REVIEW

The natural history and treatment of non-functioning pituitary adenomas (non-functioning PitNETs)

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Abstract

Non-functioning pituitary adenomas, recently alternatively termed pituitary neuroendocrine tumours (NFpitNETs), are mostly benign neoplasms that are not associated with a hormonal hypersecretory syndrome. The clinical spectrum of NFpitNETs varies from completely asymptomatic to the development of panhypopituitarism and manifestations attributed to mass effects on nearby structures. NFpitNETs follow generally an indolent course, but in 5–10% of cases they exhibit more aggressive behaviour, characterised by rapid growth, invasiveness and early recurrence. The initial size of the adenoma, the presence of symptoms and the histological subtype are related to the natural course of NFpitNETs. Active surveillance is usually the strategy of choice in the case of an asymptomatic NFpitNET, while surgical resection is recommended in case of visual and/or neurological abnormalities or rapid tumour growth. Based on previous and emerging data, approximately 50% of patients show tumour growth, while 20% of patients with NF-macroadenomas on active surveillance may require further intervention during a follow-up period of 7 years. Adjuvant radiotherapy is usually considered for large residual tumours or recurrent and/or aggressive adenomas, but there is evidence that medical therapy, especially with cabergoline, can occasionally be beneficial, whereas newer molecular agents are under investigation. Thus, while highly effective medical therapy is awaited, a move towards a more conservative approach seems appropriate, at least until we have better molecular markers of progressiveness.

Introduction

Non-functioning pituitary adenomas are defined as benign adenohypophyseal tumours that are not associated with evidence of hormonal hypersecretion, except for hyperprolactinaemia secondary to compression of the pituitary stalk (Drummond et al. 2019). Their diagnosis is usually made in the presence of symptoms related to mass effects and compression of nearby vital structures and/or the development of anterior hormonal deficiencies, but a significant number are increasingly incidentally diagnosed during imaging investigations performed for unrelated purposes (pituitary incidentalomas, PIs) (Scangas & Laws 2014). Recently, pituitary adenomas have
been suggested to be renamed pituitary neuroendocrine tumours (pitNETs) (Asa et al. 2017). The majority of these tumours follow a relatively indolent or even stable course but a subset, approximately 5–10%, may exhibit a more aggressive course with rapid growth or early recurrence following initial treatment. Although non-functioning pitNETs (NFpitNETs) constitute the majority of significant sellar lesions and have distinct imaging features, occasionally distinction from other sellar pathologies may be needed in the presence of rapid growth and unusual or equivocal imaging features (Kaltsas et al. 2019).

As pitNETs are not associated with hormonal hypersecretion, their diagnosis may be significantly delayed, often being recognised when compressive symptoms to surrounding tissues occur. Thus, at the time of diagnosis, approximately 67–90% of NFpitNETs are macroadenomas, with the median age of the patients ranging between 51.5 and 65.5 years (Raappana et al. 2010). In contrast, when they are recognised as PIs, the prevalence of microadenomas is significantly higher, ranging between 10% and 38% on CT imaging and 4–20% on MRI compared to the incidence of macroadenomas (range between 0.16% on MRI and 0.3% on CT) (Freda et al. 2011).

The management of NFpitNETs includes replacement hormonal therapy in the presence of endocrine deficiencies along with surgical resection in cases of neurological abnormalities, visual impairment and/or rapid tumour growth. Radiotherapy (RT) may also be considered as adjuvant treatment to prevent further tumour growth for aggressive tumours, while the alkylating agent temozolomide (TMZ) has been introduced for highly aggressive pituitary tumours (APTs) or pituitary carcinomas (PCs) (Chatzellis et al. 2015). More recently, active surveillance has more frequently been advocated in cases without symptoms/signs of mass effect and/or significant hormonal deficiencies; this approach is particularly useful in elderly patients and patients with comorbidities (Chanson et al. 2015). The natural course of un-operated NFpitNETs is highly heterogeneous and largely depends on the initial size of the tumour (microadenoma vs macroadenoma), the diagnostic mode of discovery (incidental vs non-incidental) and the clinical presentation (symptomatic vs asymptomatic). On the other hand, the prognosis and the course of the surgically managed NFpitNETs also show a wide diversity of outcomes; increased risk of recurrence, tumour progression, hormone deficiencies and aggravation of visual field deficits, along with various rates of perioperative morbidity and mortality, are frequently reported, depending on the experience of the neurosurgeon.

Classically, assessment of proliferation markers such as the Ki-67 labelling index (LI), mitotic activity, and p53 expression have been recommended as prognostic markers for tumour aggressiveness and risk of recurrence, but more recently the WHO has especially emphasised the role of the Ki-67 LI as well as surgical and radiological factors as being most critical (Mete & Lopes 2017).

Intense research in the field of molecular biology is currently ongoing to identify novel molecular biomarkers that could predict the biologic behaviour of these tumours in an effort to assist the clinician to properly modify the therapeutic plan and follow-up of patients with NFpitNETs. This will be vital to identify when a conservative vis-à-vis a more aggressive approach is required.

### Epidemiology

NFpitNETs account for approximately 14–54% of pituitary adenomas, the second most commonly found after prolactinomas and the commonest of all macroadenomas (Ntali & Wass 2018). In the general population, the prevalence of clinically relevant NFpitNET is 7–41.3 cases per 100,000, based on population studies from Europe, Canada and the United States of America (Fernandez et al. 2010, Agustsson et al. 2015, Al-Dahmani et al. 2016).

