Aggressive Pituitary Tumors

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Key Words
Aggressive pituitary adenomas · Atypical adenomas · Pituitary tumors

Abstract
Pituitary adenomas are common intracranial tumors that are mainly considered as benign. Rarely, these tumors can exhibit an aggressive behavior, characterized by gross invasion of the surrounding tissues, resistance to conventional treatment leading to early and frequent recurrences. Even more rarely, pituitary tumors can give rise to cerebrospinal or systemic metastases qualifying as pituitary carcinomas according to the latest WHO definition. In the same classification, a subset of tumors with relatively distinct histopathological features was identified and defined as atypical adenomas designated to follow a more aggressive clinical course. This classification, although clinically useful, does not provide an accurate correlation between histopathological findings and the clinical behavior of these tumors, neither is it adequate to convey the precise features of 'aggressive' tumors. Thus, ‘aggressive’ pituitary adenomas need to be properly defined with clinical, radiological, histological and molecular markers in order to identify patients at increased risk of early recurrence or subsequent tumor progression. At present, no single marker or classification system of pituitary tumor aggressiveness exists, and clinically useful information in the literature is insufficient to guide diagnostic and therapeutic decisions. Treatment of patients with aggressive pituitary tumors is challenging since conventional treatments often fail, necessitating multiple surgical procedures with additional radiotherapy. Although traditional chemotherapy applied in other neuroendocrine tumors has not been shown to be efficacious, newer agents, particularly temozolomide, have shown promising results and are currently used despite the lack of data from a randomized prospective trial. Molecular targeted therapies such as mTOR and epidermal growth factor inhibitors have also been applied and might prove to be useful in the management of these patients. In the present review, we provide information regarding the epidemiology and clinical, histopathological and molecular features of aggressive pituitary tumors using recent employed definitions. In addition, we review currently employed therapeutic means providing a therapeutic algorithm and highlight the need to identify more specific disease-related and prognostic markers and the necessity for central registration of these tumors.

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adenomas by an arbitrary cutoff size of 10 mm, whereas when tumors exceed 30 or 40 mm in size, the term giant adenomas is used. Most of these tumors are noninvasive and benign in nature, and remain either within the sella or exhibit slow expansive growth displacing surrounding tissues. A significant number of pituitary tumors, 25–55% depending on the criteria used, can show signs of invasion of dura, bone and/or surrounding anatomical structures [4, 5]. However, these so-called ‘invasive’ pituitary adenomas display benign behavior even in the presence of marked dural invasion and are not considered malignant by current definition. Truly malignant pituitary tumors (pituitary carcinomas) are only defined by the presence of cerebrospinal or systemic metastases and are exceedingly rare, with an incidence of 0.2% of symptomatic pituitary tumors [1, 6]. The so-called ‘aggressive’ adenomas lie between benign adenomas and malignant pituitary carcinomas and display a rather distinct clinical behavior with marked/gross invasion of nearby anatomical structures and a tendency towards resistance to conventional treatments and early postoperative recurrence.

In 2004, the WHO published a classification system for pituitary tumors based upon immunohistochemistry distinguishing them according to the presence or absence of secretory products along with various other ultrastructural features (table 1) [7]. Apart from benign typical adenomas and pituitary carcinomas, this classification also identified atypical adenomas as tumors with ‘atypical’ morphological features suggestive of an ‘aggressive behavior’, substantiated further by the presence of invasive growth, high mitotic index, a Ki67 labelling index (LI) >3% as well as extensive nuclear staining for p53. This was the first attempt to identify pituitary tumors that have the potential to exhibit a distinctive course compared to benign adenomas, characterized by extensive growth and potentially malignant transformation [5, 8]. However, invasive growth included in the WHO criteria was not clearly defined and accounted for [9] since it is usually underestimated if no relevant information from imaging studies is considered [10]. Furthermore, this classification based on histopathological markers does not closely correlate with clinical behavior, as typical adenomas may occasionally exhibit early recurrence and resistance to therapy, whereas atypical adenomas are not always invasive, and they do not always exhibit recurrence. It is also acknowledged that atypical adenomas may share morphological and histological features with carcinomas, which are distinctively characterized by craniospinal or distant metastases, poorer prognosis and an overall fatal outcome. Therefore, the validity of the term ‘atypical adenoma’ proposed by the 2004 WHO pituitary tumor classification system is now debatable, and tumors with a potential to follow an aggressive clinical course need to be properly identified, introducing a new classification system incorporating novel molecular and genetic biomarkers that have recently been evaluated [11].

