CASE REPORT

# Ten-year follow-up of a giant prolactinoma

Vera Fernandes,[1] Maria Joana Santos,[1] Rui Almeida,[2,3] Olinda Marques[1,3]

[1]Department of Endocrinology, Hospital de Braga, Braga, Portugal
[2]Department of Neurosurgery, Hospital de Braga, Braga, Portugal
[3]Department of Pituitary Tumours Group, Hospital de Braga, Braga, Portugal

**Correspondence to**
Dr Vera Fernandes,
vera.fernandes20@gmail.com

Accepted 31 October 2015

## SUMMARY

Giant prolactinomas are rare pituitary tumours of which management can be a challenge. A 28-year-old man presented with headaches, visual impairment and behavioural changes. Clinically, the patient was found to have hypogonadism and bitemporal hemianopsia. A MRI demonstrated a pituitary tumour 76 mm in diameter and blood tests revealed a serum prolactin of 158 700 µU/mL (reference range 58–254). Initially, a craniotomy was performed. Immunohistochemistry of the tumour identified a prolactinoma with a high proliferative index and the patient was started on treatment with a dopamine agonist. A year later, neurological symptoms worsened due to regrowth of the lesion's cystic component, and so further surgery was performed. After 10 years of treatment with dopamine agonists, the prolactin levels decreased by 96.8%, there was an effective reduction in tumour size, and the neurological signs and symptoms resolved.

## BACKGROUND

A giant prolactinoma is a pituitary tumour with a diameter of 40 mm or more, significant extrasellar extension, very high prolactin concentrations (usually above 1000 ng/mL) and no concomitant growth hormone (GH) or adrenocorticotrophin (ACTH) secretion.[1]

Although prolactinomas are the most common functioning pituitary adenomas, giant prolactinomas are very rare, accounting for 2–3% of prolactinomas and only 0.5% of all pituitary tumours.[1 2] These tumours have a significant male preponderance with a median age at diagnosis of 42 years (24–59).[3]

Giant prolactinomas often present with neurological rather than endocrine symptoms.[4] These occur due to compression of the surrounding structures by large or invasive tumours and include headache, visual field defects and diplopia. Some patients may have clinical features of hypogonadism, such as decreased libido and impotence and infertility.[5]

The classical therapeutic goals of prolactinomas, namely correction of hyperprolactinaemia and hypogonadism, and tumour size reduction, are usually not realistic in giant prolactinomas, therefore the first goal of treatment is to improve the neurological symptoms.[1] These entities are usually managed via medical therapy with dopamine agonists (DAs), however, surgery followed by radiotherapy may be warranted in some cases.[1 6] Nevertheless, giant prolactinomas have invasive characteristics, and so treatment is rarely curative. Patients typically need lifelong medical treatment to manage their symptoms.[1] It is clear that the therapeutic management of these tumours is a challenge and there are few reports of long-term follow-up.[5 7] Long-term follow-up of giant prolactinomas may contribute to a better understanding of the course of disease and thereby improve patients' management. We report a case of a giant prolactinoma in a young man who presented with headaches, vision impairment and behavioural changes, and discuss the long-term management challenges of these tumours.

## CASE PRESENTATION

A 28-year-old man presented at the emergency room (ER), referred by an ophthalmologist, with a 2-year history of frontal headaches and visual disturbances, and a 1 year history of behavioural changes, namely disinhibition. Additionally, in the previous 3 months, he had polyphagia and weight gain of 10 kg.

The patient had no history of head trauma and denied other neurological symptoms. The systems review was otherwise unremarkable. He had no past medical history, drug history or family history to help account for his condition.

On examination, he had poorly defined secondary sexual characteristics and was obese. There were no other stigmata of endocrine dysfunction. Peripheral nervous system examination was normal, and cranial nerve examination was normal except for a bi-temporal visual field defect. Funduscopy was also normal.

## INVESTIGATIONS

The referring ophthalmologist arranged visual field campimetry, which revealed a bitemporal hemianopsia, and so a cerebral MRI was performed.

Cerebral MRI revealed a large invasive pituitary mass, 76 mm in diameter. It had suprasellar extension, a large anterosuperior cystic component and a posteroinferior solid component, with close proximity to vascular and neural structures of the skull base (figure 1A, B).