In surgical series, the incidence of NFpitNETS ranges between 9 and 21% (Nomikos et al. 2004, Losa et al. 2013). As a component of hereditary syndromes, NFpitNETs occur in patients with multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4), and familial isolated pituitary adenomas (FIPAs). In large cohorts of patients with MEN1, pituitary tumours ranged from 14.7% (NF-macroadenomas) (Verges et al. 2002) to 42.3% (NF-microadenomas) (de Laat et al. 2015). NFpitNETs appear to occur more frequently in MEN4 compared to MEN1, although overall MEN4 is extremely rare (Alrezk et al. 2017). In FIPAs NFpitNETs occur in less than 20% of families, but present earlier than their sporadic counterparts (Daly et al. 2006). One case of an NFpitNET has also been reported in a young adult with paraganglioma in the setting of a germline mutation in succinate dehydrogenase subunit A (SDH-A) (Dwight et al. 2013). Patients with Carney complex develop GH or PRL-GH mixed tumours but, while NFpitNETs have not been reported, clinically silent GH and IGF-1 elevations have been described (Correa et al. 2015).
Classification of NFpitNETs

The immunohistochemical (IHC) profile of adenohypophyseal hormones along with the transcription factors related to pituitary ontogenesis (Fig. 1) (pituitary transcription factor 1 (Pit-1); steroiogenic factor 1 (SF-1); T-box family member TBX19 (T-Pit); guanine–adenine–thymine–adenine binding protein 2 (GATA-2)) is currently considered the gold standard for the classification system of pitNETs (Mete & Lopes 2017) (Table 1). In a recent pangenomic classification of pitNETs, Pit-1 appeared to be the main classification driver and Pit1-lineage was associated with DNA hypomethylation and chromosomal instability (Neou et al. 2020). Whether these alterations are linked to the biological behaviour of Pit1-lineage tumours, paving the way towards a molecular-based prediction of aggressiveness and treatment response, is yet to be determined.

Subtypes of non-functioning PitNETs

Non-functioning-silent gonadotroph adenomas

Silent gonadotroph adenomas (sGAs) comprise the vast majority (approximately 80%) of NFpitNETs and are characterised by focal immunostaining for β-follicle-stimulating hormone (β-FSH), β-luteinising hormone (β-LH), and α-subunit. The nuclear labelling of the SF-1 transcription factor is detected in most tumour cells and assists in confirming the diagnosis in cases with sparse or no gonadotroph hormone expression. The current definition and limitations, however, of the gonadotroph lineage were questioned in a recent multi-omic analysis of a large cohort of PitNETs (Neou et al. 2020), as the gonadotroph molecular signature was also identified in null-cell, silent corticotroph and somatotroph PitNETs.

Non-functioning/silent corticotroph adenomas

Silent corticotroph adenomas (sCAs) represent approximately 15–20% of NFpitNETs, being the second most common type after sGAs. Histologically, they can be divided into two subtypes; type I densely granulated sCAs, showing strong ACTH immunoreactivity, and type 2 sparsely granulated sCAs, demonstrating weak and focal ACTH staining.

Non-functioning/silent somatotroph adenomas

Silent somatotroph adenomas (sSAs) represent approximately 2–4% of all pituitary adenomas (Langlois et al. 2018). Growth hormone immunostaining varies widely from very weak to strongly positive, being less than in somatotrophinomas causing acromegaly. In addition, more than 50% of sSAs demonstrate mixed GH and prolactin (PRL) secretion. In cases with very low or absent GH staining, nuclear expression of the transcription factor Pit-1 is a valuable diagnostic tool, since all GH tumours express Pit-1 (Langlois et al. 2018).

Non-functioning/silent thyrotroph adenomas

Silent thyrotroph adenomas (sTAs) are extremely rare but are reported more frequently than TSH-omas (Mete & Lopes 2017). Both sTAs and TSHomas express TSH-β, and α-subunit, Pit-1 and GATA-2 transcription factors, and significant membrane immunoreactivity for somatostatin receptors (SSTR)-2A and SSTR-5.
<table>
<thead>
<tr>
<th>Tumour groups</th>
<th>Subtypes</th>
<th>Transcription factors</th>
<th>Hormones</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIT1 lineage tumour</td>
<td>Somatotroph tumour</td>
<td>PIT1</td>
<td>GH, α-subunit</td>
<td>CAM5.2 with perinuclear</td>
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<td></td>
<td>Densely granulated somatotroph tumour</td>
<td></td>
<td></td>
<td>CAM5.2 with fibrous bodies (&gt;70%)</td>
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<td></td>
<td>Sparsely granulated somatotroph tumour</td>
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<td>Lactotroph tumour</td>
<td>PIT1, ER-α</td>
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<td></td>
<td>Sparse granulated lactotroph tumour</td>
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<td>PRL (Golgi)</td>
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<td></td>
<td>Densely granulated lactotroph tumour</td>
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<td>PRL (Diffuse)</td>
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<td></td>
<td>Acidophil stem cell tumour</td>
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<td>PRLGH (variable), α-subunit</td>
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<td></td>
<td></td>
<td></td>
<td>GH, PRL, α-subunit, β-TSH, α-subunit</td>
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<tr>
<td>Mammosomatotroph tumour</td>
<td>Pit1, GATA2/3 (Mete et al. 2019, Turchini et al. 2020)</td>
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<tr>
<td>Thyrotroph tumour</td>
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<tr>
<td></td>
<td>Densely granulated thyrotroph tumour</td>
<td>PIT1, ER-α</td>
<td>GH (near diffuse/diffuse), PRL (variable), β-TSH (focal/variable)</td>
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<td></td>
<td></td>
<td>GATA2/3</td>
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<tr>
<td>Poorly differentiated PIT-1</td>
<td>Silent subtype 3 adenoma (Formerly known) Plurihormonal PIT1-positive adenoma (WHO 2017)</td>
<td>PIT1, ER-α, GATA2/3 (Mete et al. 2019, Turchini et al. 2020)</td>
<td>Focal/scattered for one or more than PIT1 lineage hormones (GH/PRL/β-TSH); can be hormone-negative</td>
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<tr>
<td>lineage tumour</td>
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<td>Tumours with no PIT1, SF1 and</td>
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<td>TPIT-lineage differentiation</td>
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<tr>
<td>SF1 lineage tumour</td>
<td>Gonadotroph tumour</td>
<td>SF1, ER-α, GATA2/3 (Mete et al. 2019, Turchini et al. 2020)</td>
<td>β-FSH ± β-LH; α-subunit, hormone negativity in 40% of cases (Mete et al. 2019)</td>
<td>CAM5.2 can be negative</td>
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<td>Corticotroph tumours</td>
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<tr>
<td>Densely granulated corticotroph tumour (silent corticotroph tumour, type 1)</td>
<td>PIT1; rare GATA2/3 (Mete et al. 2019, Turchini et al. 2020)</td>
<td>ACTH (diffuse and strong)</td>
<td>CAM5.2 with diffuse staining, p27 is often preserved in silent tumours</td>
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<tr>
<td>Sparsely granulated corticotroph tumour (silent corticotroph tumouassr, type 2)</td>
<td></td>
<td></td>
<td>ACTH (focal/weak, can be negative)</td>
<td>CAM5.2 with diffuse staining, p27 is often preserved in silent tumours</td>
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<tr>
<td>Crooke cell tumour</td>
<td></td>
<td></td>
<td>ACTH (cell periphery and juxtanuclear)</td>
<td>CAM5.2 with ring-like staining, p27 is often preserved in silent tumours</td>
</tr>
<tr>
<td>Tumours with no PIT1, SF1 and</td>
<td>Null-cell tumour</td>
<td>Negative for PIT1, ER-α, SF1, GATA2/3 (Mete et al. 2019, Turchini et al. 2020)</td>
<td>Negative for adenohypophyseal hormones</td>
<td>CAM5.2 can be negative</td>
</tr>
<tr>
<td>TPIT-lineage differentiation</td>
<td>Plurimorphous plurihormonal tumours</td>
<td>Any combination of PIT1, TPIT, SF1, ER-α, GATA2/3</td>
<td>Any combination of adenohypophyseal hormones</td>
<td>Multifocal pituitary neuroendocrine tumours do not qualify for this diagnosis</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; CAM5.2, cytokeratin; ER-α, estrogen receptor alpha; FSH, follicle-stimulating hormone; GATA-2, guanine–adenine–thymine–adenine binding protein 2; GH, growth hormone; LH, luteinising hormone; PIT1, pituitary transcription factor 1; PRL, prolactin; SF-1, steroidogenic factor 1; TPIT, T-box family member TBX19; TSH, thyroid stimulating hormone; WHO, World Health Organization.
Non-functioning/silent lactotroph adenomas
Silent lactotroph adenomas (sLAs) express PRL, Pit-1 and ER-α (Mete & Lopes 2017). Mono-hormonal SLAs are rare, usually presenting as silent mixed somatotroph-lactotroph adenomas in Pit-1 positive tumours. SLAs are classified further into sparsely and densely granulated subtypes (Mete & Lopes 2017).