### Definition of Aggressiveness

In contrast to the term ‘atypical adenomas’ which was based on proliferative and histological markers, the term ‘aggressive’ pituitary tumors is not well-defined and is interpreted differently by individual clinicians. One aspect of aggressiveness is invasive expansion into surrounding anatomical structures. The terms ‘aggressive’ and ‘invasive’ are often interchangeably and synonymously used in the literature; however, this is not always the case and creates considerable confusion as microscopic dura and cavernous sinus invasion and suprasellar expansion are commonly encountered in apparently benign adenomas [12]. There is also great variation in the literature regarding the definition of invasiveness based on imaging features, hist-

<table>
<thead>
<tr>
<th>Table 1. Classification of pituitary tumors according to the WHO [7]</th>
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<tr>
<td><strong>PRL-secreting adenoma</strong> (lactotroph adenoma or prolactinoma)</td>
</tr>
<tr>
<td>Densely granulated</td>
</tr>
<tr>
<td>Sparsely granulated</td>
</tr>
<tr>
<td><strong>GH-secreting adenoma</strong> (somatotroph adenoma)</td>
</tr>
<tr>
<td>Monohormonal</td>
</tr>
<tr>
<td>Densely granulated</td>
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<tr>
<td>Sparsely granulated</td>
</tr>
<tr>
<td>Plurihormonal</td>
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<tr>
<td>Mixed GH-PRL</td>
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<tr>
<td>Mammosomatotroph</td>
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<tr>
<td>Acidophilic stem cell</td>
</tr>
<tr>
<td><strong>ACTH-secreting adenoma</strong> (corticotroph adenoma)</td>
</tr>
<tr>
<td>Densely granulated</td>
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<tr>
<td>Sparsely granulated</td>
</tr>
<tr>
<td>Silent corticotroph subtype 1 and 2</td>
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<tr>
<td><strong>TSH-secreting adenomas</strong> (thryotroph adenoma)</td>
</tr>
<tr>
<td>Densely granulated</td>
</tr>
<tr>
<td>Sparsely granulated</td>
</tr>
<tr>
<td><strong>FSH/LH adenoma</strong> (gonadotroph adenoma or nonfunctioning adenoma – NFPA)</td>
</tr>
<tr>
<td>Null-cell adenoma (oncocytoma)</td>
</tr>
<tr>
<td>Various</td>
</tr>
<tr>
<td>Silent subtype 3 tumor</td>
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<tr>
<td>Plurihormonal</td>
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Aggressive pituitary tumors are thought to have a greater chance of giving rise to pituitary carcinomas with cerebrospinal or systemic metastases. Pituitary carcinomas develop with equal frequency in both sexes at a mean age of 44 years, with a latency period of 7 years after the diagnosis of a pituitary tumor depending on tumor subtype [1]. Although de novo development of a malignant pituitary tumor cannot be excluded, in most case series pituitary carcinomas evolve from macroadenomas that exhibit invasive and proliferative features [10, 17, 18]. This supports the view that pituitary carcinomas mainly arise from the transformation of initially ‘benign’ adenomas that accumulate genetic aberrations over time exhibiting an ‘aggressive’ behavior and eventually metastasizing [1]. However, as not all aggressive tumors transform into carcinomas, it is important to develop tools to identify the subset of tumors at higher risk and apply close clinical and radiological surveillance along with all available treatments early in the course of the disease in an attempt to minimize their morbidity.

Epidemiology

Based on the WHO definition of atypical adenomas, several retrospective cross-sectional studies have reported on the prevalence of such tumors (table 2). Saeger et

![Fig. 1. Hardy’s classification of pituitary tumors (based on Hardy [148] and Kovacs and Horvath [149]). Upper panel shows the 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: localized sellar destruction; grade IV: diffuse destruction). Only grade III and IV tumors are considered invasive. Lower panel depicts a classification of the suprasellar extension of an adenoma which may be symmetrical or asymmetrical [grade A: suprasellar cistern only; grade B: recess of the third ventricle; grade C: whole anterior third ventricle; grade D: intracranial extradural; grade E: extracranial extradural (cavernous sinus)].
al. [19] reported 12 atypical cases out of a total of 451 pituitary adenomas (2.7%) in the German Pituitary Tumor Registry. Scheithauer et al. [6] reported 6 atypical cases out of 78 total pituitary adenomas, an incidence of 14.7% similar to the one reported by Zada et al. [20]. In a more recent single-center study, 8.9% (13 out of 146) of pituitary adenomas were atypical, and 38.4% of them developed recurrence [21]. Apart from these reports, there are no further studies describing similar epidemiological data on ‘aggressive’ pituitary tumors. This is mainly at-

