REVIEW

Aggressive and malignant pituitary tumours: state-of-the-art

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Abstract

Pituitary adenomas are unique in multiple ways. They are rarely malignant in terms of metastases; yet, they may be aggressive. Their cancerous potential is defined in a classic oncological way by the ability to metastasise, and therefore, it has been crucial to differentiate this process from aggressive behaviour, characterised as a particularly invasive and/or recurrent behaviour and resistance to common modalities of therapy. Recently, however, important changes have been introduced to the diagnosis and management of aggressive and malignant pituitary tumours including the 4th edition of the World Health Organization (WHO) classification for endocrine tumours (2017) as well as ESE Clinical Guidelines (2018), although an attempt to establish predictive and/or prognostic markers of clinical aggressiveness remains difficult. In this review, we focus on a group of pituitary tumours causing significant problems in clinical practice and requiring multidisciplinary input. We summarise updates in definitions of tumour invasiveness, aggressiveness and malignant transformation, as well as histological classification, and emphasise the new considerations regarding aggressive and malignant potential and its relationship to therapeutic strategies.

Key Words

- ▶ pituitary
- ▶ tumour
- ▶ aggressive
- ▶ cancer
- ▶ carcinoma
- ▶ temozolomide

Endocrine-Related Cancer
(2018) **25**, R559–R575

Introduction

Pituitary tumours represent approximately 10–15% of intracranial tumours. Most of them are non-invasive, showing slow growth and remaining within the sella and/or displacing the surrounding tissues; however, up to 25–55% of pituitary adenomas (PAs) may show characteristics that are invasive and infiltrate surrounding structures, including the cavernous sinuses, bone, sphenoid sinuses, and, less commonly, nerve sheaths (Meij *et al.* 2002, Hansen *et al.* 2014). Pituitary carcinomas (PCs) are a rare clinical entity that represent only 0.1–0.2% of all pituitary tumours. Oncological malignant potential is defined by

the ability to metastasise (including craniospinal and/or systemic metastases). Early identification of pituitary carcinoma is difficult yet remains crucial to appropriate management (Heaney 2014). While multiple reviews have addressed the molecular pathogenesis of pituitary tumours (Dworakowska & Grossman 2009, Robertson & Heaney 2016, Wierinckx *et al.* 2017), attempts at establishing predictive and/or prognostic markers of clinical aggressiveness remain largely unsuccessful and/or controversial. There have been recent consensus guidelines published (Raverot *et al.* 2018a), based in part on the new

2017 World Health Organization (WHO) classification (Osamura *et al.* 2017a,b), and even suggestions that we abandon the term 'pituitary adenoma' entirely in terms of these all being pituitary neuroendocrine tumours (PitNETs) (Asa *et al.* 2017), with a variable propensity for invasion and malignancy, as for other NETs. We therefore feel it timely to consider the current state of play in this evolving field from our personal viewpoint.

Diagnosis

An attempt to improve the diagnostic process for aggressive pituitary tumours and PC was made in the newest European Society for Endocrinology (ESE) guidelines (Raverot *et al.* 2018a). The authors recommend the diagnosis of an aggressive pituitary tumour be considered in patients with a radiologically invasive tumour and unusually rapid tumour growth rate or clinically relevant tumour growth despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments) (R 2.1.1). For quantification of tumour dimensions, invasion and growth, they suggested MRI in most instances (R 2.1.2). Endocrine evaluation is required in all of these cases (R2.1.3) in patients with aggressive tumours, and either site-specific symptoms or discordant biochemical and radiological findings, screening for metastatic disease to diagnose PC is required (R 2.1.4) (Raverot *et al.* 2018a). It would be beneficial if the future guidelines could help further as to when and how to assess malignancy in aggressive tumours. At present, the diagnosis of malignancy requires the presence of distant metastases, but this may be too limiting.

'Atypical' PAs were in the past defined as probably aggressive tumours, harbouring a Ki-67 (MIB-1) staining index of 3% or more, and positive immunohistochemical staining for p53 protein, according to the WHO classification in 2004 (Hirohata *et al.* 2014). The newest 4th edition of the WHO classification for tumours of endocrine glands as well as the newest ESE guidelines abandon the use of this term due to its poor reproducibility and low predictive value. There was a lack of evidence for the utility and predictive capacity of this classification (Lopes 2017, Mete & Lopes 2017, Manojlovic-Gacic *et al.* 2018, Nishioka & Inoshita 2018, Raverot *et al.* 2018a).

Aggressiveness vs invasiveness

The definition of aggressiveness for pituitary tumours has been rather confusing in the past, particularly as specific histopathological features appeared to be lacking.

However, aggressive pituitary tumours, which are intermediate in phenotype between PAs and PC, exhibit distinct *clinical* characteristics as they grow rapidly, frequently recur and are often resistant to conventional treatments (Colao *et al.* 2011). Nevertheless, the invasiveness of the pituitary tumour does not always correlate with aggressiveness. Invasive PAs show a variety of different pathological features and/or clinical course (Priola *et al.* 2017). Some of them display the histopathology of an adenoma with benign behaviour, even when invading the dura, bone or the surrounding anatomical structures. Furthermore, aggressiveness and invasiveness are interpreted differently by individual clinicians: these terms are often used interchangeably, whereas they are clearly different and describe differing characteristics with discordance in their predictive ability (Sav *et al.* 2015).

Some authors suggest that invasion of specific structures (e.g. the sphenoid bone or clivus) could serve as an indicative feature of aggressive behaviour (Heaney 2014), as most tumours demonstrating, for example, cavernous sinus invasion, may still show indolent behaviour and slow progression (Priola *et al.* 2017). In the historical Hardy's 'invasiveness' classification, only grade III (focal bone erosion) and grade IV (extensive bone erosion including skull base) tumours were considered as truly invasive (Handy 1969). In the extensively used Knosp classification, only grade III and IV adenomas (especially IIIB) are considered as truly invasive, classified on the basis of the extent of parasellar/cavernous sinus on imaging (Knosp *et al.* 1993, Di Ieva *et al.* 2014, Micko *et al.* 2015) (Fig. 1 and Table 1).