Null-cell adenomas
Null-cell adenomas (NCAs) are defined by the lack of IHC staining of any anterior pituitary hormone or pituitary specific transcription factors (Mete & Lopes 2017). They are now thought to present a very small proportion of all pitNETs (Sjostedt et al. 2017), and their true frequency is probably overestimated due to lack of examination of transcription factors, such as SF-1.

Plurihormonal Pit-1 positive
Pit-1 positive plurihormonal adenomas (previously named ‘silent subtype 3 adenomas’) are a distinct entity with more aggressive behaviour (Mete & Lopes 2017). They demonstrate immunoreactivity for GH, PRL, and TSH in different combinations and, despite their ‘silent’ nature, approximately 30% are associated with clinical signs of Pit-1 lineage hormone-hypersecretion leading to hyperthyroidism, acromegaly, or hyperprolactinemia, and are found more frequently in MEN1.

Non-functioning pituitary carcinomas and aggressive pituitary tumours (APTs)
PCs are defined by the presence of cerebrospinal and/or systemic distant metastasis and account for only 0.2% of pitNETs. APTs represent a small subtype characterised by local invasion of surrounding tissues, increased risk for multiple recurrences, rapid tumour growth, and/or resistance to treatment. The precise number of APTs remains unknown but may account for approximately 10% of all pitNETs in surgical series (Raverot et al. 2018).

Clinical presentation
The clinical presentation of NFpitNETs varies from completely asymptomatic to panhypopituitarism and manifestations attributed to mass effects to nearby structures. The lack of clinical symptoms related to hormonal hypersecretion is associated with a delay in diagnosis of approximately 1.96 ± 2.9 years (Drange et al. 2000). In a recent large (>200 participants), prospectively studied cohort of NFpitNETs, the presentation was approximately 50% incidental and 50% due to tumour-related symptomatology (Freda et al. 2020). The prevalence of incidental presentation in this cohort, however, was somewhat higher than earlier reported in surgical series – where it ranged between 8.7% and 26.4% (Nomikos et al. 2004, Losa et al. 2008) – and in NFpitNETs cohorts that were followed conservatively where it ranged between 21% and 37% (Dekkers et al. 2007, Karavitaki et al. 2007).

Headache is the most common neurologic symptom observed in 19–75% of patients (Rizzoli et al. 2016). Possible mechanisms related to headache include increased intrasellar pressure and stretching of the dural membrane or invasion of the cavernous sinus and trigeminal nerve irritation, but there are no specific features (Ntali & Wass 2018).

Visual impairment is reported in 58% of patients (Cohen et al. 1985), mainly presenting as bitemporal hemianopia due to compression of the optic chiasm. However, visual field loss may be uni-, bilateral or central, as well as complete or partial, depending on the site and the degree of the nerve compression (Abouaf et al. 2015). In a recent study of 103 patients presenting to a neurosurgical unit with a pitNET, bitemporal visual field loss was the most common defect (41%), but a significant proportion of patients also had unilateral or even altitudinal defects.

Ocular motor impairment associated with large pitNETs is attributed to cavernous sinus invasion and compression of cranial nerves III, IV and VI (Abouaf et al. 2015).

Hypopituitarism is also common in patients with NFpitNETs. GH deficiency is most commonly observed followed by gonadotrophins, ACTH and thyrotrophin insufficiency (Chen et al. 2011, Ntali & Wass 2018). In addition, disconnection hyperprolactinaemia may be observed due to pituitary stalk compression and could account for some of the observed cases of hypogonadism (Karavitaki et al. 2006, Korevaar et al. 2012). Diabetes insipidus (DI) is an uncommon finding in cases of NFpitNETs and should direct investigation to another sellar pathology (Chen et al. 2011, Ntali & Wass 2018).

