolled by \( \geq 2 \) mg/week of cabergoline. This table refers to the outcome of 77 macroadenomas with sufficient radiological details at last follow-up.

<table>
<thead>
<tr>
<th>Characteristics at diagnosis</th>
<th>Macro-remnant</th>
<th>Micro-remnant</th>
<th>No remnant</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{n}</td>
<td>46</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>M/18 F</td>
<td>M/9 F</td>
<td>M/8 F</td>
<td>0.102</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.5 ± 18.1</td>
<td>33.2 ± 15.6</td>
<td>25.7 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>PRL (ng/ml)(^a)</td>
<td>2560.0 (100–25600.0)</td>
<td>819.5 (182.8–4152.0)</td>
<td>207.0 (50.6–2800.0)</td>
<td>(&lt;0.0001 )</td>
</tr>
<tr>
<td>Invasive tumors(^b)</td>
<td>30/41 (73.2%)</td>
<td>7/16 (43.7%)</td>
<td>3/11 (27.3%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA/DA + surgery/RTx(^c)</td>
<td>22/14/10</td>
<td>7/8/1</td>
<td>0/10/1</td>
<td>0.0048</td>
</tr>
<tr>
<td>Multimodal(^d)</td>
<td>24/46 (52.2%)</td>
<td>7/16 (56.2%)</td>
<td>11/11 (100%)</td>
<td>0.013</td>
</tr>
<tr>
<td>CAB(^{\text{max}}) (mg/week)</td>
<td>3.5 (2.0–10.5)</td>
<td>3.5 (2.0–7.0)</td>
<td>3.5 (2.5–9.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Outcome at last follow-up</td>
<td></td>
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</tr>
<tr>
<td>Follow-up duration (months)</td>
<td>71.5 (8–408)</td>
<td>103.0 (24–348)</td>
<td>108.0 (38–240)</td>
<td>NS</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>170.9 (0.7–6098.0)</td>
<td>41.0 (6.3–291.2)</td>
<td>18.8 (4.4–1137.5)</td>
<td>0.126</td>
</tr>
<tr>
<td>PRL normalization</td>
<td>9/46 (19.6%)</td>
<td>6/16 (37.5%)</td>
<td>6/11 (54.5%)</td>
<td>0.048</td>
</tr>
<tr>
<td>CAB at last follow-up</td>
<td>3.0 (0.0–7.0)</td>
<td>2.0 (0.0–3.5)</td>
<td>0.75 (0.0–4.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>CAB withdrawal</td>
<td>4/46 (8.7%)</td>
<td>3/16 (18.7%)</td>
<td>4/11 (36.4%)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

\(^a\)Unavailable in five cases.

\(^b\)Unavailable in five cases.

\(^c\)RTx: radiotherapy – all irradiated patients also received surgical treatment.

