

# Functioning Pituitary Adenomas – Current Treatment Options and Emerging Medical Therapies

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DOI: <https://doi.org/10.17925/EE.2019.15.1.30>

**P**ituitary adenomas are benign tumours comprising approximately 16% of all primary cranial neoplasms. Functioning pituitary adenomas (prolactinomas, somatotroph, corticotroph, thyrotroph and rarely gonadotroph adenomas) cause complex clinical syndromes and require prompt treatment to reduce associated morbidity and mortality. Treatment approaches include transsphenoidal surgery, medical therapy and radiation. Medical therapy is the primary therapy for prolactinomas, and surgery by a skilled neurosurgeon is the first-line approach for other functioning pituitary adenomas. A multimodal treatment is frequently necessary to achieve biochemical and clinical control, especially, when surgery is not curative or when medical therapy fails. Several emerging, novel, medical treatments for acromegaly, Cushing's disease and prolactinomas are in phase II and III clinical trials and may become effective additions to the current drug armamentarium. The availability of various management options will allow an individualised treatment approach based on the unique tumour type, clinical situation and patient preference.

## Keywords

Pituitary adenoma, prolactinoma, acromegaly, Cushing's disease, TSH-secreting adenoma, gonadotroph adenoma, transsphenoidal surgery, radiation, medical therapy

**Disclosures:** Maria Fleseriu has been a principal investigator for studies with research grants to Oregon Health & Science University from Chiasma, Ionis, Millendo, Novartis, Pfizer and Strongbridge, and has been an occasional scientific consultant to Chiasma, Ionis, Ipsen, Novartis, Pfizer and Strongbridge. Elena V Varlamov and Shirley McCartney have nothing to declare in relation to this article.

**Compliance with Ethics:** This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

**Review process:** Double-blind peer review

**Authorship:** All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

**Received:** 18 October 2018

**Accepted:** 11 February 2019

**Citation:** *European Endocrinology*. 2019;15(1):30–40

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**Support:** No funding was received for the publication of this article.

Pituitary adenomas are benign tumours that arise from the adenohypophysis. They are the second most frequent intracranial tumour type after meningiomas, and account for 16.2% of all primary cranial neoplasms.<sup>1</sup> Though likely an underestimate, the incidence of pituitary adenomas is approximately four per 100,000 persons per year,<sup>2,3</sup> and incidence increases with age.<sup>4</sup> Prolactinomas and non-functioning pituitary adenomas are the most common pituitary adenoma types, followed by somatotroph, corticotroph and thyrotroph adenomas. Almost all gonadotroph adenomas are clinically non-functioning, and less than 1% are hormonally active.<sup>4,5</sup> Functioning pituitary adenomas carry significant morbidity and increased mortality due to resultant clinical syndromes, concurrent hypopituitarism as well as tumour mass effect.<sup>6–8</sup> Prompt and effective treatment is crucial to disease control and a reduction in associated health risks.<sup>9–11</sup> In this review, treatment options for different types of functioning pituitary adenomas are presented, with a focus on current and emerging medical therapies.

## Pituitary adenoma therapy

Therapy for pituitary adenomas includes transsphenoidal surgery, medical treatment and/or radiation therapy.

## Surgery

Transsphenoidal surgery is the first-line therapy for most cases of functioning pituitary adenomas (except prolactinomas), as surgery can achieve rapid and sustained biochemical remission, along with decompression of the optic chiasm. However, surgery carries the risk of new pituitary deficiencies (3.6–19.4%), transient or permanent diabetes insipidus (4.3–17.7% and 0.3–7.3% respectively), hyponatremia (4.3–21%) and other surgical complications such as cerebrospinal fluid (CSF) leak (2.6–7%), haemorrhage (1.1–2.9%), infection (1.1–3.8%), carotid artery injury (0.1–1.1%) and vision loss (0.6–1.8%).<sup>12–14</sup> In a meta-analysis, hypopituitarism was more common after transsphenoidal surgery for Cushing's disease (25%) than acromegaly, prolactinoma or non-functioning pituitary adenomas (approximately 7–12%), and is thought to be related to prolonged glucocorticoid replacement and a more aggressive surgical technique used for corticotroph adenomas.<sup>15</sup> Rates of surgical success and complications vary, with more favourable outcomes achieved with experienced surgeons and in high-volume centres.<sup>13,16</sup> Microscopic and endoscopic techniques appear equally effective, with a similar complication rate.<sup>12,14</sup>

## Medical

Medical therapy is generally used as adjunct therapy after a failed transsphenoidal surgery in Cushing's disease and acromegaly, when surgery cannot be performed, or for recurrent disease. Often medical therapy becomes a long-term treatment option that requires monitoring for biochemical control and side effects. Pituitary-directed medications (somatostatin receptor ligands

[SRLs] and dopamine agonists) exert antisecretory and antiproliferative effects on pituitary tumours; prolactinomas typically respond to dopamine agonists with considerable tumour regression, while in acromegaly and Cushing's disease, tumour response to SRLs varies significantly. End-organ targeted therapy, such as inhibitors of adrenal steroidogenesis or receptor blockers, e.g. glucocorticoid or growth hormone receptor antagonists, can provide effective biochemical and/or clinical disease control (Table 1).

## Radiation

Due to slow onset of response (up to several years) and development of new pituitary deficiencies, radiation therapy is considered a third-line therapy option following unsuccessful transsphenoidal surgery and failed medical treatment, or in cases of tumour recurrence.<sup>10,11</sup> Conventional and stereotactic fractionated radiation is delivered in multiple small doses over 5–6 weeks, while stereotactic radiosurgery is performed in a single-session, high-dose treatment. Conventional and stereotactic radiosurgery therapy have similar effectiveness, although stereotactic radiosurgery may result in quicker normalisation of hypersecreted hormones.<sup>17–19</sup> Stereotactic radiosurgery is more convenient for a patient; however, it carries a higher risk of damage to the optic apparatus in tumours located very close to the optic chiasm.<sup>18–20</sup> Secondary brain tumours develop in 1.1–2.4% of patients after conventional therapy with relative risk ranging from no increased risk to 10.5 compared to the general population, and several studies have shown no increased risk compared to nonirradiated patients.<sup>21,22</sup> Conventional radiotherapy may pose a slightly higher risk of stroke, especially in acromegaly<sup>23</sup> and it has been associated with neurocognitive impairment, specifically in verbal memory and executive function, regardless of tumour type.<sup>24</sup>

## Prolactinomas

Prolactinomas are the most common functioning pituitary tumours (66%), with a female:male ratio of 10:1.<sup>2,25</sup> The majority are microadenomas (80%) and men more commonly present with macroadenomas.<sup>2,26</sup> Giant prolactinomas represent 1–5% of all prolactinomas.<sup>27</sup>