Pituitary apoplexy in NFpitNETs is occasionally seen. In a retrospective study of 485 patients, pituitary apoplexy was the first presentation in 8% (Vargas et al. 2015). A systematic review and meta-analysis regarding the natural history of PIs and NFpitNETs reported an incidence of apoplexy in macroadenomas of 1.1% per year (Fernandez-Balsells et al. 2011).
Natural history

The natural history of NFpitNETs has been studied in several, mainly retrospective, studies demonstrating a variety of biological behaviours. In most studies with long-term follow-up of un-operated NFpitNETs, initial tumour size was the main prognostic indicator of their biologic behaviour. Approximately 25–50% of patients with NF-macroadenomas demonstrate an increase in tumour size in follow-up periods of 22–73 months (Dekkers et al. 2007, Karavitaki et al. 2007) (Fig. 2). In a small cohort of un-operated NF-macroadenomas during a follow-up period of more than 7 years, tumour growth was observed in 50% of patients, 50% of whom also exhibited aggravation of a visual field defect and 25% an increase in hormone deficiencies (Table 2) (Dekkers et al. 2007). However, a spontaneous decrease in tumour volume was also reported in up to 30% in NF-macroadenomas (Table 2). NF-microadenomas grow less frequently compared to macroadenomas and the majority of them remain stable in size (Table 2), although an increase in tumour size in up to 50% of the NF-microadenomas in one cohort has also been reported (Sam et al. 2015).

The median annual growth rate differs significantly between macro- and micro-NFpitNETs; this is estimated at approximately 1.0 mm/year for macroadenomas and 0.4 mm/year for microadenomas (Sam et al. 2015), with the median time for the first radiological evidence of growth estimated at 1.4 years for macroadenomas and 1.5 years for microadenomas (Sam et al. 2015). Another significant factor appears to be the proximity of the adenoma to the optic chiasm; macroadenomas contacting the optic chiasm show a greater risk for tumour growth compared to those that do not (73% vs 29%) (Sam et al. 2015).

The underlying molecular mechanisms that drive some tumours to grow remain currently unknown, and no specific prognostic markers of tumour growth have been identified. Furthermore, the risk of malignancy and aggressive biological behaviour in NFpitNETs varies widely according to the histological type and as to whether the tumours develop in the context of a genetic syndrome or are sporadic.

SCAs, sSAs, sTAs and silent plurihormonal PIT-1-positive tumours are usually larger and exhibit more aggressive biological behaviour compared to other histologic subtypes (Trouillas et al. 2020), but the actual prognostic impact of these subtypes remains controversial. In addition, proliferative markers such as Ki-67 LI ≥3%, mitotic count >2, and p53 expression (Raverot et al. 2017, Trouillas et al. 2013) are also considered of prognostic significance (Trouillas et al. 2020).

NFpitNETs are not the predominant type in patients with MEN1, but were previously proposed to display a more aggressive behaviour, similar to their functioning counterparts (Corbetta et al. 1997, Thakker et al. 2012), although this remains controversial. In the Dutch cohort of patients with MEN1, the majority of NFpitNETs were microadenomas and remained stable after a median follow-up of approximately 6 years, while none of them progressed to macroadenomas (de Laat et al. 2015). On the other hand, in the French and Belgian multicentre cohort of patients with MEN1, the frequency of symptomatic macroadenomas was significantly higher in MEN1 compared with non-MEN1 patients (Verges et al. 2002).

A recent large retrospective cohort study in UK investigated the growth rate of tumours in patients with NFpitNETs that showed tumour growth after surgery (Tampoulou et al. 2017). In this study the 5- and 10-year
second regrowth rates were 35.3 and 46.7%, respectively, highlighting the need for long-term follow up in this patient population. In addition, a relatively high rate of patients, approximately 16%, with no visible tumour after surgery, showed the first regrowth at a follow-up period of 50 months, in line with previous studies (Greenman et al. 2003). Second surgery with or without adjuvant RT demonstrated favourable outcomes in avoiding further enlargement of the tumour compared to monitoring alone, indicating the need for active therapeutic intervention when appropriate (Tampourlou et al. 2017). In addition, a recent study observed that MRI texture analysis on T1-weighted images could predict the risk of tumour recurrence or progression after surgery, and this clearly requires further study (Galm et al. 2018).

Long-term mortality in these patients also appears to be higher than that of the general population (Pagesy et al. 1991, Tomlinson et al. 2001, Nielsen et al. 2007, Olsson et al. 2015, Ntali et al. 2016), although an improvement has been reported in the last decade, highlighting the efficacy of recent advances in the diagnosis and treatment of PitNETs. Cardio-cerebrovascular events, infections, and malignancies appear to be the most common causes of death in NFpitNETs patients with long-term follow-up (Ntali et al. 2016). However, when such patients are treated and adequately replaced, their quality of life does not appear to be different to the normal population (Capatina et al. 2013, Karppinen et al. 2016). Changes in tumour phenotype have also been reported in some subtypes of NFpitNETs, although the underlying molecular mechanisms remain unknown. A large single-centre retrospective cohort of surgically resected NFpitNETs (n = 124) over 10 years reported that 11% of sSAs and 5.6% of SCAs converted to functional adenomas during follow-up (Langlois et al. 2017). In another study, 3.9% of SCAs switched to Cushing’s disease in a transformation time of 1–7 years (Righi et al. 2017). Thus, close monitoring of such NFpitNETs is recommended not only because of their high risk of recurrence but also due to the risk of becoming functional over time.

The role of molecular biology in the pathogenesis and biological behaviour of NFpitNETs

Recent advances in molecular genetics have identified both somatic and germline mutations, associated with familial syndromes, in apparent sporadic cases of NFpitNETs (Vandeva et al. 2019).