Laboratory evaluation revealed a very high prolactin level of 158 700 µU/mL (reference range 58–254); low testosterone value (229 ng/dL, reference range 270–1734), luteinising hormone of 1.15 µIU/mL (reference range 1–9) and follicle stimulating hormone of 2.35 µIU/mL (reference range 0.7–11.1). Thyroid function tests were normal: free thyroxine (FT4) 1.02 ng/dL (reference range 0.8–1.9) and thyrotropin (TSH) 3.69 µIU/mL (reference range 0.4–4.0). The patient's GH value was 0.08 ng/mL (reference range <1.00). The ACTH and cortisol levels (obtained at 12 o'clock in the ER) were 8.9 pg/mL and 6.74 µg/dL, respectively.

**To cite:** Fernandes V, Santos MJ, Almeida R, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2015-212221

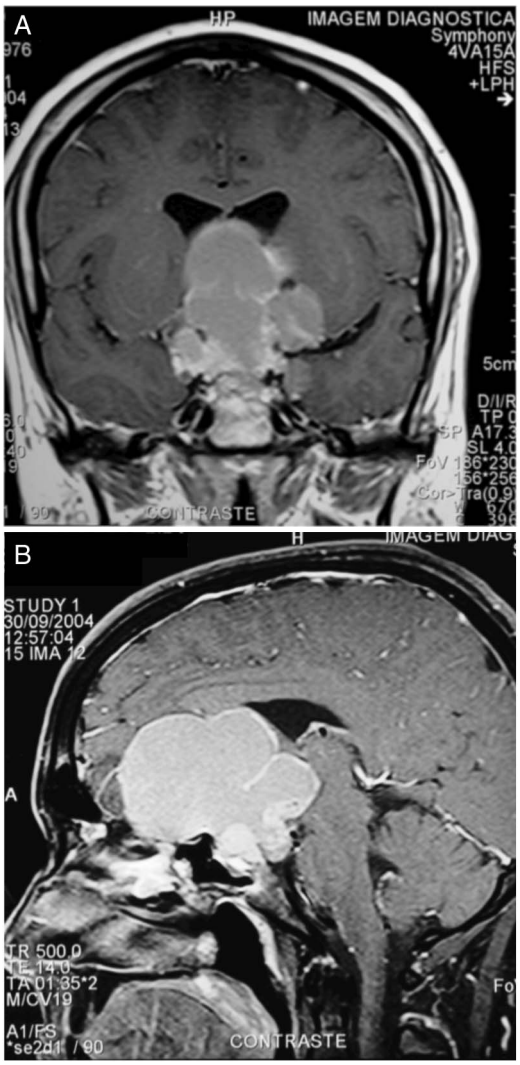



**Figure 1** (A) MRI at diagnosis (coronal view). (B) MRI at diagnosis (sagittal view).

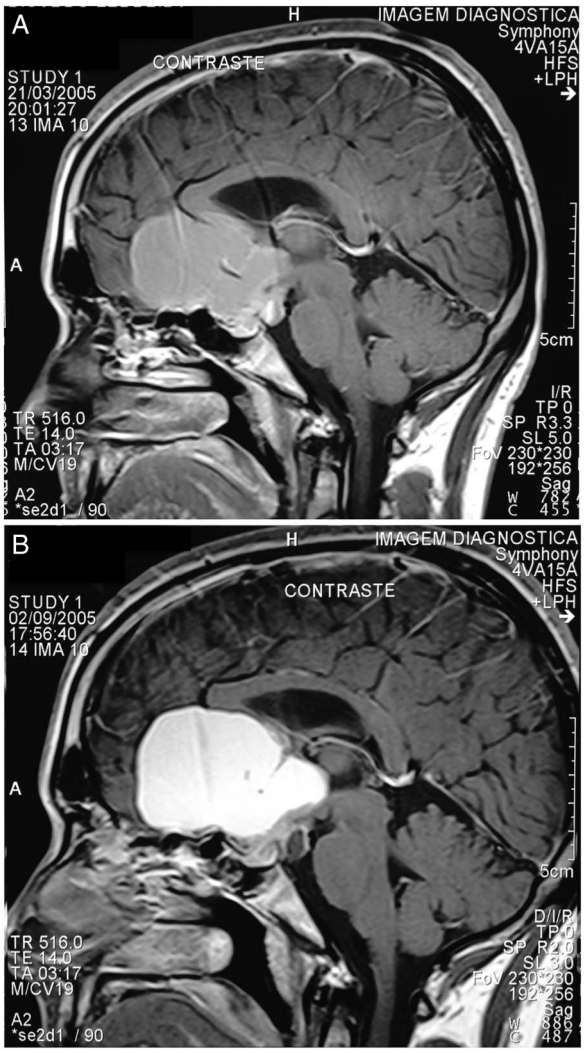



**Figure 2** (A) MRI at 6 months of follow-up. (B) MRI at 12 months of follow-up.

## TREATMENT

In view of his clinical symptoms and imaging, a craniopharyngioma was suspected, and the patient underwent a craniotomy. Surgery occurred under corticosteroid therapy and there were no complications. Immunohistochemistry revealed a densely granulated adenoma, with strong diffuse immunostaining for prolactin, a high proliferative index (Ki-67: 7%) and p53 immunoreactivity of 42%. The diagnosis of a giant prolactinoma was established. Six months later, the tumour measured 60×48 mm (figure 2A). One year after the surgery, there was regrowth of the tumour's cystic component to 65×42 mm and the patient's behavioural changes returned (figure 2B). Therefore a redo craniotomy was performed. There were no hormonal deficits after the surgeries.