Refractory tumours

Some authors propose the use of the term 'refractory' pituitary adenoma for aggressive-invasive tumours exhibiting a distinctive disease course compared to benign adenomas or PCs. According to Dai *et al.*, the 'refractory' pituitary adenoma demonstrated in their series a high Ki-67 index, rapid growth, frequent recurrence and resistance to conventional treatments and/or temozolomide (Dai *et al.* 2016). The specific criteria include proposed tumour infiltration of the adjacent structures based on radiological results or intraoperative findings. Dai *et al.* proposed not only to use the cut-off value of >3% for Ki-67 but also included an increase in tumour growth velocity as >2% per month. However, in most instances, it would be quite difficult to perform imaging so frequently. Another feature would be not only a failure to control tumour growth

Figure 1

Graphic schemes (left), coronal MR images (centre) and endoscopic views (right). (A) Grade 0: the adenoma does not encroach on the CS space. Thus, the tangent of the medial aspects of the intracavernous and supracavernous ICAs is not passed. (B) Grade 1: the medial tangent is passed, but the extension does not go beyond a line drawn between the cross-sectional centres of the intracavernous and supracavernous ICAs (the intercarotid line). (C) Grade 2: the tumour extends beyond the intercarotid line but not past the tangent on the lateral aspects of the intracavernous and supracavernous ICAs. (D) Grade 3A: the tumour extends lateral to the lateral tangent of the intracavernous and supracavernous ICAs into the superior CS compartment. (E) Grade 3B: the tumour extends lateral to the lateral tangent of the intracavernous and supracavernous ICAs into the inferior CS compartment. (F) Grade 4: there is total encasement of the intracavernous carotid artery. AD, adenoma; LCSW, lateral CS wall (seen after removing the medial CS wall); MCSW, medial CS wall; PT, pituitary gland. The asterisk indicates an invaded medial CS wall, and arrows indicate trabeculae. Reproduced with kind permission from Prof. Engelbert Knosp, Department of Neurosurgery, Medical University of Vienna, Vienna, Austria. Copyright 2015 E Knosp.

and/or hormonal hypersecretion by current treatment modalities, but also the presence of tumour recurrence within 6 months after surgery (Dai *et al.* 2016).

Endocrine oncology vs classical oncology

There are several differences in the way we view pituitary tumours, especially malignant and aggressive ones. These discrepancies do not only differentiate such tumours from 'classical' oncology but are also quite heterogeneous in endocrine oncology itself. However, over the last few years, the pituitary community has

changed its approach. PAs are no longer considered as a specific endocrine disease but rather as true tumours and cannot be readily divided into simply 'adenomas' vs 'carcinomas'. Similar to other NETs, all may be considered to have malignant potential, malignancy being defined as local invasiveness and recurrence, and resistance to therapy, with PCs just one end of the spectrum of PitNETs (Asa *et al.* 2017). This more oncological approach permits the appropriate use of chemotherapeutic drugs in some conditions and a better stratification and personalisation of the therapeutic options offered to patients (Lasolle & Raverot 2016).

Table 1 Systems for pituitary tumour invasiveness (Hardy 1969, Knosp *et al.* 1993, Micko *et al.* 2015).

	Knosp's classification of cavernous sinus invasion
Grade 0	The adenoma does not pass the tangent of the medial aspects of the internal carotid artery (ICA)
Grade I	The medial tangent is passed, but the extension does not go beyond the intercarotid line, which is the line drawn between the cross-sectional centers of the intra- and supracavernous ICA
Grade II	Tumour extends beyond the intercarotid line, but not beyond or tangent to the lateral aspects of the intra- and supracavernous ICA
Grade III	Tumour extends laterally to the lateral tangent of the intra- and supracavernous ICA
Grade IV	Total encasement of the intracavernous carotid artery
	Hardy's classification of sphenoid bone invasion
Grade 0	Intact with normal contour
Grade I	Intact with bulging floor
Grade II	Intact with enlarged fossa
Grade III	Localised sellar destruction
Grade IV	Diffuse sellar destruction
	Hardy's classification of supra- and parasellar extension
	Symmetrical suprasellar extension
Grade A	Suprasellar cistern only
Grade B	Recess of the third ventricle
Grade C	Whole anterior third ventricle
	Asymmetrical parasellar extension
Grade D	Intracranial extradural
Grade E	Extracranial extradural (cavernous sinus)

The classical understanding of the predictive factors relate to their value of prediction in response to particular treatments, whereas prognostic factors influence patient survival (overall-, disease-free or progression-free survival). These terms are used in endocrine oncology in a 'liberal' and promiscuous manner, which renders analysis difficult when comparing different sets of results.

Similar complexity comes with the interpretation of statistical analyses. In classical oncology, significance in univariate analysis of a certain marker needs to be confirmed in multivariate analysis (where several features are analysed and considered simultaneously) to become an independent prognostic factor. The number of cases included to analysis affects the quality and strength of the results. Inclusion of such multiple factors makes the analysis of results in series of rare tumours very difficult. One such example comes from a study by Zaidi *et al.* (2016) where clinically aggressive lesions (in comparison to non-aggressive) were more likely on univariate analysis to have a larger axial diameter on MRI (2.9 ± 1.9 cm vs 1.9 ± 0.7 cm, $P=0.02$), greater incidence of cavernous sinus invasion (65.2% vs 20.8%, $P<0.01$) and greater incidence of clival extension (60.9% vs 0, $P<0.01$) on preoperative imaging. On multivariate analysis, however, *only* the Ki-67 proliferative index trended towards statistical significance ($P=0.06$) (Zaidi *et al.* 2016). In that study, tumours were defined as clinically aggressive if they required additional therapeutic intervention following first surgery, including further surgery, medical therapy or radiosurgery, but in fact, of the total cohort of 569 tumours, only 23/569 were

noted to have a clinically aggressive course (according to the authors' broad definition of aggressiveness) (Zaidi *et al.* 2016), challenging the statistical significance of their findings. In another study, multivariate analysis revealed that Ki-67 was the only factor that positively correlated with tumour size and recurrence, with staining for the factors PTTG1 and FGFR4 having no independent effect (Ramirez *et al.* 2012).

p53 tumour suppressor protein

p53 protein is a product of the tumour suppressor gene playing a role in apoptosis, inhibition of angiogenesis and genomic stability. The prognostic value of its expression has been previously assessed in many cancers (Dworakowska *et al.* 2009a). Physiologic levels of p53 typically are not detectable by immunohistochemistry due to the short half-life of WT p53: some mutations of the *P53* gene may result in p53 protein nuclear accumulation (due to extension of its half-life), allowing for its immunohistochemical detection.

The reliability of p53 as a marker of clinical invasiveness in pituitary tumours is still a subject of debate (Pernicone *et al.* 1997, Scheithauer *et al.* 2005, Heaney 2011, Zaidi *et al.* 2016, Lopes 2017). Ozer *et al.* found that of 41 PAs, p53 expression was significantly increased in recurrent tumours ($P=0.002$) (Ozer *et al.* 2003). Thapar *et al.* reported that in 70 PAs and 7 PCs, p53 expression, when conclusively present, may also be of diagnostic utility as a marker of biologically aggressive behaviour (Thapar *et al.* 1996b).