Of the genes that have been implicated in the pathophysiology of pitNETs, guanine nucleotide-binding protein, alpha stimulating (GNAS), aryl hydrocarbon

Table 2 The natural course of non-functioning pituitary neuroendocrine tumours.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study cohort</th>
<th>Mean follow-up (months)</th>
<th>Increase in tumour size (%)</th>
<th>Decrease in tumour size (%)</th>
<th>Aggravation of visual impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reincke et al. (1990)</td>
<td>n = 14</td>
<td>22</td>
<td>Macro: 29</td>
<td>Macro: 0</td>
<td>NR</td>
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<tr>
<td></td>
<td>(7 macroadenomas)</td>
<td></td>
<td>Micro: 14</td>
<td>Micro: 7</td>
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<tr>
<td>Feldkamp et al. (1999)</td>
<td>n = 50</td>
<td>32</td>
<td>Macro: 26.3</td>
<td>Macro: 5.3</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>(19 macroadenomas)</td>
<td></td>
<td>Micro: 3.2</td>
<td>Micro: 3.2</td>
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<tr>
<td>Donovan &amp; Corenblum (1995)</td>
<td>n = 31</td>
<td>73</td>
<td>Macro: 25</td>
<td>Macro: 0</td>
<td>NR</td>
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<tr>
<td></td>
<td>(16 macroadenomas)</td>
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<td>Micro: 0</td>
<td>Micro: 0</td>
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<tr>
<td>Nishizawa et al. (1998)</td>
<td>n = 28</td>
<td>67.2</td>
<td>7</td>
<td>-</td>
<td>NR</td>
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<td></td>
<td>(macroadenomas)</td>
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<td>Sanno et al. (2003)</td>
<td>n = 115</td>
<td>51</td>
<td>20</td>
<td>9</td>
<td>NR</td>
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<tr>
<td></td>
<td>(macro + micro)</td>
<td></td>
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<tr>
<td>Arita et al. (2006)</td>
<td>n = 42</td>
<td>62</td>
<td>Macro: 51</td>
<td>-</td>
<td>NR</td>
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<td></td>
<td>(37 macroadenomas)</td>
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<td>Micro: 40</td>
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<td>n = 28</td>
<td>85</td>
<td>50</td>
<td>29</td>
<td>50% of the macroadenomas</td>
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<td></td>
<td>macroadenomas</td>
<td></td>
<td></td>
<td></td>
<td>with tumour growth</td>
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<tr>
<td>Karavitaki et al. (2007)</td>
<td>n = 40</td>
<td>42</td>
<td>Macro: 50</td>
<td>Macro: 16.7</td>
<td>67% of the macroadenomas</td>
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<tr>
<td></td>
<td>(24 macroadenomas)</td>
<td></td>
<td>Micro: 12.5</td>
<td>Micro: 6.3</td>
<td>with tumour growth</td>
</tr>
<tr>
<td>Sam et al. (2015)</td>
<td>n = 66</td>
<td>51.6</td>
<td>Macro: 59.6</td>
<td>Macro: 34</td>
<td>19% of the macroadenomas</td>
</tr>
<tr>
<td></td>
<td>(47 macroadenomas)</td>
<td></td>
<td>Micro: 52.6</td>
<td>Micro: 31.6</td>
<td></td>
</tr>
<tr>
<td>Iglesias et al. (2017)</td>
<td>n = 23</td>
<td>15.5</td>
<td>3.8</td>
<td>7.7</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>(macro + micro)</td>
<td></td>
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</table>

Clinical studies on the long term follow up of non-functioning pituitary neuroendocrine tumours.
Macro, macroadenomas; micro, microadenomas; NR, not reported.
receptor interacting protein (AIP), and pituitary tumour transforming gene (PTTG) have been more frequently described in NFpitNETs (Jiang & Zhang 2013, Aflorei & Korbonits 2014).

Of sporadic NFpitNETs, germline MEN1 mutations (MEN type 1) are rare (>3%) and CDKN1B mutations (MEN type 4) have not been reported thus far, whereas the role of PRKAR1A somatic mutations (Carney complex) in the development of sporadic functioning and NFpitNETs remains unknown (Kaltsas et al. 2002). Activating somatic mutations of the PIK3CA gene that encodes for the catalytic subunit of PI3-Kinase IA have also been described in NFpitNETs (Vandeva et al. 2019).

In the recent study with multi-genomic characterisation of PitNETs, the cohort of 134 tumours included 21 silent pitNETs (sCAs, sGAs, and NCAs) where no functional somatic variant or chromosome alteration was identified (Neou et al. 2020).

Other genes, encoding for proteins related to cytoskeleton and intracellular signalings, have demonstrated promising results in predicting the risk of invasiveness in NFpitNETs. Tumour growth factor-beta (TGF-β)/Smad signalling is involved in a number of cellular processes such as proliferation, differentiation, and apoptosis. Expression of TGF-β receptor type 2 at both mRNA and protein level and phosphorylated Smad3 protein were inversely correlated with tumour invasiveness in NFpitNETs (Zhenye et al. 2014, Gu & Feng 2018). In addition, tissue expression of the Ezrin (EZR) gene, a cell membrane component that links the cytoskeleton with the cell membrane, in NCAs and sGAs, was directly correlated with increased invasiveness in these tumours: in vitro silencing of the EZR gene in human pituitary adenoma cell line GH3 inhibited tumour growth (Chen et al. 2017), indicating that tissue expression of EZR can serve both as a prognostic biomarker of aggressiveness and as a novel molecular therapeutic target to control tumour growth.

Epigenetically, the DNA methylation profile of PitNETs differs between functioning and NFpitNETs, at least in some subtypes. In a genome-wide analysis, somatotrophinomas displayed higher levels of hypomethylated DNA regions compared to functioning corticotroph adenomas and sGAs (Salomon et al. 2018). In addition, sGAs displayed a high proportion of hypermethylated DNA regions while sCAs high proportion of hypomethylated DNA regions (Salomon et al. 2018). Data remain inconclusive regarding the prognostic effect of DNA methylation on the biologic behaviour of NFpitNETs.