**Table 2. Published series of atypical pituitary adenomas**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total adenomas</th>
<th>Atypical adenomas (prevalence)</th>
<th>NFPA PRL</th>
<th>GH</th>
<th>ACTH</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheithauer et al. [129]</td>
<td>78</td>
<td>6 (14.7%)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>5/6</td>
</tr>
<tr>
<td>Saeger et al. [19]</td>
<td>451</td>
<td>12 (2.7%)</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Zada et al. [20]</td>
<td>121</td>
<td>18 (14.8%)</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Yildirim et al. [21]</td>
<td>146</td>
<td>13 (8.9%)</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>796</td>
<td>49 (6.2%)</td>
<td>23</td>
<td>6</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

n.a. = Not available.

**Fig. 2.** 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 is characterized by the tumor extending beyond the intercarotid line, but not beyond or tangent to the lateral aspects of the intra- and supracavernous ICA. Grade III is characterized by the tumor extending laterally to the lateral tangent of the intra- and supracavernous ICA. Grade IV is characterized by total encasement of the intracavernous carotid artery (based on Knosp et al. [16]).
tributed to the lack of a standardized definition of an ‘aggressive’ tumor based not only on histological or proliferative markers, but also on the clinical course and behavior.

Pathogenesis

At the molecular level, there is evidence that pituitary tumors accumulate abnormalities in molecular pathways over time that contribute to their progression from ‘benign’ adenomas to aggressive recurrent pituitary tumors and in exceptional cases to pituitary carcinomas. Genetic or epigenetic abnormalities, paracrine growth factor disruptions and altered intrapituitary microenvironment may be associated with pituitary-selective oncoprotein activation or tumor suppressor gene inactivation, leading to sustained cell proliferation. However, the primary initiating cause of these events remains elusive, whereas current knowledge on pathogenesis of pituitary tumors has extensively been reviewed elsewhere and is beyond the scope of the current review [22, 23].

Histological and Molecular Biomarkers of Pituitary Tumor Aggressiveness

An accurate histopathological description and subtype recognition of pituitary adenomas based on the latest WHO classification is an independent predictor of aggressive behavior in the majority of pituitary adenomas [24]. Crooke’s cell adenomas, sparsely granulated somatotroph adenomas, densely granulated lactotroph adenomas, acidophil stem cell adenomas, thyrotroph adenomas, sparsely granulated corticotroph adenomas, silent subtype 3 adenomas and null cell adenomas (table 1) are all associated with aggressive clinical behavior [25]. Adenoma type in combination with some specific clinical features may also indicate an aggressive phenotype. This applies to large prolactinomas in male patients [26], dopamine agonist-resistant prolactinomas [27], plurihormonal and gonadotroph adenomas (nonfunctioning) that at the time of the diagnosis are usually large and display invasiveness to surrounding tissues.

Apart from the histological subtype, proliferation markers may also reflect the aggressive potential of pituitary adenomas by determining the rate of multiplication of neoplastic pituitary cells. The number of mitoses has only limited value as pituitary adenomas, even aggressive ones, have a low proliferation rate with occasional mitoses [28], whereas delayed fixation, intraobserver and interobserver variations and apoptotic features mimicking mitoses affect the diagnostic accuracy [29]. In contrast, the immunohistochemical (IHC) detection of the Ki67 antigen using the MIB-1 antibody appears to be superior to mitotic count in assessing tumor proliferation activity as it is expressed during all non-G0 phases of the cell cycle, except for the early G1 phase, and is more reliably determined. The vast majority of pituitary adenomas have Ki67 LI values between 1 and 2%, whereas values >3% are uncommon. Thapar et al. [5] reported that a 3% Ki67 LI cutoff value is associated with 72.7% sensitivity and 97.3% specificity and a positive and negative predictive value of 96 and 80%, respectively, in distinguishing noninvasive from invasive pituitary adenomas. It has also been suggested that a Ki67 LI >10% should always raise suspicion regarding the malignant potential of the tumor [30]. In the recent WHO classification [7], Ki67 LI was regarded as a major predictive indicator for distinguishing benign from atypical adenomas; however, the ability of Ki67 LI to predict tumor invasiveness remains controversial as discrepant results have been reported [13].