Trouillas *et al.* proposed a prognostic clinicopathological classification of PAs (including assessment of p53) based on a multicentre case-control study of 410 patients with 8 years of post-operative follow-up (Trouillas *et al.* 2013). The classification was validated subsequently in different cohort, demonstrating the prognostic value of p53 (Raverot *et al.* 2017). Contradictory studies have indicated that p53 is an inadequate marker for tumour aggressiveness and behaviour and that the p53 protein detected by immunohistochemistry is actually a WT form and thus unrelated to pituitary tumour invasiveness ($P=0.71$) (Suliman *et al.* 2001, Zaidi *et al.* 2016). For this reason, the new WHO classification advises that it is not a useful marker for aggressiveness for routine use, although in some circumstances, it may aid in decision making (Osamura *et al.* 2017a,b, Nishioka & Inoshita 2018).

Tumour proliferation

The MIB-1 labelling index (LI) stains for the Ki-67 antigen and is associated with cell proliferation. Recent work has demonstrated that it acts as a surfactant to separate chromosomes during mitosis, and is thus a marker of cell division (Cuylen *et al.* 2016). It is upregulated in dividing cells and involved in ribosomal RNA transcription. Since the initial description of Ki-67 in PAs by Burger *et al.* (1986), multiple researchers have attempted to correlate its value with clinicopathological parameters and its predictive and prognostic value (Salehi *et al.* 2009, Heaney 2011, 2014, Zaidi *et al.* 2016, Raverot *et al.* 2018a), much as has been achieved with NETs (Kloppel 2017, Panzuto *et al.* 2017). Thapar *et al.* reviewed the Ki-67 index in 77 PAs and carcinomas and suggested that the cut-off value of 3% distinguishes invasive from non-invasive adenomas with 97% specificity and 73% sensitivity (Thapar *et al.* 1996a); this cut-off was therefore adopted in the previous WHO criteria in 2004. However, several groups have demonstrated conflicting results, either supporting the use of this marker as a predictor of pituitary tumour recurrence or arguing against its utility (Zaidi *et al.* 2016). Salehi *et al.* considered that the contradictory reports on the role of the Ki-67 index are most probably the result of the variation in the definition of recurrence as well as the differing techniques of Ki-67 immunohistochemistry (Salehi *et al.* 2009).

In spite of these discordant conclusions, to help inform potential predictors of tumours aggressiveness in pituitary tumours, the ESE guidelines recommend histopathological analysis, which should include as a minimum immunodetection of pituitary hormones and

Ki-67 proliferative index evaluation. They also recommend p53 immunodetection and the evaluation of the mitotic count when the Ki-67 index is $\geq 3\%$ (R 2.2.1) (Lopes 2017, Raverot *et al.* 2018a). The ESE recommendations also suggest that interpretation of histopathological results should be in the clinical, radiological and surgical context of the individual patient, with the particular caveat that no marker alone is sufficient to predict tumour behaviour (R 2.2.2) (Raverot *et al.* 2018a).

Histology

The WHO classification of tumours of endocrine organs was revised in 2017 (4th edition) (Nishioka & Inoshita 2018). This new classification has been reviewed in several updated and very comprehensive papers (Lopes 2017, Mete & Lopes 2017, Manojlovic-Gacic *et al.* 2018, Nishioka & Inoshita 2018). According to recent knowledge on tumour development and prognosis, important changes in the new classification of PAs were introduced (Lopes 2017, Osamura *et al.* 2017a,b). The new classification focuses on adeno-hypophyseal-cell lineage for the designation of a pituitary adenoma. Based on this classification, assessment of pituitary transcription factors is also recommended to complement an accurate diagnosis, especially in hormone-negative tumours. Subsequently, based on this revision, null cell adenomas have been shown to be extremely rare, as ultrasensitive techniques have shown that the majority of previously reported 'null cell' adenomas are in fact gonadotrophic in origin (Nishioka & Inoshita 2018).

There are three major pathways of adeno-hypophyseal cell differentiation and relevant transcription factors: corticotrophs (demonstrable by the T-box pituitary transcription factor (T-pit)), somatotrophs/lactotrophs/mammotrophs/thyrotrophs (demonstrable by pituitary transcription factor 1 (Pit-1)), and gonadotrophs (demonstrable by steroidogenic factor-1 (SF-1) and/or GATA-2 in the presence of estrogen receptor- α (ER α)). At present, however, there are still no reliable commercial antibodies for T-pit (Fig. 2) (Nishioka & Inoshita 2018).

As noted above, the 4th edition of the WHO classification recommended assessment of tumour proliferation markers and other clinical/radiological parameters such as invasion to predict aggressiveness. According to this classification, 'high-risk adenomas' were characterised as those with rapid growth, radiological invasion and a high Ki-67 proliferation index. This classification does emphasise recognition of adenomas which are 'special variants' known for more aggressive

Figure 2

Adenohypophysial cell lineage and the transcription factors. Corticotroph are determined by T-pit and neuro D1; gonadotrophs are determined SF-1, GATA-2 and ER; Somato-, Lacto- and Thyrotroph are determined by Pit-1 (Nishioka & Inoshita 2018).

behaviour with a higher probability of recurrence, regardless of histological grading, which include sparsely granulated somatotroph adenomas, pluri-hormonal PIT-1-positive adenomas, silent corticotroph adenomas, lactotroph adenomas in men and Crouke cell adenomas (Lopes 2017, Mete & Lopes 2017). Furthermore, silent corticotroph tumours also tend to exhibit aggressive clinical features including local invasion (cavernous sinus, sphenoid sinus and bone), apoplexy and recurrence (Webb *et al.* 2003, Heaney 2011, Jahangiri *et al.* 2013, Mete *et al.* 2013, Heaney 2014, Xu *et al.* 2014, Cooper 2015). Nelson's syndrome (occurring after removal of cortisol-mediated negative feedback following bilateral adrenalectomy in Cushing's disease) is also associated with a propensity to increased pituitary tumour growth and progression to metastasis (Kaltsas *et al.* 2005, Heaney 2014).

Crouke cell adenomas are aggressive corticotrophic pituitary tumours: they are commonly invasive, recurrent and may progress to a carcinoma (Heaney 2011, 2014). One case series of 31 patients with Crouke cell adenoma showed 60% of cases with recurrence, 24% with multiple recurrences and two patients progressing to metastases (George *et al.* 2003).

Immunohistochemical staining for T-PIT staining has made possible the identification of

hormone-immunonegative adenomas, which show differentiation towards the corticotroph lineage and which may help to identify more aggressive tumours (with a clinical behaviour similar to silent corticotroph adenomas) (Lopes 2017).