In contrast to the other epigenetic mechanisms that modulate gene transcription, non-coding RNAs, including long-non-coding RNAs (lncRNAs), short miRNA and circular RNAs (circRNAs), control gene expression at the post-transcriptional level and are associated with the pathogenesis of various diseases including cancer. miRs are small single-stranded RNA molecules of 22 nucleotides that modulate the gene expression of mRNA genes. In a recent study, the expression of specific miRs, namely miR-26b-5p, miR-30a-5p, and miR-508-5p, was significantly and inversely correlated with histological and clinical parameters of tumour aggressiveness (Viechio et al. 2020). In addition, two circRNAs that were identified in tissue samples of NFpitNETs, circRNA-0000066 and circRNA-0069707, were significantly associated with tumour recurrence post-surgery (Guo et al. 2019): they may act synergistically to modulate the response of transport vesicles and cells to unfolded proteins at the cellular and tissue level (Guo et al. 2019). IncRNAs are transcripts of more than 200 nucleotides and act as ‘sponges’ for miRs and a guide for chromatin modifiers. Certain IncRNAs, namely HOX transcript antisense RNA (HOTAIR), maternally expressed 3 (MEG3) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) appear to associate with the development and biological behaviour of NFpitNETs (Li et al. 2017).

However, as of now, molecular studies on NFpitNETs have not essentially been able to predict which tumours could be managed conservatively vs surgically, a major requirement for clinicians.

Management
Active surveillance

Although few data are available regarding the treatment of asymptomatic and incidentally discovered NFpitNETs, there is a trend towards a conservative approach. However, there is no established follow-up algorithm and guidelines are typically based on clinical experience (Freda et al. 2011, Chanson et al. 2015). All patients with a PI or a clinically apparent NFpitNET should undergo complete evaluation of anterior pituitary function, as in many cases hormone hypersecretion or hypopituitarism may be subtle and slowly progressive (Freda et al. 2011, Chanson et al. 2015, Ntali & Wass 2018) (Table 3). Formal visual field assessment may also be reassuring in some cases. In the case of a macroadenoma, it is also recommended to undertake clinical and biochemical assessment of anterior pituitary function for the development of hypopituitarism 6 months after diagnosis and at least annually afterwards.
Management of non-functioning PitNETs (Yavropoulou et al.). New anterior pituitary deficits developed in 9% of patients (Tampourlou et al.). Post-operative complications occur in 3–6 months post-operatively to estimate tumour resection achieved, as appropriate. A sellar MRI should be performed at 6 months and at least annually thereafter or when symptoms arise. Visual assessment may be performed every 6 months (Chanson et al. 2015).

Surgical treatment

Surgical treatment of NFpNETs is performed in patients with visual or neurological abnormalities, in tumours that display significant growth, cause loss of endocrine function, or are close to the optic chiasm, in patients with persistent headache, or in women planning to become pregnant (Freda et al. 2011, Chanson et al. 2015). Active surveillance may be a better approach for older patients as they display a higher surgical intervention risk, while also having a shorter lifetime probability of tumour enlargement. Currently, the standard surgical technique is endoscopic- or microscopic-assisted transsphenoidal surgery (TSS). A recent meta-analysis showed that endoscopic surgery was associated with higher gross tumour removal and lower risk of septal perforation compared with the microscopic approach (Li et al. 2017). Intra-operative MRI has been recently introduced as a means to improve the surgical resection of the tumour, but its use remains controversial as it is unclear as to whether the extra time and expense are worth the technique, other than in exceptional cases (Tandon et al. 2017).

TSS, when performed by an experienced surgeon, is a safe procedure with relatively low complication rates: a total resection is achieved in 60–73% of NFpNETs (Yu et al. 2018). Immediate tumour volume decrease was observed in nearly all patients with a residual tumour rate of 10–36% (Lucas et al. 2016). Visual improvement is observed in 75–91% of patients, while 35–50% of patients display an improvement in hypopituitarism (Lucas et al. 2016). It has been reported that a post-operative improvement in gonadal, thyroid and adrenal axes occurs in 64.9, 71.9 and 33.9% of cases, respectively (Nomikos et al. 2004). Post-operative complications occur in less than 5% of patients, while the mortality rate is low (<1%) in expert hands (Murad et al. 2010, Casanueva et al. 2017). New anterior pituitary deficits developed in 9% of patients in one series, while deterioration of central hypoadrenalism, hypothyroidism and hypogonadism was reported in 39, 17 and 10% of cases, respectively (Murad et al. 2010). DI occurs in 18–31% of patients after pituitary surgery but in most cases is transient and attributed to the temporary dysfunction of vasopressin/ADH-secreting neurons (Esposito et al. 2019).

Assessment of pituitary function and visual field examination should be performed 1–3 months post-operatively and hormone deficiencies reassessed and treated, as appropriate. A sellar MRI should be performed 3–6 months post-operatively to estimate tumour resection and to serve as baseline MRI during subsequent follow-up. In the case of no residual tumour on imaging, the 10-year regrowth rate ranged between <6% (Reddy et al. 2011) and 16% (Tampourlou et al. 2017), while with residual tumour the regrowth rate increases reaching 42 to 53% or 77 to 80% dependent on whether the residual is intrasellar or extrasellar, respectively (O’Sullivan et al. 2009, Reddy et al. 2011).

Table 3 Initial endocrine evaluation of non-functioning pituitary neuroendocrine tumours.

<table>
<thead>
<tr>
<th>Evaluation for hormone hypersecretion</th>
<th>Measure serum IGF-1.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Measure serum prolactin (in dilution in case of large macroadenomas). Screening for glucocorticoid excess in case of clinical suspicion (overnight dexamethasone suppression test, late-night salivary cortisol).</td>
</tr>
</tbody>
</table>

A baseline hormonal evaluation and assessment of potential hypopituitarism is strongly suggested for all non-functioning pituitary neuroendocrine tumours.

Routine follow-up for hypopituitarism is not suggested for microadenomas whose clinical picture and MRI rarely change over time (Freda et al. 2011, Chanson et al. 2015) (Fig. 3).