The patient was started on bromocriptine after the first surgery and this drug was titrated up to 45 mg/day. However, biochemical response to the bromocriptine was poor and this DA was changed to cabergoline. Again his dose was titrated up to 5 mg/week.

## OUTCOME AND FOLLOW-UP

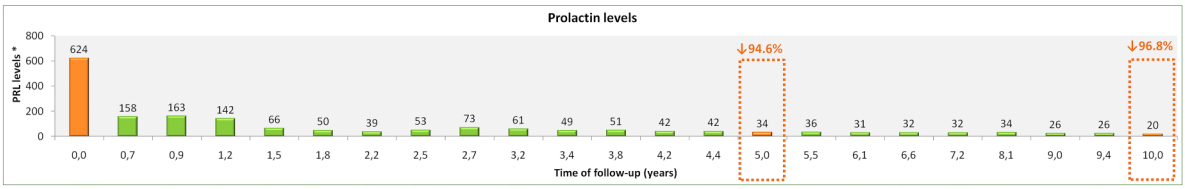
After the second surgery there was significant clinical improvement, with complete resolution of the neurological and visual symptoms. However, 2 years after the initial diagnosis, the patient developed seizures and was therefore started on anticonvulsants. Although hypogonadism resolved 6 months after the initial surgery (testosterone 431 ng/dL, normal range 270–1734) it returned 2.5 years later and testosterone therapy was initiated (testosterone enanthate 250 mg, intramuscular, every 4 weeks). Secondary hypothyroidism developed 4 years after presentation and the patient was started on levothyroxine 75 µg/day.

At 5 years of follow-up, prolactin levels had decreased by 94.7% (figure 3) and pituitary MRI showed persistence of a tumour capsule adherent to the visual pathways, skull base and its vessels, extending to the third ventricle (figure 4A, B).

After 10 years of follow-up, the patient is continued on cabergoline 5 mg/week, with no associated cardiac complications. Prolactin levels have decreased by 96.8% and the lesion remains stable (figure 3). His most unstable and frequent clinical features are convulsions in the form of absence seizures and simple partial seizures (average 2–3 episodes per year), despite treatment with several different antiepileptic drugs. This complication has led to partial loss of autonomy and decreased quality of life.