Tumour functionality and other clinicopathological features

Oncological potential differs in varying subtypes of PAs. In a study by Lv *et al.* (2018), clinically aggressive lesions ($N=26$) were more likely to be functional (46.2% vs 17.4%, $P=0.0388$) and be detected in males (65.4% vs 21.7%, $P=0.0037$). Clinically aggressive adenomas had a higher Ki-67 index (5.0 (5.3)% vs 4.1 (1.3)%, $P=0.0011$) and presented with larger tumours (11.83 (11.95) cm^3 vs 5.39 (6.08) cm^3 , $P=0.0174$). The importance of the functional status as an independent predictor of clinical aggressiveness was confirmed in a multivariate analysis ($P=0.009$) along with gender ($P=0.017$) and the Ki-67 index ($P=0.024$): a Ki-67 index of more than 4.45% was associated with a shorter progression-free survival. Non-functioning pituitary adenomas (NFPAs) do not cause endocrine symptoms related to hypersecretion of adenohypophyseal hormones and are clinically characterised by symptoms due to a growing sellar tumour mass.

Histopathological classification of this tumour group has always been challenging due to their heterogeneity, limited knowledge of their biology and diverse methodological problems (Manojlovic-Gacic *et al.* 2018, Raverot *et al.* 2018b).

Ceccato *et al.* reported recently a series of a homogeneous consecutive cohort of PAs ($N=100$). Patients with NFPAs were older than those with functioning tumours, and the diagnosis might be delayed until mass symptoms occur as they lacked symptoms related to hormonal hypersecretion. They reported that the characteristics of aggressiveness were similar between silent adenomas and NFPAs, even separately analysing silent corticotrophinomas and gonadotrophinomas (Ceccato *et al.* 2018).

In a study by Ogawa *et al.* (2018), the clinical characteristics and mid-term prognosis of patients with NFPAs with a high proliferative potential were retrospectively investigated. This study identified 53/845 NFPA patients with a Ki-67 LI of $>3\%$ (6.3% of the total), initially treated by surgery. In that cohort, no prophylactic treatment was used for patients with residual tumour, but salvage therapy was given for tumour progression. Comparison of gross total removal ($n=22$) and non-total removal ($n=31$) groups showed a significantly longer progression-free period in the former group ($P<0.001$). As salvage treatment, gamma knife radiosurgery was used resulting in 10/11 patients remaining progression free. Fractionated irradiation was given to ten patients, resulting in two patients remaining progression free; deaths occurred in five patients including three of transformation to pituitary carcinoma, dementia was seen in one patient caused by frontal lobe dysfunction and progression reported in two patients requiring additional surgery and gamma knife radiosurgery. Temozolomide was administered to two patients, resulting in deaths in both patients including one transformation to a pituitary carcinoma. The authors concluded that a good prognosis in NFPAs with high proliferative potential can be expected where there is total removal of the tumour, with gamma-knife radiosurgery used as a salvage treatment. However, this therapy is limited to residual tumour, which is distant from optic pathways, and the poor results from standard radiation therapy are surprising. In a large and more recent series, recurrent NFPAs which subsequently received standard external beam radiotherapy showed a lower recurrence rate than those observed or who were treated by surgery alone, so it may be that the efficacy of radiotherapy is contingent on the centre as much as on the specific type (Tampourlou *et al.* 2017).

It should also be emphasised that 'functionality' is a relative concept: some tumours may be truly secretory and cause a significant functional syndrome, while some (in effect, very few) may show no functionality and completely negative immunostaining for any pituitary hormone or transcription factor. In fact, many tumours may show transcription factor positivity and even hormone immunostaining without a functional syndrome, 'silent tumours', while others may show mild biochemical abnormalities, possibly referred to as 'whispering tumours'. Thus, there is actually a spectrum of functionality in practice (Drummond 2018).

Progression and malignant transformation

The malignant transformation of a 'benign' pituitary adenoma has always been a matter of controversy, and the progression from benign to aggressive/malignant character poorly understood. PCs are thought to arise either *de novo*, or more frequently, from a malignant transformation of a pre-existing 'benign' adenoma (Lopes *et al.* 2005, Scheithauer *et al.* 2005, Sbardella *et al.* 2016). Highly aggressive transformation, including that to a carcinoma, is rare, and mainly occurs in prolactin- and ACTH-secreting tumours, possibly because these tumours are less likely to show markers of senescence, compared with those of other adenoma types (Alexandraki *et al.* 2012). It is unclear what proportion of these aggressive adenomas will progress into carcinomas, and most importantly, how to predict when this is likely (Pernicone *et al.* 1997, Ragel & Couldwell 2004, Mete & Lopes 2017). When non-compliance is ruled out, escape from the control by initial medical therapies (as reported in prolactin-producing adenomas) may be associated with de-differentiation of the tumour and thus the potential for malignant transformation (Sbardella *et al.* 2016).

Several case reports suggest that the latency between the first presentation of a pituitary adenoma and its transformation to a carcinoma depends on the type of endocrine function of the tumour: the average latency period for ACTH-secreting carcinomas was reported as 9.5 years and for prolactin-secreting carcinomas as 4.7 years (Yang *et al.* 2016).

The mechanism of invasion seems to be similar to other malignancies as it is based on the ability to freely pass through the extracellular matrix and vascular endothelium, an epithelial-mesenchymal transition, spreading by the bloodstream with some evidence suggesting a possible role for deregulation of gene expression (Gurlek *et al.* 2007). Having said that,

the mechanisms underlying the metastatic activity of PCs remain unclear, and the variation of gene expression in the primary is not always concordant in the metastases (Pei *et al.* 1994).

The matter becomes more complicated if we try to assess the role of previous radiotherapy in malignant transformation. Radiation has been reported to be implicated in the development of fibrosarcoma, but may also induce malignant changes in PAs (Casson *et al.* 1986, Tanaka *et al.* 2013). Tanaka *et al.* presented a case report showing cerebro-spinal metastases after radiation and gamma-knife treatment, suspecting that repeated radiation therapy for the pituitary and intracranial tumours may induce malignant transformation and the multiple spinal metastases (Tanaka *et al.* 2013). However, this concept is very difficult to prove, as aggressive tumours are more likely to be irradiated and such a correlation does not prove cause and effect.

An unusual case presented by Krueger *et al.* complicates the matter even further (Krueger & Seibly 2017). They reported a 52-year-old man who had a pituitary adenoma removed via a craniotomy. The tumour recurred 3 years post-operatively near the surgical tract, and slowly enlarged before removal 2 years later. Technically, this lesion could be defined as a pituitary carcinoma; however, the origin of the secondary mass(es) in this case is quite unclear, with similar histology in the second mass compared to that initially removed (Krueger & Seibly 2017). While this patient received *CyberKnife* therapy for a residual mass following the initial surgery, there is no evidence to support radiation-induced PAs specifically (Minniti *et al.* 2005), and it remains possible that there was iatrogenic seeding along the surgical tract (Taylor *et al.* 1994). Tanaka *et al.* described a case of a patient who developed multiple supra-tentorial, cerebellar and cervical spine dural metastases 13 years after initial surgical operation for a pituitary adenoma (Tanaka *et al.* 2013). Thus, even apparently benign adenomas require long-term follow-up (Krueger & Seibly 2017).