\(^d\)Multimodal therapy includes pharmacological treatment, surgery, and radiotherapy.
Table 3  Details of patients with malignant prolactinomas and locally aggressive prolactinomas.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Clinical presentation at diagnosis</th>
<th>Final diagnosis</th>
<th>Characteristics and DA response</th>
<th>Nonpharmacological treatments</th>
<th>Chemotherapy</th>
<th>Last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43/M</td>
<td>Macroadenoma</td>
<td>Carcinoma with multiple bone metastasis and mediastinum dissemination</td>
<td>Multiple local recurrences with progressively increasing pharmacological resistance to DA drugs, including CAB up to 7.0 mg/week at last follow-up. Metastasis diagnosed after 15 years of evolution in the absence of pituitary remnant.</td>
<td>Five pituitary surgeries (four TC, one TS), pituitary RTx (five times), RTx for bone metastasis (lumbar vertebrae)</td>
<td>None</td>
<td>Died from metastatic disease in a palliative unit. PRL at last follow-up 45 500 ng/ml. Follow-up duration: 17 years since initial diagnosis, including 14 months since carcinoma diagnosis.</td>
</tr>
<tr>
<td>2</td>
<td>18/F</td>
<td>Macroadenoma</td>
<td>Carcinoma with multiple dural metastases</td>
<td>Multiple local recurrences with a highly aggressive local evolution starting 16 years after initial diagnosis and increasing pharmacological resistance to DA drugs, including CAB up to 7.0 mg/week. Dural metastasis diagnosed after 22 years of evolution.</td>
<td>Four pituitary surgeries (three TS, one TC), ventriculo-peritoneal shunt for hydrocephalus, one surgical approach for dural metastasis, and pituitary RTx (twice), spinal RTx</td>
<td>5-FU/doxorubicin while local aggressive</td>
<td>Died from neurological complications in a palliative unit. PRL at last follow-up 3114 ng/ml. Follow-up duration: 27 years since initial diagnosis, including 51 months since carcinoma diagnosis.</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31/M</td>
<td>Macroadenoma, cavernous sinus invasion, PRL 800 ng/ml</td>
<td>Carcinoma with bone metastasis and SNC dissemination (liquor)</td>
<td>Highly aggressive local recurrence in a sporadic MEN1 patient. Primary CAB resistance up to 7.0 mg/week. Metastasis diagnosed after 10 years of evolution.</td>
<td>One pituitary surgery (TS), pituitary RTx</td>
<td>TMZ (28 cycles) at carcinoma stage (withdrawn due to side effects)</td>
<td>PRL sub-normalization persisting after TMZ withdrawal. PRL at last follow-up: 80 ng/ml. Follow-up duration: 16 years since initial diagnosis, including 6 years since carcinoma diagnosis.</td>
</tr>
<tr>
<td>4</td>
<td>65/F</td>
<td>Macroadenoma suprasellar extension, maximal diameter 22 mm, PRL 4000 ng/ml</td>
<td>Highly aggressive</td>
<td>Highly aggressive evolution with invasion of the third ventricle, hydrocephalus, diabetes insipidus and hypopituitarism. Increasing resistance to DA drugs, including CAB 3.0 mg/week.</td>
<td>One pituitary surgery (TS), pituitary RTx (twice)</td>
<td>None</td>
<td>Died from neurological complications. PRL at last follow-up 2400 ng/ml. Total follow-up duration: 5 years.</td>
</tr>
<tr>
<td>5</td>
<td>23/F</td>
<td>Macroadenoma</td>
<td>Highly aggressive</td>
<td>Invasive regrowth 15 years after first successful surgery, followed by multiple recurrences in a familial MEN1 patient. Increasing resistance to DA drugs, including CAB up to 8.0 mg/week.</td>
<td>Four pituitary surgeries (four TS), pituitary RTx</td>
<td>TMZ (20 cycles)</td>
<td>Marked shrinkage and PRL normalization. PRL at last follow-up 12.0 ng/ml. Total follow-up duration: 27 years.</td>
</tr>
</tbody>
</table>
imbalance increased with patients’ age at diagnosis. There was a 1.5:1 female to male ratio before the age of 50 that inverted to a 3.7:1 male to female ratio thereafter. This differs from unselected prolactinomas, which are characterized by a 10:1 female to male ratio before the age of 50, decreasing to 1:1 thereafter (2).

iii) Significant gender-related differences were found at presentation, which are reminiscent of unselected prolactinomas, with microadenomas being observed almost exclusively in women and giant prolactinomas preferentially occurring in men. Resistant prolactinomas in men were more frequently invasive and presented with significantly higher PRL levels than in women. Additionally, women were diagnosed 12 years earlier than men. These characteristics appear to be quite distinct from the general experience with CAB in the endocrine setting. In the large unselected population reported by Verhelst et al., the proportion of patients that required more than 2.0 mg/week of CAB was ~10%. As compared with those CAB-responsive patients, the current study population had a higher proportion of males (45.7 vs 22.4%), a higher proportion of macroadenomas (83.7 vs 51.0%), and hence, a more frequent reliance on surgery (60.9 vs 25.5%) and radiation (14.1 vs 3.1%). The median final dose used among the total population reported by Verhelst et al. was 1.0 mg/week as compared with a median final dose of 3.5 mg/week in the current study. Interestingly, among patients who were considered resistant to CAB in the Verhelst et al. study, the median final CAB dose was also 3.5 mg/week. Although early recognition of hyperprolactinemia is easier in women, gender-related differences in prolactinoma growth potential have been shown (14) and pharmacological resistance was already reported more frequently in men (10). Genetic predisposition to PAs appeared as a risk factor to develop pharmacological resistance. Indeed, a genetic background was found in 12 patients, which would represent 13% of the series but may be underestimated due to the lack of systematic genetic analysis. The contribution of MEN1 (5.4% clinical and 3.2% genetic) is not surprising since prolactinomas are the most common MEN1-related PAs and are more hormonally resistant than sporadic PAs (3). Prolactinomas are also the most prevalent phenotype in FIPA kindreds (4, 5), and a FIPA context was recognized in 3.3% of our patients. Excluding the intronic variant of uncertain significance, AIP mutations were found in 1/3 FIPA patients and in the majority of sporadic patients (13.6%). Such data are in agreement with AIP mutations associated with aggressive prolactinomas in FIPA and in young sporadic patients, with a male predominance in FIPA and in young sporadic patients. The biological basis of pharmacological resistance remains poorly understood (9, 18). Research has mainly focused on the D2R, reporting a reduced expression but not a reduced density of D2Rs in resistant prolactinomas (15, 16, 17). Research has mainly focused on the D2R, reporting a reduced expression but not a reduced density of D2Rs in resistant prolactinomas (15, 16, 17).