## DISCUSSION

As described in almost all reports of giant prolactinomas, our patient is a young man. It has been described that




| Follow-up (years) | 0 | 0,7 | 0,9 | 1,2 | 1,5 | 1,8 | 2,2 | 2,5 | 2,7 | 3,2 | 3,4 | 3,8 | 4,2 | 4,4 | 5,0 | 5,5 | 6,1 | 6,6 | 7,2 | 8,1 | 9,0 | 9,4 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bromocriptine (mg/day) | 7,5 | 15 | 15 | 15 | 25 | 35 | 45 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Cabergoline (mg/week) | - | - | - | - | - | - | - | 2 | 3 | 3,5 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Figure 3** Prolactin levels in 10 years of follow-up and corresponding medical treatment. * PRL (prolactin) levels represented in number of times the upper limit of normal.

microprolactinomas are more prevalent in women and macroprolactinomas more common in men.[8] This is probably due to an earlier diagnosis in women, due to easier recognition of the endocrine consequences of hyperprolactinaemia, namely galactorrhoea, menstrual disturbances and infertility.[8 9] Some authors also argue that prolactinomas tend to be more aggressive in males, and that this fact could explain the highest prevalence of giant prolactinomas in this gender.[10]

In our case, the patient presented with neurological symptoms (headache and visual disturbance) that resulted from compression of pituitary surrounding structures by a very large and invasive tumour of 76 mm of diameter, and his behavioural changes could be explained by the antero-superior growth of the tumour to the frontal lobe.[3]

Currently, DAs are the first-line treatment for all prolactinomas, including giant prolactinomas.[1 8] There are several reports of a pronounced and fast response of these tumours to this medical therapy.[4 7 11] Nevertheless, the majority of patients with giant prolactinomas need lifelong medical therapy and cure is very rare.[1]

When our patient was observed for the first time in the ER, none of the doctors from the pituitary group were present. A presumptive diagnosis of craniopharyngioma was performed and clinical presentation, with behavioural changes and visual impairment, led to a rapid surgical intervention. However, it is worth emphasising the need to determine serum prolactin in all invasive skull base tumours and to consider DA therapy as primary treatment when the prolactin level is above 1000 ng/mL (21 000 mU/L).

One year later, despite treatment with DA, regrowth of the lesion's cystic component and worsening of the neurological symptoms led to a redo craniotomy for mass resection. The aggressiveness of the lesion was then evident and proved by immunohistochemistry of the removed adenoma tissue. At 10 years of follow-up, after two surgeries and under high doses of cabergoline, the patient remains with hyperprolactinaemia, hypogonadism and residual tumour on MRI. At this point, our main concerns are the maintenance of prolactin secretion and hypogonadism, the high doses of cabergoline needed and the eventual requirement of other treatment options in the future. We could not achieve the classic prolactinoma treatment goals, but these goals are not realistic in giant prolactinomas. Some authors consider that the priority in the management of these tumours is the control of the mass effect.[1 3] In our case, there was an effective and progressive reduction in tumour size and its secretion, leading to the recovering of neuronal changes.

The residual tumour can explain the maintenance of hormonal hypersecretion.[12] Albeit very slowly, the tumour continues to decrease its secretion, resulting in consecutively lower prolactin serum values. DA resistance can be defined as failure to normalise prolactin on maximally tolerated doses of DAs and the absence of tumour size reduction ≥50%.[13] Moraes *et al* contend that in giant prolactinomas the term 'insufficient response to DAs' may be more appropriate because, as in our case report, there is a response to DA drugs in these tumours, but a normal prolactin level may not be achieved due to tumour size and very high prolactin levels at diagnosis.[3] This demonstrates the need for long-term therapy in giant prolactinomas.[1]

The high doses of cabergoline used are a real concern. Our patient has been treated for 7 years with a high dose of cabergoline (cabergoline cumulative dose: almost 1800 mg). However, until now, no side effects, namely pathological changes in