However, while the majority of aggressive pituitary tumours require multiple operations as well as radiation therapy, it seems (albeit on evidence which is incomplete at present) that therapeutic modalities of surgery and radiation are unlikely to be major mediators of malignant transformation (Tanaka *et al.* 2013).

The incidence of distant metastases is very high in corticotroph carcinomas when compared with other PCs (Tanaka *et al.* 2013): 71% and 57% of ACTH- and prolactin-secreting PCs, respectively, showed systemic dissemination rather than presenting with intracranial

metastases (Pernicone *et al.* 1997). Somatotroph tumours are rarely malignant, and distant metastases exceedingly rare. However, Taya *et al.* described a patient with GH-producing adenoma with intracranial dissemination, requiring surgery 7 years after initial trans-sphenoidal surgery for a pituitary 'adenoma' (Taya *et al.* 2004). Endo *et al.* reported a case of a 66-year-old woman with a malignant transformation of an ectopic GH-producing pituitary tumour, which was mainly located in the clivus. The initial presentation included left oculomotor and abducens nerve palsies, clearly a feature of aggressiveness. The initial histology following surgery revealed tumour cells with slightly irregular nuclei but without mitoses. Interestingly, even though the Ki-67 was 8.7%, p53 immunohistochemistry was negative. This tumour acutely enlarged causing a subarachnoid haemorrhage only 2 months after the initial operation. Pathologic findings of the second surgical specimen showed a significant change in tumour histology including significant nuclear atypia, an increase in Ki-67 to 27.7% and positive p53 staining and a loss of the previous GH immunopositivity (Endo *et al.* 2018). Lenders and McCormack recently reported malignant transformation in NFPAs (Lenders & McCormack 2018).

Pituitary carcinomas

Pituitary carcinoma is a rare disease with high mortality rate: its low incidence results in a diagnostic and therapeutic challenge. Based on the 2004 WHO classification, pituitary tumours were previously divided into typical, atypical and carcinoma. As noted earlier, current WHO criteria have abandoned grading tumours as 'atypical' due to its limited prognostic value (Lopes 2017, Mete & Lopes 2017).

The diagnosis of a pituitary carcinoma is often preceded by the presence of unusual symptoms such as hearing loss, ataxia, motor impairment or a neck mass, prompting further diagnostic testing (Kaltsas *et al.* 2005). Metastases rarely dominate the clinical picture in the early stages of disease and, at times, cases are only discovered *post mortem* (Pettersson *et al.* 1992, Stewart *et al.* 1992, Kemink *et al.* 1999, Kaltsas *et al.* 2005). Early identification of pituitary tumours at risk for progression to pituitary carcinoma is difficult, and no combination of histopathological or immunohistochemical analyses has conclusively been able to identify PAs that will progress to carcinoma. Suspicion should be raised when patients present with tumours of aggressive subtypes and histological features and with multiple recurrences.

Prior to an analysis published by Yoo *et al.* (2018), there had been no large-scale clinical trials or retrospective analyses of large patient samples. The analysis of published PCs indicate high mortality rates of 66% at 1 year and nearly 80% within 8 years after diagnosis of PC, despite aggressive therapies (Pernicone *et al.* 1997, Ragel & Couldwell 2004). In the review by the Yoo *et al.* 69 studies were included, with 72 unique cases, showing that the PCs were more common in males in comparison to females (55.6 vs 44.4%, respectively). The average age at diagnosis was 46.3 years. Corticotroph tumours were most common (34.7%), followed by prolactinomas (23.6%) and null cell tumours (15.3%). The average latency period from pituitary tumour diagnosis to metastasis was 9 years. The patients underwent surgical therapy (100% with an average of 2.76 procedures), radiotherapy (84.7% of cases) and chemotherapy (33.3%, with temozolomide in 22.2%). The mortality rate was 54.8% with average time to death after diagnosis of approximately just 10 months (Yoo *et al.* 2018).

In the analysis performed by Yoo *et al.*, the metastases in PC were intracranial or spinal, 43.1 and 37.5%, respectively. Liver metastases were seen in 13.9%. Cervical lymph node and bone metastases were seen in 11.1% and 9.7% of PC cases, respectively. Central nervous system metastasis was found in 58.3%, systemic metastasis in 31.9%, and both central nervous system and systemic metastasis identified in 8.3% of cases (Yoo *et al.* 2018). However, Pernicone *et al.* reported previously that 71% and 57% of ACTH- and prolactin-secreting PCs, respectively, reported systemic dissemination rather than presenting with intracranial metastases (Pernicone *et al.* 1997).

Molecular biology

Our limited understanding of the molecular pathogenesis of pituitary tumours and the malignant transformation to PC does not help in the development of the new therapeutic strategies or increase the efficacy of current ones. Many previous reviews have demonstrated genes promoting malignant transformation, angiogenesis, invasion, metastasis and recurrence. Although most of these genes and proteins have not been fully analysed with regard to their downstream mechanisms, diagnostic or therapeutic application, and they at least have the potential to become candidate PC biomarkers and/or molecular targets for guiding personalised treatment (Dworakowska & Grossman 2012, Yang *et al.* 2016).

Pituitary carcinomas rarely occur in genetic syndromes: examples of PC patients with MEN1 mutations have

been documented (Scheithauer *et al.* 2005, 2009, Gordon *et al.* 2007), while *AIP*, *PRKARIA*, *DICER1* and *GPR101* mutations have not been associated with metastatic spread to date (Tufton *et al.* 2017), although there is one report of a PC in a patients with an *SDH-B* germline mutation (Tufton *et al.* 2017). A comprehensive review has been recently been published by Yang *et al.* (2016) showing a clear correlation with tumour cell cycle progression, angiogenesis, metastases, invasion and upregulation of cyclin D1, VEGF, MMP-9, miRNAs and p21Cip1, possibly contributing to malignant transformation of adenomas to PCs. The group also showed that downregulated factors including MGMT, p16Ink4A, p27Kip1, Bcl-2, Bax, Bcl-x and MT3 were involved in the cell cycle, apoptosis, tumour suppression, metabolism and enhanced TMZ sensitivity (Yang *et al.* 2016).