### Table 3 Continued

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</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>58/F</td>
<td>Macroadenoma, suprasellar extension, cavernous sinus invasion, maximal diameter 35 mm, PRL 1260 ng/ml</td>
<td>Highly aggressive</td>
<td>Multiple recurrences with a highly aggressive evolution starting 3 years after diagnosis in MEN1-like patient</td>
<td>Two pituitary surgeries (two TS), pituitary RTx</td>
<td>5-FU/doxorubicin, cisplatin</td>
<td>Died from severe general and neurological complications PRL at last follow-up 8.0 ng/ml Total follow-up duration: 5 years</td>
</tr>
<tr>
<td>7</td>
<td>48/F</td>
<td>Macroadenoma</td>
<td>Highly aggressive</td>
<td>Multiple aggressive recurrences with CAB resistance, up to 3.5 mg/week</td>
<td>Five pituitary surgeries (three TS, one TEMS, one TC), pituitary RTx (three times)</td>
<td>None</td>
<td>Tumor progression PRL at last follow-up 1832 ng/ml Total follow-up duration: 24 years</td>
</tr>
</tbody>
</table>

DA, dopamine agonists; CAB, cabergoline; NET, neuroendocrine tumors; RTx, radiotherapy; TC, transcranial; TEMS, transethmoidosphenoidal; TMZ, temozolomide; TS, transphenoidal.

*Clinical details on patients 1 and 3 have been reported in references (38, 40) respectively.

*Age at first diagnosis.
number of binding sites (19), reduced gene expression (20), impaired balance between its short and long isoforms (21), and genetic polymorphisms (22). Additional factors involved in the aggressiveness of prolactinomas may interfere with D2R signaling or exert opposing biological effects on lactotroph cells. These include abnormalities in growth factors signaling (18, 23) and in extracellular matrix components (24, 25), the increased expression of genes involved in cell proliferation (25, 26), and loss of tumor suppressor genes at various loci (24). The promoting effects of estrogens on prolactinoma formation are well known (27), and gender-related differences in sex steroid receptor expression, especially the estrogen receptors (ERs), and in the steroid milieu, may contribute to the aggressiveness of prolactinomas in men (28). Interestingly, although estrogens induce dopamine resistance in lactotrophs (27), ER does not appear to be differentially expressed in resistant prolactinomas (20, 29), and most prolactinomas in men respond to treatment (30). In the current study, the maximal weekly CAB dose used was similar in both sexes and the rate of PRL normalization was not significantly higher in women. Complete shrinkage tended to be more frequently observed in women, even in macroadenomas, but macroadenomas in men tended to be more aggressive. In particular, giant adenomas often require high CAB doses to be controlled (31). Further work is needed to better evaluate potential gender-related differences in the tumor-shrinking potential of CAB. Finally, the unusual proportion of genetic forms strongly suggests that alterations in the MEN1 and AIP genes are able to negatively impact the pharmacological response in prolactinomas (3, 15, 32). This is further supported by the higher CABmax doses used in these patients.

The first recommended step in the treatment of resistant prolactinomas is to switch to a more potent DA where available, and CAB is currently the drug of choice (6, 13). Where PRL fails to normalize at a 2.0 mg CAB weekly dose, a stepwise dose increase is recommended, provided that each step improves PRL secretion and/or disease-related symptoms (6, 31, 33). Some authors failed to observe beneficial effects in increasing CAB dose over 3.5 mg/week (6), whereas others have reported successful increases up to 7.0 mg or more (12, 31, 33, 34). In this study, the use of pharmacological treatment alone was associated with PRL normalization in 22% and tumor shrinkage > 50% of the cases. However, due to the retrospective character of this study, the follow-up duration was shorter with medical therapy alone than that with multimodal treatment. Exclusive high-dose CAB regimen, which was used in all but one participating center, proved to be effective in a significant subset of patients, and represents a valid option for those that do not respond to doses up to 2.0 mg/week.