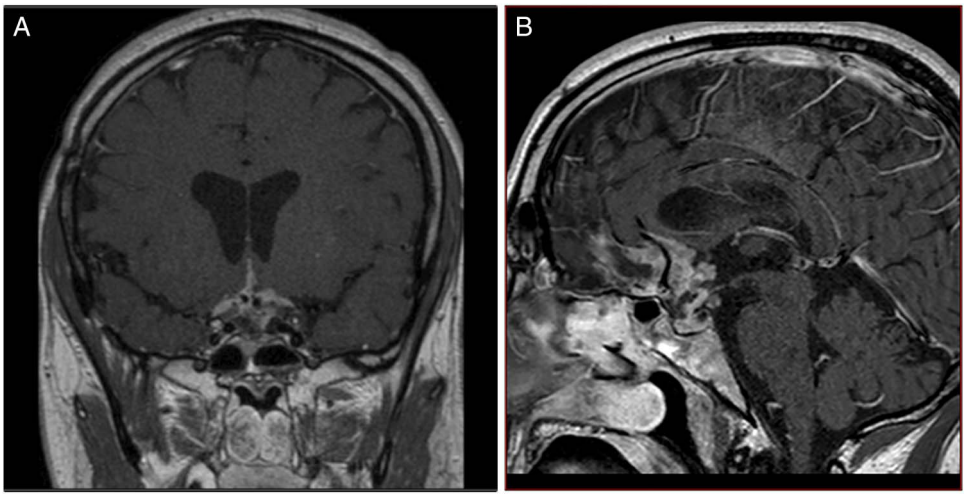



**Figure 4** (A) MRI at 5 years of follow-up (coronal view). (B) MRI at 5 years of follow-up (sagittal view).

annual echocardiograms, have been observed. Treatment with cabergoline has been associated with unusual short-term side effects related to tumour shrinkage, such as cerebrospinal fluid leakage, chiasmal herniation and pituitary apoplexy. However, the main concerns of cabergoline use are related to its cumulative dose and long-term potential cardiac effects.[4 14 15] This drug has been associated with subclinical lesions, such as aortic calcifications and tricuspid regurgitation and periodic echocardiographic monitoring is recommended in these patients.[3 15–17] Mitral valve insufficiency has also been reported in Parkinson's disease patients treated with high doses of cabergoline.[14 18] Therefore, use of the lowest effective dose should be recommended in order to minimise the risk of side effects. In the large study by Delgrange *et al*,[19] there was no advantage in increasing the dose above 3.5 mg/week, but very few studies have tried to define a dose threshold above which further response is unlikely to occur.[4 7] Despite this, prolonged treatment with high doses of cabergoline has been reported to be safe in patients with giant prolactinomas.[14] Reassuring data have been provided by studies in patients with Parkinson's disease treated with high doses of carbergoline (up to 21 mg per week).[18]

Another important concern in our patient is epilepsy, as it affects his quality of life. Although different antiepileptic drugs have been used, he still has, on average, more than three seizures per year. This problem can result from sequelae of the craniotomies and/or from the pituitary lesion's mass effect before treatment.

Other treatment options have been considered. The remaining tumour is an infiltrative lesion that is adherent to the visual pathways, skull base and its vessels. These anatomical characteristics make surgery and radiotherapy (even γ knife radiation) unattractive and possible side effects unacceptable. According to Moraes *et al*,[3] in a residual unresectable tumour without mass effect and no biochemical control despite increasing cabergoline dose, the most correct approach is hypogonadism treatment.

Immunohistochemistry of the tumour revealed a high proliferative index of 7% (using the Ki-67 antibody) and p53 immunoreactivity of 42%. This is illustrative of the aggressiveness of this tumour, which can explain its clinical course and highlights the requirement for lifelong follow-up of the patient.[20] Another important point is the malignant potential of the tumour. At present, it remains responsive to cabergoline and the MRI is stable. However, if unresponsiveness to DAs develops or metastases appear, other treatment options must be considered. Temozolamide is a chemotherapy agent that has been used in aggressive pituitary tumours, including giant prolactinomas, with good results, and can be a helpful option.[1 21]

Therefore, in our opinion, the maintenance of 5 mg of cabergoline per week and hypogonadism treatment with careful surveillance seems to be the most appropriate management at this time. New medical therapies are being studied and might become important options in the future.

## Learning points

- The therapeutic goals of prolactinomas (normalisation of hormone levels, re-establishment of eugonadism and reduction of tumour size) are often not realistic in giant prolactinomas.
- The therapeutic management of giant prolactinomas is a challenge.
- The first-line therapy of giant prolactinomas is dopamine agonist therapy, but other therapeutic approaches may be necessary.
- Lifelong medical therapy in giant prolactinomas is usually needed.

**Acknowledgements** The authors would like to thank Rui Ramos for his support in revising this article.

**Contributors** VF contributed to the case study, analysis of data and conception of the manuscript. MJS, RA and OM contributed to the case study and critical review of the case report. All the authors contributed to the final approval of the version to be published.