The co-occurrence of PAs and paragangliomas is a rare event. Such association was first described in 1952 (Iversen 1952), but it is only recently that the underlying genetic mutations have been elucidated in some of these cases (Tufton *et al.* 2017). Mutations in one of the five succinate dehydrogenase (*SDHA-D*, *SDHA2F*) genes are the most common, followed by mutations in *MEN1* and *RET* (Gill *et al.* 2014, Denes *et al.* 2015). *SDH* mutation-related pituitary tumours have a more aggressive phenotype than is commonly seen in sporadic tumours. PAs occurring in patients with *SDH* mutations or adenomas bearing somatic mutations are more often prolactinomas followed by gonadotroph adenomas and somatotroph tumours (Denes *et al.* 2015). A case of a pituitary carcinoma occurring in a patient with a succinate dehydrogenase subunit B (*SDHB*) mutation and history of paraganglioma has been reported, as noted earlier (Tufton *et al.* 2017).

Subtype III PAs, now known as 'pluri-hormonal Pit-1 positive adenomas', are clinically non-functional adenomas that are more invasive and recur more often than conventional null cell tumours. Richardson *et al.* showed that their specific feature is an enlarged and fragmented Golgi apparatus, as detected by immunohistochemistry. They subsequently performed whole-transcriptome sequencing (*RNAseq*) and quantitative RT-PCR on four such tumours and four conventional null cell adenomas: the genes that were highly upregulated in all the pluri-hormonal Pit-1-positive tumours included two secreted proteins involved in the suppression of T-lymphocyte activity, i.e., *ARG2* and *SEMA3A*. Highly downregulated genes in all these adenomas included *HLA-B*, suggesting reduced antigen presentation by the adenoma to cytotoxic T-cells: they also found a relative decrease in the overall concentration of T-lymphocytes. These results suggest

that pluri-hormonal Pit-1-positive adenomas actively suppress the immune system and raise the possibility that they may be treatable with immune checkpoint inhibitors or nonspecific cancer immunotherapies (Richardson *et al.* 2017).

Genetic screening

The ESE guidelines indicate the need for the germline genetic testing based on young age at presentation or family history of pituitary or endocrine neoplasia, as recommended for patients with non-aggressive pituitary tumours (R 2.2.3). Even though these recommendations are useful, the quality of evidence behind them was classified as very low (+000) (Raverot *et al.* 2018a).

ESE guidelines summary

The ESE guideline provides clinical guidance on diagnosis, treatment and follow-up in aggressive pituitary tumours and carcinomas (Raverot *et al.* 2018a). The authors systematically reviewed the literature according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Raverot *et al.* included to their analysis 14 single-arm cohort studies (total number of patients=116) with first- and second-line treatment for aggressive pituitary tumours and PCs, of whom most were treated with temozolomide ($n=11$ studies, total number of patients=106). In this review, temozolomide resulted in a positive treatment effect in nearly half of the patients (47%; 95% CI: 36–58%). The guideline was additionally supported by the data coming from an ESE survey on aggressive tumours (165 patients) (McCormack *et al.* 2018). The ESE recommended that patients with aggressive tumours or carcinomas should be discussed and managed by expert multidisciplinary teams (endocrinologist, neurosurgeon, pituitary pathologist, neuro-radiologist, radiation oncologist, medical oncologist, R 1.1.1). They recommend that surgery should be performed by a neurosurgeon with extensive experience in pituitary surgery and further discussion with an expert neurosurgeon regarding repeat surgery prior to consideration of other treatment options (R3.1.1 and R3.1.2, respectively with the quality of the evidence behind these recommendations classified as low (++00) (Raverot *et al.* 2018a). They recommend standard medical treatment with maximally tolerated doses in order to control tumour growth (R 3.3.1). Current reviews on the medical therapy of pituitary tumours summarised all the agents

available these days to treat functioning tumours (Langlois *et al.* 2017). In non-functioning tumours, radiotherapy was recommended in cases with clinically relevant tumour growth despite surgery, whereas for functioning tumours, it was recommended after surgery and standard medical treatment (R 3.2.1, ++00). Adjuvant radiotherapy should be considered in cases with clinically relevant invasive tumour remnant with pathological markers (Ki-67 index, mitotic count, p53 immunodetection) strongly indicating aggressive behaviour (R 3.2.2, +000). The different radiotherapy options (taking into consideration tumour size and location, pathology) should be discussed prior to treatment with an expert radiation oncologist (R 3.2.3). Lastly, the guidelines provide information about the follow-up, which for aggressive tumours should be lifelong (R 4.3, ++00). Monitoring requires both radiological and biochemical evaluation; MRI (in most instances) to be performed every 3–12 months, guided by prior tumour growth rate and/or location of tumour (proximity to vital structures) (R4.1, +000), whereas repeat full endocrine evaluation should be performed every 3–12 months as guided by the clinical context (R 4.2, +000).

A review by Trouillas *et al.* complemented the ESE survey, commenting in detail on some clinicopathological findings, specifically differentiating aggressive tumours from carcinomas (Table 2) (Trouillas *et al.* 2018). The authors underlined that given that the diagnosis of a malignant pituitary tumour remains difficult, and aggressive tumours and true carcinomas alike result in premature death as a result of tumour progression, they propose that an aggressive tumour should be considered a tumour with malignant potential (Table 3) (Trouillas *et al.* 2018). This was appropriately followed by a consensus view that all pituitary tumours should be considered as pituitary neuroendocrine tumours (*PitNETs*), as NETs elsewhere are generally assumed to have malignant potential (Asa *et al.* 2017).

Table 2 Similarities between the 125 aggressive pituitary tumours (APT) and 40 pituitary carcinomas (PC): modified from the diagram by Trouillas *et al.* (2018).

	Gender (%)	Tumour type (%)	Ki-67 ≥3%	p53 IHC (%)	Mortality (%)
APT	Male 65	Corticotroph 45	81	73	28
PC	Male 63	Corticotroph 48	85	78	43

Table 3 Potential pituitary neuro-endocrine tumour (PitNET) behaviours: modified from the diagram by Trouillas *et al.* (2018).

MRI	Pathology	Grade	Surgery and/or medical treatment	± RT	TZM	Clinical classification
Non-invasive (60–65%)*	Non-proliferative	1a	Cured	n/a	n/a	Adenoma
	Proliferative	1b	Cured or remission	n/a	n/a	
Invasive (35–40%)*	Non-proliferative	2a	Persistent disease	Controlled	n/a	Invasive PitNET
	Proliferative	2b (10%)*	Persistent disease	Recurrence	Yes	APT: invasive PitNET with malignant potential
		3	Persistent disease	Progression Metastasis	Yes	PC (0.2%)*

*Frequencies from the surgical series.

APT, aggressive pituitary tumour; MRI, magnetic resonance imaging; PC, pituitary cancer; RT, radiotherapy; TZM, temozolomide.