## Medical

Dopamine agonists, the mainstay of medical therapy, are very effective at normalising prolactin levels and reducing pituitary adenoma size; resulting in a rapid, often within days, visual improvement and gradual restoration of hypogonadism and fertility.<sup>28,29</sup> Cabergoline and bromocriptine are dopamine agonists available in the United States. Another dopamine agonist, quinagolide, is used in some European countries. Cabergoline is recommended over bromocriptine due to higher potency and effectiveness when compared with bromocriptine.<sup>28</sup> Cabergoline normalises prolactin in 83% versus bromocriptine in 59% of women with hyperprolactinaemic amenorrhoea.<sup>30</sup> A meta-analysis of six observational studies and three randomised trials showed superiority of cabergoline at reducing prolactin levels and associated symptoms of hypogonadism in women.<sup>31</sup> The effect on tumour volume reduction has not been assessed in randomised controlled trials. However, data extracted from two separate studies suggest greater efficacy of cabergoline on tumour volume reduction, 96% versus 64% with bromocriptine.<sup>32–34</sup> This difference in efficacy is thought to be related to cabergoline having a stronger affinity for dopamine D2 receptors and a longer duration of action.<sup>28</sup>

Resistance, defined as inability to achieve normoprolactinaemia or 50% reduction in tumour volume with standard doses of dopamine agonist, occurs in 25% of patients treated with bromocriptine and 10% treated with cabergoline.<sup>28,35</sup> It is estimated that up to 80% of those resistant to

bromocriptine can achieve normal prolactin levels with cabergoline.<sup>28</sup> The mechanism of resistance is also poorly understood, but may be due to decreased number of D2 receptors, presence of different receptor isoforms or downstream signalling changes in resistant prolactinomas.<sup>28,36,37</sup> Cabergoline dose may be increased, typically (1–2 mg/week) to a maximal tolerable dose, though this is rarely reported to overcome resistance.<sup>28</sup>

Common side effects of dopamine agonists are nausea, dizziness and headache, with nausea being more pronounced in patients treated with bromocriptine. Additionally, there is growing evidence of an association of dopamine agonist use with impulse control disorders such as pathologic gambling and hypersexuality.<sup>38</sup> Although the prevalence of these disorders in patients with prolactinomas is still unknown, one study reported that the risk of developing an impulse control disorder was 9.9 times higher in males treated with dopamine agonists compared to those with non-functioning adenomas.<sup>38,39</sup> A very rare but serious complication is CSF leak in giant prolactinomas eroding the sellar floor, which typically requires urgent neurosurgical intervention.<sup>40</sup> Although standard cabergoline doses are not associated with increased risk of valvular heart disease, doses >2 mg/week and high cumulative doses may still carry some risk, and monitoring with echocardiograms has been recommended by some groups.<sup>41–45</sup> Few studies have reported association of bromocriptine with non-clinically significant valve fibrosis,<sup>46,47</sup> and larger studies have reported no association.<sup>43</sup>

Investigation of emerging medical therapies is underway (Table 2). Lapatinib is a tyrosine-kinase inhibitor of epidermal growth factor receptor (EGFR) and receptor tyrosine-protein kinase (ErbB2 or human epidermal growth factor receptor 2 [HER2]), which shows promise as a treatment for resistant prolactinomas. Lapatinib has been demonstrated to decrease prolactin levels by 60% and 40% in transgenic mice with pituitary expression of EGFR and HER2, respectively; prolactin remained unaltered in control mice.<sup>48</sup> In two human subjects, addition of lapatinib to cabergoline after prolonged treatment with high dose cabergoline allowed for 22% tumour volume reduction and almost normalisation of prolactin at 6 months in one case, and suppression of tumour growth with 42% prolactin reduction in the other case.<sup>49,50</sup> Side effects were mild alopecia, rash, diarrhoea and anorexia. Lapatinib is currently being evaluated in the phase II trial, Targeted Therapy with Lapatinib in Patients with Recurrent Pituitary Tumors Resistant to Standard Therapy (ClinicalTrials.gov Identifier; NCT00939523).

## Surgery

Transsphenoidal surgery is reserved for patients with resistant prolactinomas, those with intolerance or contraindications to medical therapy, as well as emergent situations such as apoplexy and CSF leak. Several studies have examined the outcomes of transsphenoidal surgery and reported variable remission rates; range 30–93%,<sup>51</sup> with lower remission rates reported for invasive prolactinomas. Following transsphenoidal surgery, new pituitary deficiencies developed in 17.1% of patients in one study (7.0% anterior pituitary hypofunction), while improvement of existing deficiencies occurred in 14.6%.<sup>52</sup> Although prolactinomas in men tend to be more aggressive, it has not been clearly demonstrated that men have poorer surgical outcomes.<sup>26,53</sup> However, a recent study of prolactinomas in males who required surgery reported a high rate of residual tumour (92.6%) and frequent need for additional surgery and radiation.<sup>26</sup> Preoperative dopamine-agonist therapy does not appear to significantly affect surgical cure.<sup>26,51,53</sup> Following debulking surgery, medical therapy normalises prolactin levels in almost half of resistant adenomas, and with lower dopamine agonists doses.<sup>51</sup>

Table 1: Current medical options for prolactinoma, acromegaly and Cushing's disease