It is recommended that microadenomas are followed-up at 6 months with MRI and then every 1–2 years until there has been absence of progression over 2 years. No surveillance is routinely recommended for microadenomas with a diameter <5 mm (Chanson et al. 2015). In case of a macroadenoma that is not close to the optic chiasm, follow-up with MRI 1 year after initial diagnosis is performed; if no progression is observed, surveillance is recommended every 1–2 years. Formal visual field assessment is suggested if the tumour enlarges to abut or compress the optic chiasm during follow-up. In the instance of a macroadenoma close to the optic chiasm, MRI should be performed at 6 months and at least annually thereafter or when symptoms arise. Visual assessment may be performed every 6 months (Chanson et al. 2015).

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Management of recurrent tumours

Apparent complete resection of NFpitNETs after initial surgery is achieved in 69 and 64.5% of patients in case of endoscopic or microscopic approach, respectively (Ammirati et al. 2013). However, as noted previously, tumour relapse has been reported in approximately 7–12% of cases at 10 years, while growth of residual disease is frequently observed in case of incomplete resection (O’Sullivan et al. 2009, Reddy et al. 2011, Chen et al. 2012).

In the past, RT was administered post-operatively in some centres to all patients to prevent recurrence or growth of residual tumour. However, today the role of RT as adjuvant treatment is under debate. ‘Conventional radiotherapy’ has been replaced by much more precise techniques, intensity-modulated fractionated stereotactic radiotherapy and gamma-knife radiosurgery, which aim to deliver high precision radiotherapy with lower complication rates (Minniti et al. 2016).

Several studies have evaluated the efficacy of adjuvant RT on tumour growth or recurrence. A recent study has reported 85–95% of tumour control at 5–10 years post-operatively in patients with NFpitNETs (Minniti et al. 2016). Mean progression free survival (PFS) at 5 years post-operatively was 95% after RT compared to 70% in patients not treated with RT. At 15 years post-operatively, mean PFS was calculated as 93% after RT compared to 33% if no RT was administered (Gittoes et al. 1998). However, there are no randomised controlled trials indicating the superiority of adjuvant post-operative RT compared to active surveillance, while the potential side-effects of RT render the indication for RT debatable (Chanson et al. 2019). Furthermore, a recent meta-analysis reported that residual tumour growth occurs slowly as the tumour doubling time is only 3.4 years with no growth observed during follow-up in 50–60% of patients (Chen et al. 2012). There is thus no consensus regarding adjuvant treatment with RT after surgical resection of NFpitNETs. Certainly, unless the tumour exhibits especial aggressiveness radiologically and/or histopathologically, we believe RT should be reserved for the time of disease progression during follow-up, while immediate post-operative treatment should be reserved for cases with significant tumour remnant and high risk of progression (Lucas et al. 2016). Furthermore, adjuvant RT should be considered for patients presenting with aggressive NFpitNENs, large tumours with suprasellar extension or cavernous sinus invasion or displaying aggressive histopathological characteristics such as a LI Ki-67 >3% or extensive immunostaining for p53 (Chanson et al. 2019). RT may also be used as primary treatment in cases where surgery is not feasible.
The most common side effect of RT is the high incidence of hypopituitarism. Five years after treatment with RT, the incidence of GH, gonadotrophin, ACTH and TSH deficiency has been calculated to 100, 91, 77 and 42, respectively (Littley et al. 1989). Follow-up with assessment of anterior pituitary function is recommended every 6 months post-treatment with RT. Rare side effects of RT include optic neuropathy, neurocognitive dysfunction, a probably increased risk of secondary malignancies of the CNS, and an increased risk of cerebrovascular events (Brada et al. 1993, Chanson et al. 2019). Visual problems are exceptionally rare for fractionated RT as long as the daily dose is <1.80 Gy and the total dose does not exceed 45 Gy, and for single-dose radiosurgery, the dose to the optic apparatus is <8 Gy, although it may still occur.

There are currently few data regarding revision TSS in case of recurrent NFpitNETs. Overall, the results are less favourable after revision surgery compared to the primary procedure. It has been reported that gross total resection is achieved in 46–53.5% of cases after revision surgery compared to 69–71% after primary surgery (Esquenazi et al. 2017). A recent study comparing the outcomes of primary and revision TSS observed no significant difference in the length of hospital stay and the post-operative hypopituitarism or hyponatraemia, but reported higher rates of DI and CSF leak after revision compared to primary cases (Jahangiri et al. 2014). Hence, revision surgery is indicated in the case of progressive residual tumour that can be completely resected, in symptomatic compression of the optic chiasm, and in cases of progression after treatment with RT (Chanson et al. 2015).

**Medical treatment**

As incomplete resection of NFpitNETs is a common clinical outcome, the development of effective medical treatment would be of great value. Based on observations that NFpitNETs express dopamine receptors (DR) and SSTRs (particularly DR2, SSTR2 and SSTR5), several studies have evaluated the efficacy of dopamine agonists (DAs) and somatostatin analogues (SSAs) in patients with operated or un-operated NFpitNETs (Colao et al. 2008, Greenman et al. 2016). Earlier studies showed no effect of bromocriptine (Grossman et al. 1985). However, in a recent cohort of 79 patients with post-operative residual tumour treated with bromocriptine (2.5–10 mg qd) or cabergoline (0.5–3.5 mg weekly), either upon imaging detection of residual tumour or after tumour growth, a positive effect was observed. In the first group, tumour control (shrinkage or stabilisation) was observed in 87% of patients, while in the latter tumour stabilisation or shrinkage was achieved in 58 and 29%, respectively (Greenman et al. 2016). A recent randomised clinical trial that compared cabergoline (3.5 mg weekly) with non-intervention in patients with residual adenoma after TSS found that cabergoline was associated with a high rate of tumour shrinkage (28.8%), while tumour stabilisation was observed in 66.1% of patients (Batista et al. 2019). There is limited clinical experience regarding the use of SSAs in NFpitNETs (Colao et al. 2008). A case-control study evaluated the efficacy of long-acting SSA octreotide LAR in patients with residual tumours that displayed positive SSTR scintigraphy (Fusco et al. 2012). Tumour stabilisation was observed in 81% of patients that received treatment compared with 47% in the control group during a mean follow-up time of 37 months. However, neither tumour shrinkage nor visual field changes, and no pituitary function improvement, were observed in any patient after treatment with SSAs. There are no clinical studies evaluating the treatment with pasireotide in patients with NFpitNETs, while in vitro studies have shown conflicting results (Ibanez-Costa et al. 2016).