Temozolomide

Temozolomide (TMZ) is an oral alkylating drug, which has become a promising treatment option for aggressive tumours and carcinomas. An update on its use has very recently been summarised by Syro *et al.* (2018), and we therefore simply underline the most important facts. TZM has been demonstrated to cause not only shrinkage of pituitary tumours but also a normalisation of hormone hypersecretion in many instances. It has thus formed an important part of the armamentarium of therapies for aggressive tumours, particularly in view of its relatively high tolerability and freedom from adverse effects (Raverot *et al.* 2018a). However, its role in the sequencing of therapy remains unclear, and there is no doubt that in many cases improvements are temporary and recurrence/regrowth frequent (Hirohata *et al.* 2014, Lasolle *et al.* 2017, McCormack *et al.* 2018).

TMZ is available in an oral form, and its ability to cross the blood–brain barrier makes it superior to other chemotherapy drugs (Losa *et al.* 2016). It acts through methylation of the O6 position of guanine in DNA to form a potent cytotoxic DNA adduct, which causes a disturbance in the DNA sequence and leads to apoptosis (Knizhnik *et al.* 2013). MGMT is a DNA repair enzyme, which reverses alkylation at the O6 position of guanine, resulting in removal of alkylating adducts and counteracting the pro-apoptotic effect induced by TMZ (Almalki *et al.* 2017). The anti-tumour efficacy of TMZ is limited by high levels of MGMT activity as this is thought to offset alkylator modification of tumour DNA (Bello *et al.* 2006). MGMT assessment by immunohistochemistry and its inverse relationship with therapeutic responsiveness has been proposed by Kovacs *et al.* and McCormack *et al.*, who suggested that low MGMT expression conferred a better response to therapy compared with cases of high MGMT expression, which showed resistance (Kovacs *et al.* 2007, 2008, Almalki *et al.* 2017, McCormack *et al.* 2018).

Nevertheless, there is considerable overlap between responders and non-responders in terms of MGMT staining, and the techniques of assessment of MGMT are highly variable. It therefore would be unwise to rely on such a factor to decide on the use of TMZ in any specific case.

Another factor affecting the anti-tumour efficacy of TMZ is the mismatch repair pathway (MMR). It is involved in the removal of DNA base mismatches caused either by DNA replication errors or through DNA damage. Mutations in the genes involved in that pathway (e.g. *MSH2*, *MLH1*, *PMS2* and *MSH6*) play important roles in the tumour response to therapy. MMR mediates reaction to certain forms of DNA damage-inducing agents that can modify the structure of bases, including alkylating agents such as TMZ. MMR-deficient cells are resistant to chemotherapy due to suppression of the cell cycle and apoptotic responses to these compounds. Negative MSH6 staining is related to resistance to TMZ therapy with continued tumour growth (summarised by Martin *et al.* 2010).

Based on the currently available evidence, the ESE guidelines suggest that TZM monotherapy should be the first-line chemotherapy after failure of standard therapies (R3.4.1, ++00) (generally, 150–200 mg/m² for 5 consecutive days every 28 days, R3.4.3, +000). The response should be assessed after initial three cycles of therapy (R3.4.2, ++00), with treatment continuation for at least 6 months in total but only in responder patients (R3.4.7, +000) (Raverot *et al.* 2018a) (Fig. 3). Since the MGMT status carries a predictive value of the response to TZM, its immunohistochemical evaluation by an expert neuropathologist is needed, and high MGMT expression is suggestive of a lack of response; however, there may be exceptions R 3.4.6 (++00) (Raverot *et al.* 2018a), and we personally would not rely on this in making therapeutic decisions.

TMZ therapy requires careful clinical observation for potential adverse effects and monitoring of haematological parameters and liver function tests (R3.4.4, +++0). In the

Figure 3

Therapeutic algorithm for APT and PC after failure of standard medical treatment with maximally tolerated doses in order to control tumour growth as per ESE guidance. MGMT status* – ESE suggests that evaluation of MGMT status by immunohistochemistry by an expert neuropathologist should be performed. High MGMT expression is suggestive of a lack of response; however, there may be exceptions ((++00) R 3.4.6) (Raverot *et al.* 2018a,b).

group of patients with rapid tumour growth in whom maximal doses of radiotherapy have not been reached, combining TMZ and radiotherapy might be beneficial (R3.4.5, +000) (Raverot *et al.* 2018a).

A recent survey by McCormack *et al.* confirmed the role of TMZ as first-line chemotherapeutic treatment of aggressive pituitary tumours and carcinomas. This survey provided further information on predictive markers of response to TMZ including hormonal activity, low MGMT and concurrent radiotherapy, all associated with a better response. The data from an electronic survey to ESE members (Dec 2015–Nov 2016) included 40 PCs, 125 aggressive tumours and 1 unclassified case, with a median age at diagnosis of 43 (range 4–79) years. In that cohort 69% of the tumours were hormonally active, with corticotrophs being the most frequent functioning subtype (45%). The Ki-67 index did not distinguish aggressive tumours from carcinomas. TMZ as a first-line chemotherapy was used in 157/166 patients, resulting in 6, 31, 33 and 30% of radiological complete responses (CRs), partial responses (PR), stable disease (SD) and progressive disease (PD), respectively, at the end of the treatment (median nine cycles). Patients receiving concomitant radiotherapy and TMZ responded more frequently in general, whereas CRs were seen only in patients with low MGMT expression. Interestingly, hormonally active tumours were more likely to respond to TMZ than non-functioning ones, independent of MGMT status. Of patients with CR, PR and SD, 25, 40 and 48% respectively progressed after a median of 12-month follow-up (McCormack *et al.* 2018). However, despite encouraging initial results, TMZ treatment appears to be effective in only about half of the patients and does not provide long-term control of aggressive tumours (Lasolle & Raverot 2016, Losa *et al.* 2016, Halevy & Whitelaw 2017). The poor efficacy of

other drugs highlights the need to identify additional effective therapies (McCormack *et al.* 2018).

Alternative treatments for TMZ-resistant pituitary tumours

The ESE guidelines make recommendations for patients who either did not respond to TMZ treatment or subsequently recurred. In the group of patients who recurred following response to TMZ, a second trial of three cycles could be a therapeutic option R 3.4.9 (+000). In patients with rapid tumour progression on TMZ, a trial with other systemic cytotoxic therapy should be considered. Given the variety of chemotherapeutic agents that have been reported, the experts were unable to suggest a particular regimen R3.4.8 (+000). Historical pre-TMZ papers reported that the combination of lomustine/5-fluorouracil proved easy to administer with minimal toxicity, although the response rate was only 14% (Kaltsas *et al.* 1998).