Disease treatment, medication and dose	Medication		
	Class	Advantages	Notes of special interest
<b>Prolactinomas</b>			
<i>Cabergoline</i> • 0.25–1 mg / twice weekly, oral	D2 receptor agonist	<ul style="list-style-type: none"> <li>• More effective and better tolerated than bromocriptine</li> <li>• Longer acting, allowing twice weekly dosing</li> </ul>	<ul style="list-style-type: none"> <li>• Higher doses, average 3–4 mg/week, may be needed for resistant prolactinomas</li> <li>• In a few patients, up to 7–11 mg/week have been reported, but efficacy and safety is unknown</li> <li>• May require echocardiography to monitor for valvular defects if used in high doses for prolonged period of time</li> </ul>
<i>Bromocriptine</i> • 2.5–15 mg/day, oral; may divide into 2x day dosing	D2 receptor agonist	<ul style="list-style-type: none"> <li>• Preferred in pregnancy (more safety data than with cabergoline)</li> <li>• Less expensive</li> </ul>	<ul style="list-style-type: none"> <li>• Causes more nausea than cabergoline</li> <li>• Less effective than cabergoline</li> </ul>
<b>Acromegaly</b>			
<i>Octreotide SC</i> • 50–100 µg / 3x day, SC	Somatostatin receptor ligand	<ul style="list-style-type: none"> <li>• May be used in addition to long-acting SRLs to treat acromegaly-associated headaches</li> </ul>	<ul style="list-style-type: none"> <li>• Short acting, requires multiple daily injections</li> </ul>
<i>Octreotide LAR</i> • 10–40 mg/month, IM	Somatostatin receptor ligand		<ul style="list-style-type: none"> <li>• In the US, can only be administered by a healthcare professional</li> </ul>
<i>Lanreotide</i> • 60–120 mg/month, deep SC	Somatostatin receptor ligand	<ul style="list-style-type: none"> <li>• Packaged in prefilled syringes, can be self-administered</li> </ul>	<ul style="list-style-type: none"> <li>• Some patients develop subcutaneous nodules at injection site</li> </ul>
<i>Pasireotide LAR</i> • 40–60 mg/month, SC	Somatostatin receptor ligand, higher SSTR5 affinity	<ul style="list-style-type: none"> <li>• More efficacious than octreotide</li> </ul>	<ul style="list-style-type: none"> <li>• Causes hyperglycaemia in more than half of patients and glucose needs to be closely monitored</li> <li>• QTC prolongation</li> <li>• LFT elevation</li> </ul>
<i>Cabergoline</i> • 0.5–2 mg/week, oral	D2 receptor agonist	<ul style="list-style-type: none"> <li>• Oral route</li> </ul>	<ul style="list-style-type: none"> <li>• Higher doses have been reported but unlikely to be beneficial</li> <li>• Less effective than somatostatin receptor ligands, used mostly in combination therapies</li> </ul>
<i>Pegvisomant</i> • 10–40 mg/day, SC	GH receptor antagonist	<ul style="list-style-type: none"> <li>• Highly effective</li> <li>• Improves insulin resistance</li> </ul>	<ul style="list-style-type: none"> <li>• Does not have anti-tumour effect</li> <li>• Cannot use GH to monitor disease control</li> </ul>
<b>Cushing's disease</b>			
<b>Pituitary-directed drugs</b>			
<i>Pasireotide</i> • 0.3–0.9 mg / 2x day, SC	Somatostatin receptor ligand, higher SSTR5 affinity	<ul style="list-style-type: none"> <li>• Anti-tumour effect with tumour shrinkage in some patients</li> </ul>	<ul style="list-style-type: none"> <li>• Controls mild-to-moderate hypercortisolism, less effective for severe disease</li> <li>• Causes hyperglycaemia</li> </ul>
<i>Pasireotide LAR</i> • 10–40 mg/month, SC	Somatostatin receptor ligand, higher SSTR5 affinity	<ul style="list-style-type: none"> <li>• Anti-tumour effect with tumour shrinkage in some patients</li> <li>• Monthly administration</li> </ul>	<ul style="list-style-type: none"> <li>• Controls mild-to-moderate hypercortisolism, less effective for severe disease</li> <li>• Causes hyperglycaemia</li> </ul>
<i>Cabergoline</i> • 0.5–7 mg/week, oral	D2 receptor agonist	<ul style="list-style-type: none"> <li>• Possible anti-tumour effect</li> </ul>	<ul style="list-style-type: none"> <li>• Usually used only in combination with other drugs</li> <li>• Risk of treatment escape</li> </ul>
<b>Inhibitors of adrenal steroidogenesis</b>			
<i>Ketoconazole</i> • 400–1,200 mg/day, oral; divided into 2–4 doses	Inhibitor of CYP17A1, CYP11A1 and CYP11B1	<ul style="list-style-type: none"> <li>• Rapid effect</li> <li>• Relatively inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>• No anti-tumour effect</li> <li>• Multiple daily dosing</li> <li>• Interaction with many drugs</li> </ul>
<i>Metyrapone</i> • 0.5–6.0 g/day oral; divided into 4 doses	Inhibitor of CYP11B1, CYP11B2 and CYP17A1	<ul style="list-style-type: none"> <li>• Rapid effect</li> <li>• Limited availability in most countries</li> </ul>	<ul style="list-style-type: none"> <li>• No anti-tumour effect</li> <li>• Multiple daily dosing</li> </ul>
<i>Mitotane</i> • 2–4 g/day oral; divided into 3–4 doses	Inhibitor of CYP11A1, CYP11B1 and CYP11B2	<ul style="list-style-type: none"> <li>• Very potent</li> </ul>	<ul style="list-style-type: none"> <li>• No anti-tumour effect</li> <li>• Slow onset of effect</li> <li>• Usually requires steroid replacement</li> </ul>
<i>Etomidate</i> • 0.03 mg/kg bolus, followed by 0.02–0.08 mg/kg/hr	Inhibitor of CYP11B1, CYP17A1 and CYP11A1	<ul style="list-style-type: none"> <li>• Rapid effect</li> <li>• Can be used short term for severe hypercortisolism</li> </ul>	<ul style="list-style-type: none"> <li>• No anti-tumour effect</li> <li>• IV, requires monitoring in ICU</li> </ul>
<b>Glucocorticoid receptor blockers</b>			
<i>Mifepristone</i> • 300–1,200 mg/day, oral	GC receptor antagonist; antiprogestin	<ul style="list-style-type: none"> <li>• Effective for hyperglycaemia in Cushing's syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• No anti-tumour effect</li> <li>• Dose adjustment only based on clinical grounds (cannot follow cortisol levels)</li> </ul>

D = diarrhoea; D2 = dopamine receptor D2; GC = glucocorticoid; GH = growth hormone; ICU = intensive care unit; IM = intramuscular; IV = intravenous; LFT = liver function test; SRL = somatostatin receptor ligand; SSTR5 = somatostatin receptor 5; SC = subcutaneous; V = vomiting. QTC = electrocardiogram calculated duration of time from the start of the Q wave to the end of the T wave adjusted for a patient's heart rate.