Recently, newly synthesised chimeric somatostatin/dopamine compounds (‘dopastatins’) have shown some efficacy in the management of pitNETs in *in vitro* and *in vivo* studies. The chimeric molecule BIM-23A760 inhibited *in vitro* cell proliferation in two-thirds of NFpitNETs. Chronic administration of BIM-23A760, however, produced a metabolite with dopaminergic activity that interfered with the activity of the initial compound (Culler 2011). The new generation chimeric agonist for SSTR2/SSSTR5/DR2, BIM-065, designed with a different chemical structure to avoid the accumulation of metabolites with loss of dopaminergic activity, also increased apoptosis in NFpitNETs cell cultures (Vázquez-Borrego et al. 2020). A chimeric compound with potent agonist activity both at D2R and SSTR2, TBR-760, was tested *in vivo* in a mouse model of an aggressive NFpitNET, the pro-opiomelanocortin gene knockout (POMC-KO) mouse that expresses D2R and SSTR2 at a similar level to human NFpitNETs. TBR-760 completely suppressed tumour growth in this mouse-model, despite the highly aggressive nature of the POMC-KO tumours (Halem et al. 2020).

In addition, there are some reports of symptomatic improvement and tumour control achieved in patients with atypical adenomas treated with peptide receptor radionuclide therapy (PRRT) (Komor et al. 2014). However, prospective clinical trials are required to establish the efficacy and safety of this therapeutic option.
Management of aggressive tumours

The management of APTs is difficult due to their large size, rapid growth, invasiveness and increased rate of recurrence. Therapeutic options include surgery, RT, medical treatment and PRRT, best managed by a multidisciplinary expert team (Casanueva et al. 2017, Raverot et al. 2018). Temozolomide is an alkylating agent currently approved for the treatment of brain gliomas and glioblastomas. Recently, the European Society of Endocrinology (ESE) recommended the use of TMZ as first-line treatment for APTs and PCs either as monotherapy or in combination with radiotherapy in patients with rapid tumour growth that have not received the maximal radiotherapy dose (Raverot et al. 2018). In a recently published series of patients with APTs or PCs treated with TMZ as first-line chemotherapy, a radiological response was observed in 37% of the patients, disease stability in 33% and progression in 30%. The peak radiological response was observed within 3 and 6 months in 23 and 59% of cases, respectively (McCormack et al. 2018). However, tumour recurrence is common after cessation of treatment and 2-year PFS has been calculated to be 47.7% (Losa et al. 2016). In addition, it has been observed that NFpitNETs display lower response rates to temozolomide compared to functioning tumours (Raverot et al. 2018). The DNA repair enzyme O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT) that reverses the methylation caused by TMZ represents the major mechanism of resistance on treatment with TMZ, but the absence of MGMT expression could not always predict the tumour response to treatment (Chatzellis et al. 2015). The ESE has recommended an initial trial of three cycles of TMZ and subsequent radiological assessment of disease response. Cessation of treatment is suggested if radiological progression is observed (Raverot et al. 2018).

Raf/MEK/ERK and PI3K/Akt/mTOR pathways are upregulated in pitNETs (Dworakowska & Grossman 2009). As a result, several studies suggest that newly targeted agents may be effective in controlling pitNET growth (Raverot et al. 2018, Ilie et al. 2019). Everolimus, an mTOR inhibitor, was tested in APTs and PCs, but was found to be unsuccessful in most cases (Ilie et al. 2019). Preclinical trials have observed that the efficacy of everolimus may be enhanced when administered in combination with SSAs (Zatelli et al. 2010). There is some evidence suggesting the use of tyrosine kinase inhibitors in the treatment of APTs. Lapatinib, erlotinib and sunitinib have been used as first- or second-line treatment, but tumour progression was demonstrated in most cases (Raverot et al. 2018 Ilie et al. 2019). Combination treatment of TMZ and apatinib was successful in a patient with recurrent invasive GH-secreting adenoma for 31.5 months without recurrence (Wang et al. 2019). In addition, vascular endothelial growth factor (VEGF)-targeted therapy (bevazucimab) has been administered, either as monotherapy or in combination with TMZ, with promising results (Ilie et al. 2019). However, few patients have been treated so far and further investigation is required to introduce the use of targeted agents in the treatment of APTs.

There is also limited experience with PRRT in APTs, and tumour shrinkage or disease stability has been observed in some cases. However, disease progression was observed in some patients during treatment or shortly after the cessation of treatment. As PRRT seems a promising treatment option, recent in vivo and in vitro studies aim to investigate the possibility of upregulating the expression of SSTR2 in order to increase the efficacy of PRRT (Taelman et al. 2016).

Combination of two immune checkpoint inhibitors, nivolumab and ipilimumab, was effective in the management of a case with a corticotroph carcinoma (Lin et al. 2018). A clinical trial (NCT02834013) is also ongoing investigating the efficacy of this combination in PCs.

Conclusions

NFpitNEs comprise a heterogeneous group of tumours that usually follow an indolent course, although in some cases they may display aggressive behaviour characterised by rapid growth, early recurrence and resistance to conventional treatment. Identification of clinical and/ or histological characteristics, and molecular-based biomarkers that can accurately predict aggressiveness of these tumours, is currently under intense investigation. The most recent data suggest that a conservative approach may often be most appropriate, as even if surgery is offered there is still a high chance of recurrence, especially if scanning shows residual tumour. Medical therapy looks promising but is in its infancy, although cabergoline or possibly dopastatins will play increasing roles. Highly aggressive tumours will need particular care, including the use of TMZ and newer agents. What is clear is that we need molecular markers able to predict future behaviour, and these are still unavailable. Perhaps the next decade will more clearly establish a role for such markers and improve our prognostic capacity. For the moment, active surveillance remains a key part of the therapeutic strategy.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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