In patients with isolated metastases, a consideration of loco-regional therapies should be made, regardless of discussions on systemic treatment R 3.5.1 (+000) (Raverot *et al.* 2018a).

Some case reports suggested that other chemotherapeutic agents might be useful in combination with TMZ. Thearle *et al.* reported a case with an aggressive ACTH-oma treated with TMZ and capecitabine. In this case, although the tumour decreased remarkably in size and serum ACTH levels, it recurred after 5 months, transforming to a more malignant phenotype (Thearle *et al.* 2011).

Somatostatin receptors (types 1, 5 and 2) are widely expressed in different pituitary tumour subtypes (Cakir *et al.* 2010a,b). Bode *et al.* reported a case with a widespread intracranial and systemic metastatic ACTH-secreting PC treated with TMZ and pasireotide who demonstrated tumour control for 12 months in combination with TMZ,

and for a subsequent 9 months on monotherapy with pasireotide (Bode *et al.* 2010).

Pituitary uptake of ^{68}Ga -DOTATATE or other radiolabelled somatostatin analogues has been shown to be elevated on PET/CT scanning (Xiao *et al.* 2015), suggesting that peptide receptor radionuclide therapy (PRRT) could be an alternative option for pituitary tumours resistant to TZM (Goglia *et al.* 2008). However, very few patients are reported in the literature. A giant prolactinoma resistant to dopamine agonists, radiotherapy and somatostatin analogues was treated with ^{111}In -DTPA-octreotide and achieved an over 50% reduction in tumour size, maintained for 2 years (Baldari *et al.* 2012). Maclean *et al.* reported on three patients, one with a non-functioning pituitary carcinoma, one with a silent corticotroph tumour and one with a mixed GH- and prolactin-secreting tumour, all treated with ^{177}Lu -DOTATATE. Only the non-functioning pituitary carcinoma showed SD for 40 months, the remaining two rapidly progressing to death (Maclean *et al.* 2014).

PI3K/Akt/mTOR signalling is upregulated in pituitary tumours (Dworakowska *et al.* 2009b), and the anti-proliferative effect of mTOR inhibitor, everolimus (on pituitary cell lines or primary cultures), has been demonstrated *in vitro* (Cerovac *et al.* 2010). Jouanneau *et al.* reported an ACTH-secreting PC treated with the combination of everolimus and octreotide: this combined therapy, however, neither controlled tumour growth nor ACTH secretion (Jouanneau *et al.* 2012).

The epidermal growth factor receptor (EGFR), which activates MAPK and AKT pathways, stimulates cell growth and hormone production in prolactin, GH and ACTH-secreting tumours *in vivo* and *in vitro*. Lapatinib, a dual HER2/EGFR inhibitor, and gefitinib, a more specific EGFR inhibitor, were shown to have anti-proliferative effects *in vitro* (Fukuoka *et al.* 2011a,b). Two resistant macroprolactinomas patients were treated with lapatinib for a 6 months, showing in a first case a 78% of reduction in prolactin levels and a 22% decrease in tumour size, whereas in the second case a 42% of reduction in prolactin levels was observed and the tumour size remained unchanged (Cooper *et al.* 2014). A clinical trial is currently underway to validate these encouraging results in a larger cohort of patient with non-functioning tumours after recurring after resection, in patients with prolactinomas resistant to dopamine agonist therapy, and in patients with recurrent Cushing's disease (NCT00939523; <https://clinicaltrials.gov/ct2/show/NCT00939523>) (Lasolle & Raverot 2016).

Anti-angiogenic therapy was attempted in the treatment of malignant pituitary tumours. Ortiz *et al.*

reported a case with an aggressive silent corticotroph tumour, progressing to a carcinoma after TMZ. Anti-vascular endothelial growth factor (bevacizumab) therapy was introduced, and a control of the tumour was achieved for 26 months (Ortiz *et al.* 2012). We have recently treated a patient with a progressive metastatic corticotroph tumour with capecitabine, lomustine and bevacizumab, with SD for nearly 6 months, but he then succumbed to an infective illness (unpublished data).

Programmed death 1 (PD-1) blockade has shown durable objective responses in a variety of malignancies, and the key predictive markers for this immunotherapy were PD-L1 and CD8+ tumour-infiltrating lymphocyte (TILs) expression. A recent study by Wang *et al.* reported that PD-L1 was frequently expressed in functioning PAs with aggressive behaviour; immunotherapy could thus be a promising treatment option for aggressive pituitary tumours. One hundred and ninety one patients with PAs were retrospectively involved in this study, consisting of 106 non-functioning adenomas (NFPAs, 55.5%), 40 prolactinomas (20.9%), 31 GH-secreting tumours (16.2%), 9 corticotrophinomas (4.7%) and five pluri-hormonal adenomas (2.6%) respectively: 36.6% of them were PD-L1 positive and 86.9% were CD8+ TILs positive. Positive PD-L1 immunostaining presented more frequently in functioning tumours (58.8%) compared with the non-functioning group (34.3%, $P=0.000$). Moreover, the rates of PD-L1 expression were more associated with increased blood levels of prolactin, GH, ACTH and cortisol. In contrast, positive CD8+ TILs immunostaining only correlated with elevated blood level of GH. For the analysis of immune markers with pathological results, PD-L1 expression was associated with prolactin and GH immunostaining and a higher Ki-67 index, while CD8+ TILs was only correlated with prolactin immunostaining (Wang *et al.* 2018).

Summary

Recent changes to the WHO classification of pituitary tumours and new ESE guidelines have clarified our assessment of pituitary tumours in general, and 'aggressive tumours' in particular. There is an increasing move to consider all such tumours to be a variant of generic neuroendocrine tumours, and thus, to have at least some malignant potential. There is no specific histopathological marker of such potential, although the Ki-67 index is useful, and the dividing line between an aggressive tumour and a carcinoma is blurred. Furthermore, there appears to be a spectrum

of functionality from those tumours which are truly non-functioning to those which are highly secretory. Thus, radiological, surgical and clinical factors all need to be taken into account in addition to pathology when considering the optimal therapeutic strategy and its sequencing. Surgery (usually trans-sphenoidal), radiotherapy (in its various guises), and more recently temozolomide, may all play a role, but for the future a more precise understanding of tumorigenesis may help us customise individual treatments and employ more specifically targeted therapies for the most aggressive of tumours. For the time being, it is fortunate that the majority of pituitary tumours remain benign and are readily controllable.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution statement

Each co-author contributed to the manuscript equally.

Acknowledgements

Dr D Dworakowska was supported by Foundation for Polish Science within a programme BRIDGE, which was co-financed by the EU within 7th FP.

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Received in final form 27 June 2018

Accepted 9 July 2018

Accepted Preprint published online 9 July 2018