Table 2: Emerging investigational drug medical therapies for pituitary adenomas

Name	Class	Dosage/route/schedule	Side effects	Notes / current testing phase	ClinicalTrials.gov number or reference
<b>Prolactinomas</b>					
Lapatinib	Tyrosine-kinase inhibitor	1,250 mg PO daily	Fatigue, nausea, diarrhoea, paraesthesias, insomnia	May be effective for resistant prolactinomas Phase II	NCT00939523
<b>Acromegaly</b>					
Oral octreotide	Somatostatin receptor ligand	20–40 mg PO twice daily	Nausea, vomiting, diarrhoea, dyspepsia, cholelithiasis, headaches, dizziness, dysglycemia	Oral route Phase III	NCT02685709 NCT03252353
ATL1103	Antisense oligonucleotide inhibitor of growth hormone receptor	200 mg SC once or twice weekly	Injection site reaction, LFT elevation, headache	Completed phase II	Trainer et al., 2018 <sup>108</sup>
ISIS 766720	Antisense oligonucleotide inhibitor of growth hormone receptor, in liver	60–80 mg SC every 4 weeks	To be determined	Phase II	NCT03548415
CRN00808	Somatostatin receptor 2 biased agonist	PO once daily	Not available	Phase II	NCT03789656
Raloxifene	Selective oestrogen receptor modulator (partial oestrogen agonist in bone and cardiovascular system; anti-oestrogen in endometrial and breast tissues)	60 mg PO twice daily	Flushing, leg cramps, peripheral oedema, venous thromboembolism	Studied as adjuvant therapy in men, postmenopausal women and hypogonadal premenopausal women	Imani et al., 2018 <sup>106</sup>
Tamoxifen	Selective oestrogen receptor modulator (oestrogen agonist in bone, cardiovascular system, and endometrial tissue; anti-oestrogen in breast tissue)	20–40 mg PO daily	Hot flushes, venous thromboembolism, endometrial cancer	Studied as adjuvant therapy in men and postmenopausal women	Balili and Barkan, 2014 <sup>104</sup>
Clomiphene	Selective oestrogen receptor modulator (blocks central oestrogen receptors causing increase of LH and FSH; weak oestrogen agonist on periphery)	50 mg PO daily	Hot flushes, headaches, dizziness, gynecomastia	Studied as adjuvant therapy in men	Duarte et al., 2015 <sup>105</sup>
<b>Cushings Disease</b>					
<b>Pituitary directed</b>					
Roscovitine	Cyclin-dependent kinase 2/cyclin E inhibitor	400 mg PO twice daily	Weakness, nausea, vomiting, hypokalaemia	Phase II	NCT02160730
Gefitinib	Epidermal growth factor receptor inhibitor	250 mg PO daily	Dermatologic, diarrhoea, weakness, LFT elevation	Targets USP8-mutated adenomas Oral Phase II	NCT02484755
Retinoic acid	Retinoic acid receptor agonist	80 mg PO daily	Nausea, headache, arthralgia	Anti-tumour effect in animal studies	Pecori Giraldi et al., 2012 <sup>156</sup> Vilar et al., 2016 <sup>157</sup>
<b>Inhibitors of adrenal steroidogenesis</b>					
Levoketoconazole	Inhibitor of cytochrome P450: – CYP17A1 – CYP11A1 – CYP11B1 – CYP21A2	200–1200 mg PO twice daily	Headache, back pain, nausea, LFT elevation, QTC prolongation	More potent than ketoconazole  Phase III	NCT03277690
Osilodrostat	Inhibitor of cytochrome P450: – CYP11B2 – CYP11B1 at higher doses	2–30 mg PO twice daily	Nausea, diarrhoea, asthenia, adrenal insufficiency, hirsutism, acne, headache, hypokalaemia	Very effective in phase II clinical trial Phase III	NCT02697734
ATR -101	Acetyl-CoA Acetyltransferase 1 inhibitor	125–1000 mg PO twice daily	Vomiting, diarrhoea in animal study	Phase II	NCT03053271
<b>Glucocorticoid receptor blockers</b>					
Relacorilant	Glucocorticoid receptor antagonist	100–400 mg PO daily	Headache, nausea, vomiting, thirst, musculoskeletal pain	No antiprogestin properties Phase II	NCT02804750

FSH = follicle stimulating hormone; LFT = liver function test; LH = luteinizing hormone; PO = per os (by mouth); SC = subcutaneously. QTC = electrocardiogram calculated duration of time from the start of the Q wave to the end of the T wave adjusted for a patient's heart rate.

Recurrence of hyperprolactinaemia after initial remission following transsphenoidal surgery is common, reportedly varying between 5–58%; higher rates are reported in studies with longer follow up.<sup>51,52,54</sup>

### Radiation

Radiation therapy is used for resistant and aggressive or malignant prolactinomas.<sup>55</sup> Prolactin levels normalise in 26–52% of patients post radiation therapy, tumour growth is controlled in 89–92%<sup>55–57</sup> and hypopituitarism occurs in one-third of patients.<sup>55</sup> Some authors have reported that dopamine agonist use at the time of radiation may reduce remission rates, while others did not find this association.<sup>55,58,59</sup> Therefore, there is no universal recommendation to withhold dopamine agonists prior to radiation.

### Acromegaly

Growth hormone-producing adenomas represent approximately 9.0–13.2% of pituitary adenomas; 73.0% are macroadenomas,<sup>2,5,60</sup> and giant adenomas constitute about 4.5%.<sup>27</sup> Acromegaly affects males and females equally and is most commonly diagnosed during the fifth decade of life.<sup>61</sup>

### Surgery

Transsphenoidal surgery is recommended as the first-line treatment due to rapid control of growth hormone levels. When performed by an experienced surgeon, remission is greater than 85% for microadenomas<sup>62,63</sup> and 40–66% for macroadenomas.<sup>63,64</sup> If biochemical remission is not achieved, patients require adjunctive medical therapy and/or radiation therapy. Even when the likelihood of cure is low, such as in the case of large or invasive adenomas, debulking surgery is still recommended as it provides better postoperative control by SRLs.<sup>65–8</sup> Five-year recurrence after surgery is reported as 0.7–5.4% in various studies, and 10–15-year recurrence as 0.1–10%.<sup>64,69–71</sup> Incidence of pituitary deficiencies after transsphenoidal surgery include 6.50% for adrenal insufficiency, 4.39% for central hypothyroidism, 6.70% for hypogonadism, 14.95% for growth hormone deficiency and 10.05% for transient and 2.42% for permanent diabetes insipidus, as assessed by a meta-analysis.<sup>72</sup>

Overall, surgery is more effective than primary medical therapy for treatment-naïve patients. A meta-analysis of prospective and retrospective studies demonstrated that surgically treated patients had higher remission rates than their medically treated counterparts (67% versus 45%,  $p=0.02$ ).<sup>73</sup>

Finally, surgery can provide additional information about tumour granulation type and presence of somatostatin receptor (SSTR) on pathology. Densely granulated adenomas and SSTR2A-positive adenomas respond better to SRLs than sparsely granulated adenomas and SSTR2A-negative adenomas.<sup>74,75</sup> This knowledge allows for an SRL response prediction, which serves to guide physicians in selecting individualised patient treatment plans (e.g. SRL monotherapy versus pegvisomant or early combination therapy).