Surgery is often necessary in prolactinomas resistant to the maximal tolerated dose of DA (6, 33, 35). In our series, only 15 patients (16%) underwent first-line surgery, which was replaced by first-line DA therapy over time. Overall, 36 patients were operated on (~60%), including nine patients (10%) who underwent repeated surgery. Surgery helped by reducing tumor mass, but postoperative PRL normalization was obtained in a minority of cases (<10%, none after first-line surgery). Remission rates up to 36% have been reported in resistant prolactinomas, but most patients achieving normal postoperative PRL had moderate preoperative hyperprolactinemia (36). An important finding of this study is the significant debulking effect of surgery, which could be documented in a subgroup of patients who received CAB before and after surgical treatment, and experienced during their postoperative follow-up a further significant reduction in PRL levels while reducing their weekly CAB dose by 50%. This finding extends the role of surgery in the endocrine control of secreting adenomas (37). At last follow-up, patients treated by combined surgical and pharmacological approaches achieved a rate of PRL normalization and/or complete tumor shrinkage of 33.0 and 36.8% respectively, with a minority showing disease progression (5.3%). Although no significant benefit of postoperative irradiation was found in terms of PRL normalization (30.8%) or complete tumor shrinkage (<10%), the high CABmax/w used in this subgroup confirms that radiotherapy was proposed for severely resistant tumors. Indeed, radiotherapy is recommended in patients who are uncontrolled by DA and surgery with the main goal of controlling tumor growth (2, 30). Its potential effects on PRL decline are delayed, PRL normalization may not be achieved, and radiation-induced hypopituitarism is frequent. Occasional but severe neurological side effects or second tumors should also be considered (38).

Severely resistant prolactinomas remain a major therapeutic challenge. In this series the rate of uncontrolled patients was remarkably high, with > 70% uncontrolled hyperprolactinemia, ~15% tumor progression during periods of follow-up on CAB treatment, leading to highly aggressive tumors in 4.4% and malignant evolution in 3.3%, with a disease-related mortality rate of 4%. Malignancy was more frequent than in unselected pituitary tumors, where it has been reported in <0.5% (39). Of note, most highly aggressive or malignant prolactinomas occurred in women, and three occurred in the setting of MEN1. Malignant transformation is generally a late event in pituitary tumors, as supported by metastasis recognized in our patients 10–22 years after the initial diagnosis of prolactinoma. As reported herein, it is heralded by multiple local recurrences, a progressive worsening of the hypersecretory state, and an increasing degree of pharmacological resistance (39), highlighting the need for long-term close surveillance in such patients. An appropriate use of extra-pituitary magnetic resonance imaging (MRI) and/or nuclear imaging (39, 40) may
lead to an earlier recognition of PRL-secreting carcinomas and increase their clinical relevance. Various chemotherapy regimens have been proposed (39), but TMZ is becoming a mainstream choice (33, 41). In our series, TMZ was successfully used in two carcinomas and a highly aggressive prolactinoma. Tumors showing reduced methylation of DNA methyltransferase expression may be more sensitive to TMZ (41), but this finding is debatable and a 3-month trial is generally able to identify TMZ responders (42). Observational data on early chemotherapy associated with long-lasting responses in pituitary carcinomas (39) support the need for an early recognition of their metastatic potential.

Few alternative pharmacological options are available for resistant prolactinomas not requiring chemotherapy. Excessive estrogen exposure (even via testosterone replacement therapy in men) should be avoided (13) and benefits of anti-estrogens or aromatase inhibitors have been occasionally reported (2). Available somatostatin analogs are poorly effective (43) but encouraging in vitro data with SOM230 have been reported (44). Animal models lacking the D2R may be helpful to develop new strategies in resistant prolactinomas (45).

An additional concern in resistant prolactinoma patients is the long-term use of high CAB doses, which has been associated with cardiac valve fibrosis in Parkinson’s patients (46). Although several studies performed in hyperprolactinemic and prolactinoma patients indicate only modest valve dysfunction, if any (47), a relationship between cardiac valve abnormalities and the cumulative dose of CAB cannot be ruled out entirely in all cases. Periodic echocardiography is warranted in resistant prolactinoma patients and potential reduction of CAB requirement by surgical debulking could be considered.

In conclusion, this large series confirms that relative pharmacological resistance to CAB defines a group of patients with more aggressive disease and underlines the potential risk of highly aggressive or malignant evolution in severely resistant patients. It also supports the potential role of genetic factors in determining dopamine resistance and the benefits of debulking surgery in terms of disease control and safety. Because uncontrolled evolution remains largely unpredictable, future research should focus on the early identification of potentially aggressive tumors and alternative pharmacological approaches.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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