**Competing interests** None declared.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

1 Maiter D, Delgrange E. Therapy of endocrine disease: the challenges in managing giant prolactinomas. *Eur J Endocrinol* 2014;170:R213–27.
2 Shrivastava RK, Arginteanu MS, King WA, *et al*. Giant prolactinomas: clinical management and long-term follow up. *J Neurosurg* 2002;97:299–306.
3 Moraes AB, Silva CM, Vieira Neto LV, *et al*. Giant prolactinomas: the therapeutic approach. *Clin Endocrinol (Oxf)* 2013;79:447–56.
4 Prague JK, Ward CL, Mustafa OG, *et al*. Delayed presentation of late-onset cerebrospinal fluid rhinorrhoea following dopamine agonist therapy for giant prolactinoma. *Endocrinol Diabetes Metab Case Rep* 2014;2014:140020.
5 Murphy FY, Vesely DL, Jordan RM, *et al*. Giant invasive prolactinomas. *Am J Med* 1987;83:995–1002.
6 Almalki MH, Buhary B, Alzahrani S, *et al*. Giant prolactinomas: clinical manifestations and outcomes of 16 Arab cases. *Pituitary* 2015;18:405–9.
7 Cho EH, Lee SA, Chung JY, *et al*. Efficacy and safety of cabergoline as first line treatment for invasive giant prolactinoma. *J Korean Med Sci* 2009;24:874–8.
8 Javorsky BR, Aron DC, Findling JW, *et al*. Hypothalamus and pituitary gland. In: Gardner DG, Shoback D, eds. *Greenspan's basic & clinical endocrinology*. New York: The McGraw-Hill. 2011:65–114.
9 Bjerg ML, Rosendal F, Nielsen E, *et al*. Giant prolactinoma presenting as a skull base tumor with erosion of the cervical vertebrae: pronounced responsiveness to dopamine agonist treatment. *Br J Neurosurg* 2014;27:1–3.
10 Delgrange E, Trouillas J, Maiter D, *et al*. Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. *J Clin Endocrinol Metab* 1997;82:2102–7.
11 Rahmanian M, Meybodi HA, Larijani B, *et al*. Giant prolactinoma: case report and review of literature. *J Diabetes Metab Disord* 2013;12:3.
12 Davis JR, Sheppard MC, Heath DA. Giant invasive prolactinoma: a case report and review of nine further cases. *Q J Med* 1990;74:227–38.
13 Molitch ME. Dopamine resistance of prolactinomas. *Pituitary* 2003;6:19–27.
14 Alsubaie S, Almalki MH. Cabergoline treatment in invasive giant prolactinoma. *Clin Med Insights Case Rep* 2014;7:49–51.
15 Auriemma RS, Piovonello R, Ferreri L, *et al*. Cabergoline use for pituitary tumors and valvular disorders. *Endocrinol Metab Clin North Am* 2015;44:89–97.
16 Valassi E, Klibanski A, Biller BM. Clinical Review#: potencial cardiac valve effects of dopamine agonists in hyperprolactinemia. *J Clin Endocrinol Metab* 2010;95:1025–33.
17 Delgado V, Biermasz NR, van Thiel SW, *et al*. Changes in heart valve structure and function in patients treated with dopamine agonists for prolactinomas, a 2-year follow-up study. *Clin Endocrinol (Oxf)* 2012;77:99–105.
18 Gillam MP, Middler S, Freed DJ, *et al*. The novel use of very high doses of cabergoline and a combination of testosterone and an aromatase inhibitor in the treatment of a giant prolactinoma. *J Clin Endocrinol Metab* 2002;87:4447–51.
19 Delgrange E, Daems T, Verhelst J, *et al*. Characterization of resistance to the prolactin-lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. *Eur J Endocrinol* 2009;160:747–52.
20 Lloyd, RV, Kovacs K, Young WF. Jr *et al*. (2004) Pituitary tumours: introduction. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. *World Health Organization classification of tumours pathology and genetics of tumors of endocrine organs*. Lyon: IARC Press, 2004:10–13.
21 Whitelaw BC, Dworakowska D, Thomas NW, *et al*. Temozolomide in the management of dopamine agonist-resistant prolactinomas. *Clin Endocrinol (Oxf)* 2012;76:877–86.