### Medical

Medical therapy may be used as primary therapy in poor candidates for surgery, in those who decline surgery or if surgery is unlikely to provide biochemical cure due to extent of the disease.<sup>10</sup> Occasionally, medical therapy is used preoperatively in high-risk patients with a goal of reducing growth hormone levels and decreasing anaesthesia complications such as laryngeal oedema, high-output heart failure and uncontrolled hypertension.<sup>76,77</sup> SRLs, growth hormone receptor

antagonists (pegvisomant) and dopamine agonists are the three classes of medications currently used to treat acromegaly. They are used as a single agent or in combination.<sup>7,78</sup>

SRLs act on SSTR subtypes 2 and 5 located on somatotroph cells. First-generation SRLs (octreotide [OCT] long-acting release [LAR], lanreotide slow release and lanreotide autogel) seem to be equally effective in controlling growth hormone and insulin-like growth factor 1 (IGF-1) level in approximately 55% of patients (reported clinical studies range 17–70%).<sup>10,79,80</sup> The wide range in reported efficacy can be explained by different clinical study methodology, selection bias, previous surgery or medical treatment, dose, duration of follow-up and other factors.<sup>79</sup> Biochemical control can be maximised by escalating the dose of OCT-LAR (60 mg every 4 weeks)<sup>81</sup> and lanreotide (180 mg every 4 weeks or 120 mg every 3 weeks) in treatment-responsive patients.<sup>82–84</sup> First-generation SRLs are effective at shrinking the tumour in 30–66% of patients by 10–77%.<sup>85–87</sup> Approximately one-third of patients experience 50% tumour volume reduction with primary medical therapy.<sup>86</sup> Common side effects include gastrointestinal distress, gallstones and dysglycaemia.

Pasireotide is a multi-SRL with a high affinity for SSTR5 compared to other SRLs and has been demonstrated to have higher efficacy than OCT-LAR in a randomised controlled trial (31.3% versus 19.2%, respectively,  $p=0.007$ ), while tumour volume reduction was similar, approximately 40%.<sup>88</sup> Additionally, pasireotide can normalise biochemical control in 20% of patients resistant to first-generation SRLs;<sup>89</sup> however, hyperglycaemia occurs in 57% of patients. Pasireotide-induced hyperglycaemia has been attributed to a reduction in insulin secretion, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide levels.<sup>90</sup> Close monitoring in patients with impaired glucose tolerance and diabetes is required and treatment with metformin, dipeptidyl peptidase-4 (DPP-4) inhibitor or GLP-1 receptor agonist has been recommended for the management of hyperglycaemia.<sup>91</sup>

Pegvisomant is a highly selective growth hormone receptor antagonist that blocks growth hormone receptor to reduce IGF-1 production by the liver. Pegvisomant is used in patients who remained uncontrolled after transsphenoidal surgery or radiation therapy and sometimes as primary therapy if transsphenoidal surgery is not feasible or desired.<sup>10,92</sup> In clinical trials, pegvisomant effectiveness was remarkable, with IGF-1 normalisation rates of up to 97% on maximal doses of 40 mg daily.<sup>93</sup> However, long-term surveillance studies indicated that a real-world control rate was approximately 60%, likely reflecting lower standard doses used in everyday practice compared with clinical trials.<sup>10,82</sup> Liver function tests are monitored and treatment should be discontinued if transaminases increase to greater than five-times the upper limit of normal (ULN). Despite a theoretical concern that lack of IGF-1 feedback may stimulate pituitary tumour growth, progression of tumour was noted only in 3% of patients.<sup>94</sup> Although this may represent natural tumour progression independent of pegvisomant, serial magnetic resonance imaging (MRI) has been recommended.<sup>10</sup>

Dopamine agonists normalise IGF-1 and growth hormone in one-third of patients,<sup>95,96</sup> and induce tumour volume reduction in up to 62%.<sup>95</sup> Due to modest efficacy in acromegaly, cabergoline plays a role mostly as adjunctive therapy in cases with mildly elevated IGF-1.

### Combination medical therapy

Pegvisomant can be used in combination with first-generation SRLs in patients who are uncontrolled on SRL alone. This may result in IGF-1 normalisation in up to 95% of cases.<sup>97</sup> A combination of

pegvisomant and pasireotide may potentially allow for lower doses. This has been examined in one study to date,<sup>98,99</sup> where it was demonstrated that switching from first-generation SRLs to pasireotide allowed for a reduction in pegvisomant dose by half. Pegvisomant did not offset or prevent pasireotide-induced hyperglycaemia. Diarrhoea was a common side effect, but no elevation of transaminases was observed.

Dopamine agonists in combination with SRLs achieve normalised IGF-1 levels in approximately half of patients who are uncontrolled on SRLs alone.<sup>95</sup> Cabergoline plus a low-dose pegvisomant combination is also a modestly effective option when liver enzyme elevation, diabetes or SRL-induced hyperglycaemia is a concern.<sup>100</sup>

Oestrogen is capable of lowering IGF-1 through inhibition of liver growth hormone receptor expression or through upregulation of suppressors of cytokine signalling-2, leading to decreased growth hormone signalling.<sup>101,102</sup> Selective oestrogen receptor modulators bind to oestrogen receptors and exhibit oestrogen agonistic or antagonistic effects in different tissues. Raloxifene, tamoxifen and clomiphene have been studied as an add-on therapy in men and post-menopausal women with uncontrolled acromegaly.<sup>103–106</sup> In one study, tamoxifen normalised IGF-1 in eight (47%) patients and decreased IGF-1 in 14 (82%) patients.<sup>104</sup> A recent head-to-head open label study of raloxifene versus cabergoline add-on therapy to long-acting SRL showed similar lowering effect on IGF-1; IGF-1 normalised in 45.5% of patients with raloxifene and in 40.9% of patients with cabergoline.<sup>106</sup> Adverse effects included flushing. A study of clomiphene in men has shown a decrease in IGF-1 by 41%, including normalisation of IGF-1 in 44% without reported side effects.<sup>105</sup> Selective oestrogen receptor modulators are not part of standard acromegaly management and longer-term studies are needed to assess their safety and efficacy.<sup>106</sup>

### Emerging medical therapy

Several new acromegaly treatment agents as well as a new SRL formulations are being tested in human clinical trials (*Table 2*). In a phase III clinical trial, oral OCT maintained biochemical control in 62% of patients who were switched from a long-acting SRL (from 89% controlled on SRL at baseline).<sup>107</sup> There are two other ongoing phase III trials: Comparison of Oral Octreotide Capsules to Injectable Somatostatin Analogs in Acromegaly (MPOWERED; ClinicalTrials.gov Identifier: NCT02685709) and Efficacy and Safety of Octreotide Capsules (MYCAPSSA) in Acromegaly (OPTIMAL; ClinicalTrials.gov Identifier: NCT03252353).

An antisense oligonucleotide inhibitor of growth hormone receptors is a novel and promising therapy. A phase II study of ATL1103 demonstrated a 27.8% reduction of IGF-1 at week 14, with good tolerability but mild-to-moderate injection-site reaction occurring in 85%.<sup>108</sup> A newer generation antisense oligonucleotide ISIS 766720, targeting hepatic expression of growth hormone receptor, is currently being investigated in a phase II trial (Safety, Tolerability, and Efficacy of IONIS-GHR-LRx in up to 42 Adult Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands; ClinicalTrials.gov Identifier: NCT03548415).

Another emerging therapeutic agent is an orally bioavailable nonpeptide SSTR2 biased agonist, CRN00808. CRN00808 is biased for SSTR2 activation (a process that causes reduction of growth hormone secretion) over receptor internalisation (which is a process that limits therapeutic activity of SSTR agonist). Preliminary phase I clinical trial data (Single and Multiple-Ascending Dose Study of CRN00808 in Healthy Volunteers; ClinicalTrials.gov Identifier: NCT03276858) show

that a 2.5 mg once-daily dose lowers growth hormone-releasing hormone-induced growth hormone release by 73% in healthy volunteers.<sup>109</sup> A phase II study evaluating CRN00808 in patients with acromegaly treated with SRLs is ongoing (A Study to Evaluate the Safety and Efficacy of CRN00808 for the Treatment of Acromegaly [ACROBAT EDGE]; ClinicalTrials.gov Identifier: NCT03789656).

### Radiation

Radiation therapy is reserved for patients with persistent disease after surgery who failed medical therapy. However, remission onset is slow, taking many years and requiring medical therapy in the interim. Hormonal remission rates are 50–60% at 10–15 years with both stereotactic radiosurgery and conventional radiation, with stereotactic radiosurgery slightly more effective.<sup>23,110,111</sup> Hypopituitarism develops in up to 50% of patients at 5 years.<sup>23,110</sup> Some suggested that SRLs may prevent a full effect of radiation, but this has not been a consistent observation and may be due to the fact that in non-randomised studies, patients with more severe disease were more likely to continue SRL prior to treatment.<sup>20,112,113</sup> Although not clearly recommended by current guidelines, some centres withhold SRLs for four to eight weeks prior to radiation therapy.<sup>20</sup>

### Cushing's disease

Adrenocorticotrophic hormone (ACTH)-producing adenomas represent 4–6% of all adenomas, occurring more frequently in females (3:1 ratio).<sup>2,5</sup> Only about a third are macroadenomas, while the majority are microadenomas, and approximately 12% of those are not detectable on MRI.<sup>5,114</sup> Aggressive corticotroph adenomas are usually biochemically silent, and have an approximately 30% risk of recurrence.<sup>115</sup>

### Surgery

Transsphenoidal surgery is the recommended treatment of choice for ACTH-producing adenomas. Remission rates range from 65–98%, with higher rates when a pituitary adenoma is identified on MRI and removed completely by an experienced and specialised surgeon.<sup>116,117</sup> If a pituitary adenoma is not found during surgical exploration, hemi-hypophysectomy/pan-hypophysectomy may be performed, with remission rates reported as 60–75%.<sup>116</sup> However, more extensive transsphenoidal surgery carries greater risk of hypopituitarism. Postoperative pituitary deficiencies develop in 25% of patients with Cushing's disease compared to approximately 7–13% in other pituitary adenomas.<sup>15</sup> Transient diabetes insipidus is the most common postoperative pituitary dysfunction occurring in 4–48% of patients, while permanent diabetes insipidus has been reported in 3–46% of patients.<sup>15,118</sup> Rates of postoperative thyrotropin and gonadotropin deficiency are 11–20% and 8–17% respectively.<sup>118–120</sup> In one study, prevalence of growth hormone deficiency was 65% in patients who achieved long-term surgical remission.<sup>121</sup>

Failure of remission occurs when a pituitary adenoma is incompletely excised or missed on surgical exploration, if dural invasion is present, or if a pituitary adenoma is extra-pituitary.<sup>116,122,123</sup> Repeat surgery is an option for those with persistent hypercortisolism; however, remission rates are lower, 57–71%.<sup>124,125</sup> Given the possibility of delayed remission, the decision to repeat surgery should be postponed until persistent disease is biochemically confirmed. Hypercortisolism can recur in up to 35% of cases.<sup>116,126</sup>

### Medical

Medical therapy is necessary for persistent or recurrent hypercortisolism after transsphenoidal surgery or if surgery is contraindicated or declined. Additionally, medical therapy can be used post-radiation therapy until

radiation effect occurs. Current medical therapy is directed at three targets: ACTH production by a corticotroph tumour, steroidogenesis in the adrenal gland, and glucocorticoid receptors.

Pituitary-directed drugs include pasireotide and cabergoline. Pasireotide binds to SSTR5 receptor, which is predominantly expressed on corticotroph adenoma cells, and inhibits ACTH production. In a 12-month clinical trial of pasireotide in Cushing's disease, subcutaneous pasireotide decreased urinary free cortisol (UFC) by approximately 50% and normalised levels in more than 20% of patients, mainly in those with mild-to-moderate cortisol hypersecretion. Tumour volume reduction was 43% on a maximum dose of 900 µg daily.<sup>127</sup> A long-acting monthly intramuscular formulation, pasireotide LAR, is available and has a similar efficacy as the subcutaneous pasireotide.<sup>128</sup> The most frequent side effect of both formulations is hyperglycaemia, occurring in more than half of patients. Gastrointestinal side effects such as nausea, diarrhoea and cholelithiasis are similar in frequency to other SRLs.<sup>127</sup> Cabergoline acts via D2 receptors on corticotroph tumours. It is mostly used as an add-on therapy. Short-term response with UFC normalisation is observed in 25–35% of patients,<sup>129–131</sup> while long-term efficacy is lower, mainly due to treatment escape.<sup>129,132</sup> The dose range is 1–7 mg/week, with a commonly used dose of 2–3.5 mg/week.

Currently available inhibitors of steroidogenesis are ketoconazole, metyrapone, mitotane and etomidate. Ketoconazole is an antifungal agent used off-label in the United States (licensed in Europe) for Cushing's syndrome. Ketoconazole inhibits cytochrome P450 enzymes on multiple levels of steroidogenesis and at higher doses effectively lowers glucocorticoid and androgen synthesis.<sup>133</sup> Studies report efficacy in 30–90% of patients. The largest retrospective study to date showed that 49% of patients with Cushing's disease achieved normal UFC and 25% had at least 50% reduction in UFC; however, 15% experienced escape from control after 2 years of treatment.<sup>134–7</sup> Severe ketoconazole-induced hepatotoxicity (black box warning in the United States) is rare; however, mild liver enzyme elevation is relatively common and therefore requires close monitoring.<sup>138</sup> Gynecomastia and hypogonadism due to inhibition of androgen synthesis limits use in males.

Metyrapone can effectively lower cortisol in 43–76% of patients with Cushing's syndrome without apparent escape.<sup>139</sup> Blockade of 11-beta hydroxylase causes accumulation of mineralocorticoid and androgenic precursors resulting in hypertension, hypokalaemia, oedema, hirsutism and acne. Mild gastrointestinal symptoms are common. Mitotane plays a major role in the treatment of adrenal carcinoma due to its adrenolytic effect on tumour cells, but it is occasionally used in Cushing's disease. Very potent, but with a slow onset of action, mitotane induces eucortisolaemia in 72–82% of patients<sup>11</sup> and often leads to adrenal insufficiency, requiring hydrocortisone replacement. Side effects include gastrointestinal upset, lethargy and abnormal liver function. Etomidate is a parenteral anaesthetic, which at lower, sub-hypnotic doses, rapidly inhibits cortisol production and thus has been used in patients with severe Cushing's syndrome in the acute setting as well as preoperatively to decrease the risk of hypercortisolaemia related complications.<sup>140</sup>

Mifepristone is a glucocorticoid receptor antagonist that has been shown to significantly improve clinical manifestations of Cushing's syndrome, including glucose metabolism, hypertension and weight gain.

Overall, a clinical response was observed in up to 87% of patients.<sup>141</sup> However, its mechanism of action causes ACTH and cortisol levels to rise during treatment, and therefore, they cannot be used to guide management; caution is required for potential tumour enlargement, especially in the case of macroadenomas.<sup>142</sup> When encountered, adrenal insufficiency due to glucocorticoid receptor blockade should be treated with high doses of dexamethasone. Additionally, unopposed mineralocorticoid activity of cortisol can cause hypertension, oedema and hypokalaemia. The latter can be ameliorated by use of the mineralocorticoid blocker spironolactone. Also, an antiprogesterin effect may result in endometrial hyperplasia.<sup>143</sup>

### Combination medical therapy

Combination therapy is increasingly used for those patients who have failed monotherapy or if side effects of a single agent do not permit a dose increase. Regimens such as pasireotide plus cabergoline, ketoconazole plus cabergoline, and ketoconazole plus metyrapone have been successfully utilised.<sup>144,145</sup>

### Emerging medical therapy

Multiple new medical therapies are currently in development and are undergoing clinical testing (*Table 2*). New inhibitors of steroidogenesis include levoketoconazole, osilodrostat and ATR-101.

Levoketoconazole is a more potent enantiomer of ketoconazole and was proposed to achieve similar effectiveness with smaller doses and less pronounced side effects than ketoconazole. In a phase III, open-label trial, 81% of patients had initial UFC normalisation at the end of the dose titration period (up to 21 weeks), but only 30% of patients had normal UFC levels during the maintenance phase without a dose increase.<sup>146</sup> Nausea and headache were most common side effects and liver function test elevation of >3 ULN in 11% of patients is relatively similar to the ketoconazole data from retrospective and observational data, although the studies are not comparable.<sup>139</sup> Levoketoconazole is currently being assessed in a phase III, double-blind, withdrawal and rescue/restoration study (A Study to Assess the Safety and Efficacy of Levoketoconazole in the Treatment of Endogenous Cushing's Syndrome; ClinicalTrials.gov Identifier: NCT03277690).

Osilodrostat is an oral nonsteroidal corticosteroid biosynthesis inhibitor that inhibits 11 beta-hydroxylase with higher affinity than metyrapone and has a longer half-life.<sup>147</sup> In an open label study, osilodrostat induced normalisation of UFC in 84% of patients at week 10 and 79% at week 22.<sup>148</sup> Despite the increase in the precursor 11-deoxycorticosterone, hypokalaemia was mild and hypertension has not been observed. Hirsutism and acne occurred in one-third of women due to elevated testosterone. Two phase III studies are ongoing: Safety and Efficacy of LCI699 for the Treatment of Patients with Cushing's Disease (ClinicalTrials.gov Identifier: NCT02180217) and Efficacy and Safety Evaluation of Osilodrostat in Cushing's Disease (LINC-4) (ClinicalTrials.gov Identifier: NCT02697734).

ATR-101, is a selective acyl-coenzyme A:cholesterol acyltransferase 1 (ACAT1)1 inhibitor that reduces cholesterol ester formation from cholesterol, thereby decreasing the substrate supply for steroidogenesis in the adrenal glands. ATR-101 was shown to reduce cortisol level by 50% in animal studies and is currently being studied in a phase II, double-blind study in humans (A Study of ATR-101 for the Treatment of Endogenous Cushing's Syndrome; ClinicalTrials.gov Identifier: NCT03053271).

Relacorilant (CORT125134) is a selective antiglucocorticoid receptor antagonist that has an advantage of avoiding the progesterone receptor inhibitory effects of mifepristone. A phase II trial is ongoing (Study to Evaluate CORT125134 in Patients with Cushing's Syndrome, ClinicalTrials.gov Identifier: NCT02804750). Preliminary results of the low-dose arm showed improvement in glucose control, blood pressure, marker of bone formation and, somewhat surprisingly, a relatively small increase in ACTH and cortisol.<sup>149</sup>

Pituitary-targeted therapies in phase II trials include roscovitine and gefitinib. Roscovitine is a cyclin-dependent kinase inhibitor that suppresses 2/cyclin E on corticotroph tumour cells causing inhibition of the ACTH precursor hormone, proopiomelanocortin (POMC), with a subsequent decrease of ACTH production, although with a minimal antiproliferative effect.<sup>150</sup> It is currently studied in a dose of 400 mg orally twice daily for 4 days every week, for a total of 4 weeks in Cushing's disease (Treatment of Cushing's Disease with R-roscovitine; ClinicalTrials.gov Identifier: NCT02160730).

Roscovitine has also been assessed in phase I trials in patients with various malignant solid tumours; some showed stabilisation of growth.<sup>151,152</sup> Side effects were dose dependent and included fatigue, skin rash, hyponatremia and hypokalaemia occurring at doses of 800 mg and higher.<sup>151</sup> Gefitinib is an EGFR inhibitor approved for non-small cell lung cancer. EGF binds to EGFR on corticotroph tumour cells and promotes POMC and ACTH synthesis.<sup>152</sup> Approximately half of corticotroph tumours harbour a somatic USP8 mutation which causes over-expression of EGFR.<sup>153</sup> Gefitinib has been shown to inhibit ACTH production in USP8-mutated corticotroph tumours.<sup>76,152</sup> A study of gefitinib 250 mg once daily for 4 weeks is ongoing (Targeted Therapy with Gefitinib in Patients with USP8-mutated Cushing's Disease; ClinicalTrials.gov Identifier: NCT02484755). Common adverse events are rash, diarrhoea and elevation of liver enzymes.<sup>153</sup> Interstitial lung disease of grade 3–4 occurs in 0.7% of patients (package insert).<sup>154</sup> Other mutations harboured by corticotroph tumours (e.g. USP48 and BRAF) are being actively investigated, but are beyond the scope of this review.<sup>155</sup>

Retinoic acid decreases ACTH by suppressing pro-opiomelanocortin gene transcription and exerts an anti-tumour effect in corticotroph adenomas.<sup>156</sup> In a small prospective study, retinoic acid at 80mg daily for 6–12 months decreased UFC to 22–73% of baseline levels; however, some patients were non-responders.<sup>156</sup> Another small study (16 patients) showed a normalisation of UFC in 25% of participants at study end.<sup>157</sup>

Emerging pituitary-targeted drug treatments not yet in clinical trials include heat shock protein inhibitors, histone deacetylase inhibitors, monoclonal ACTH antibodies and others.<sup>158,159</sup>

## Radiation

Radiation therapy is used when pituitary surgery is unsuccessful, in invasive adenomas or in poor surgical candidates. All patients should receive medical treatment while awaiting radiation effects, which may take several years. Control of hypercortisolism is achieved in up to 83% of patients undergoing conventional radiation and 70% undergoing stereotactic radiosurgery.<sup>18,160</sup> Time to remission with stereotactic radiosurgery appears to be shorter, 14.5 months versus 18.0–42.0 months with conventional radiation.<sup>161</sup> Recurrence after initial control has been observed in 18% of patients after stereotactic radiosurgery, which confirms the need for lifelong monitoring.<sup>161</sup>

## Bilateral adrenalectomy

Bilateral adrenalectomy is reserved as a third-line treatment option for patients with uncontrolled hypercortisolism despite pituitary surgery, appropriate medical therapy and/or pituitary radiation. It can be life-saving in patients with severe and prolonged Cushing's syndrome who require rapid and permanent control of hypercortisolism.<sup>162,163</sup> Lastly, it may be selected earlier in patients desiring fertility options in whom pituitary irradiation or surgery is likely to result in irreversible hypogonadism. Rarely, hypercortisolism may persist or recur due to remnant adrenal tissue. Corticotroph tumour progression (Nelson's syndrome) occurs in 0–47% of patients post bilateral adrenalectomy,<sup>164,165</sup> and some data suggest that prior pituitary radiation may reduce the risk.<sup>166,167</sup> It is important to periodically monitor ACTH and pituitary MRI. Mortality in the first year seems to be high post bilateral adrenalectomy.<sup>164</sup>

## Thyroid stimulating hormone-secreting adenomas

Thyroid stimulating hormone (TSH)-secreting adenomas are rare, 0.5–3.0% of all pituitary adenomas, with equal male–female distribution, and are mostly macroadenomas at diagnosis.<sup>168</sup> Surgical resection is the first-line treatment, with remission rates of 55–83%.<sup>169,170</sup> Complete surgical removal is often impossible due to the fibrotic nature of these tumours and parasellar extension/invasion, necessitating adjunct medical therapy and/or radiation.<sup>168</sup> Pre-treatment with antithyroid drugs, beta-blockers and SRLs is necessary in some cases to control severe hyperthyroidism to reduce the risk of perioperative thyroid storm.<sup>169,171</sup> In a series of 68 operated patients (67% macroadenomas), six patients (9%) developed new hypopituitarism; hypogonadism in two, hypoadrenalism in two, both hypoadrenalism and hypogonadism in one, and panhypopituitarism in one patient.<sup>169</sup> A smaller series of 13 patients reported postoperative hypopituitarism in five patients (38%); hypoadrenalism in three, hypothyroidism in one, growth hormone deficiency in two and hypogonadism in one patient.<sup>172</sup> Radiation for persistent disease controls hyperthyroidism in 20–50% and produces tumour volume reduction in 26% of patients, and hypopituitarism occurs in approximately one-third of patients.<sup>169</sup>

Octreotide and lanreotide reduce TSH and normalise thyroid hormone levels in more than 80% patients.<sup>169,173</sup> In a study of pre-operative OCT-LAR for a median of 33.5 days, T4 normalisation occurred in 84% of patients.<sup>172</sup> Another study of mixed patient population (post pituitary surgery with or without additional radiation or medical therapy and those who were treatment-naïve) showed that lanreotide was effective at normalising thyroid hormone levels in 81% of patients.<sup>174</sup> Resistance and escape from therapy are uncommon. As marked suppression of thyroid function can occur, patients should be monitored for hypothyroidism. SRLs induce tumour shrinkage in 39–61% of patients.<sup>171,174</sup> Although TSH-secreting tumours express D2 receptors, dopamine agonists are less effective, with favourable results observed mostly in mixed prolactin/TSH-secreting adenomas.<sup>168,175</sup>

## Gonadotroph adenomas

Functioning gonadotroph adenomas are very rare and treatment algorithms are limited to case reports and small case series. Adenomectomy is, however, the principal treatment approach; it restores gonadal function in men and women, and leads to the resolution of ovarian and testicular enlargement caused by hyperstimulation by gonadotroph adenoma.<sup>176</sup> Radiation has been used as adjunct therapy

after surgery, as well as for recurrent adenomas.<sup>177–180</sup> Dopamine agonists, SRLs, gonadotropin-releasing hormone agonists and antagonists have been tried both as primary therapy and after transsphenoidal surgery, and in the majority of cases showed no benefit for clinical symptoms or tumour shrinkage.<sup>176</sup>

### Aggressive pituitary adenomas

Aggressive pituitary adenomas are those that exhibit clinically significant growth despite appropriate medical, surgical and radiation therapy.<sup>181</sup> They are often characterised by an elevated Ki68 index ( $\geq 3$ –10%), high p53 immunoreactivity and increased number of mitoses; however, these criteria have not been validated as strong prognostic markers of aggressiveness. Debulking surgery or near-total resection is recommended, especially for tumours with mass-effect on optic chiasm. Radiation therapy following surgery should be considered in patients without contraindication to radiation therapy, as it can provide a durable control of tumour growth. Medical therapy usually includes the use of temozolomide, an alkylating agent, alone or in combination with standard medical therapy for functioning pituitary adenomas (dopamine agonist, SRLs).<sup>182,183</sup> Temozolomide is typically

administered in cycles of 5 days every 28 days, with a maximum number of cycles of 9–12. Response rate (tumour shrinkage) differs by tumour type and is estimated from a small case series to be 44% in prolactinomas, 56% in corticotroph tumours, 38% in somatotroph tumours and only 22% in non-functioning tumours.<sup>182</sup> Absent or low expression of O6-methylguanine-DNA methyltransferase, a DNA repair enzyme that interferes with temozolomide action, has been correlated with better response to temozolomide by some, but not all, authors.<sup>184,185</sup> Temozolomide is usually well tolerated; however, myelosuppression can occur.<sup>185</sup>

### Conclusion

Management of functioning pituitary adenomas often requires multiple treatment modalities to achieve rapid and durable remission and thus improve morbidity, mortality and quality of life. Treatment should be tailored individually based on the tumour type, availability of each therapeutic option and patient preference. Emerging medical therapies are being developed and may present future suitable options for patients with uncontrolled disease or intolerance to other medications.  $\square$

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