Another histopathological marker related to aggressive pituitary tumor behavior is p53 IHC expression, a tumor suppressor protein encoded by the TP53 gene [31]. In normal cells, p53 is present at very low levels which are undetectable by IHC, whereas mutant forms have a longer half-life, are more stable, accumulate in the nucleus and are detected by IHC [31]. p53 immunoreactivity appears to correlate with tumor invasiveness, as it is present in 15% of invasive adenomas and all pituitary carcinomas, but is absent in noninvasive adenomas [8]; however, this finding has not been reproduced in all studies [32]. In the latest WHO definition, p53 IHC expression was included along with Ki67 LI as a criterion of atypical pituitary adenomas; however, due to discrepant results, its predictive value as an independent factor has been questioned. Moreover, there are some limitations concerning the validity of its quantification [8, 33] as positive IHC is defined by the presence of >10 strongly stained nuclei per 10 HPFs.

From all these studies, it is evident that no single morphological or histological feature can serve as a reliable predictor of pituitary tumor behavior. Therefore, efforts have been made to combine morphological, clinical and radiological features to provide a more comprehensive and conclusive tool to differentiate benign (typical) from aggressive and potentially malignant pituitary tumors. One such classification that combines radiological and histological findings based on invasiveness (histological and/or radiological signs of cavernous sinus or sphenoid

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sinus invasion) and proliferative markers (2 of the following 3 criteria: Ki67 index ≥3%; >2 mitoses per 10 HPFs; or p53 immunopositivity) has recently been proposed by Trouillas et al. [10]. On the basis of these criteria, pituitary tumors are subdivided into 3 grades: grade 1, noninvasive (1a, noninvasive and nonproliferative; 1b, noninvasive and proliferative); grade 2, invasive (2a, invasive and nonproliferative; 2b, invasive and proliferative), and grade 3, metastatic (carcinomas). Applying these criteria retrospectively in 410 patients with pituitary adenomas, patients classified as grade 2b exhibited a 25-fold and 12-fold higher probability of tumor persistence or recurrence, respectively, after 8 years of follow-up, compared to patients with grade 1a tumors [10]. From the same study, it became apparent that imaging findings of cavernous or sphenoid sinus invasion were more sensitive in identifying invasive tumors compared to histology (175/410, 42.7% vs. 16/410, 9%, respectively). During a follow-up period of 8 years, 4 adrenocorticotropic hormone (ACTH)- and 4 prolactin (PRL)-producing pituitary carcinomas developed from previously nonmetastatic tumors (6 grade 2b adenomas, 1 grade 2a and 1 grade 1b). This proposed classification system, although requiring validation from further prospective studies with longer follow-up, has shown that a multimodal approach, considering morphological, molecular, clinical and radiological features, seems to be the most efficient way to accurately classify pituitary tumors according to their prognostic potential [34].

### Evolving Biomarkers of Pituitary Tumor Aggressiveness

Following the extensive research and knowledge on pituitary tumorigenesis acquired over the last decades, several novel biomarkers have been studied in order to assess their validity as predictive markers of pituitary tumor aggressive behavior. These include chromosomal alterations and microRNAs (miRNAs), proliferation markers, oncogenes, tumor suppressor genes, growth factors and their receptors, and factors related to angiogenesis or cell adhesion (table 3). However, no single biomarker has been found to independently predict aggressive behavior in pituitary neoplasms.

Genomic imbalance has been reported to occur frequently in pituitary tumors [35–37]. The most frequent and extensive alteration observed in aggressive tumors corresponds to the allelic loss of the short arm of chromosome 11 (11p), particularly in PRL-producing tumors [38]. Pituitary tumors show a wide range of DNA aneuploidy through image analysis cytometry and flow cytometry, and some authors have reported a positive correlation of aneuploidy with the mitotic index and tumor recurrence [39], although this view is not widely accepted [28].

Differential gene expression profiling using microarray analysis revealed a genetic signature of invasive tumors characterized by overexpression of 4 genes (IGFBP5, MYO5A, FLT3 and NFE2L1) compared to noninvasive

<table>
<thead>
<tr>
<th>Table 3. Biomarkers of aggressiveness</th>
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<tr>
<td><strong>Histological</strong></td>
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<tr>
<td>Crooke’s cell adenomas</td>
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<tr>
<td>Sparsely granulated somatotroph adenomas</td>
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<tr>
<td>Densely granulated lactotroph adenomas</td>
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<tr>
<td>Acidophil stem cell adenomas</td>
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<tr>
<td>Thyrotroph adenomas</td>
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<tr>
<td>Sparsely granulated corticotroph adenomas</td>
</tr>
<tr>
<td>Silent subtype 3 adenomas</td>
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<tr>
<td>Null cell adenomas</td>
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<tr>
<td>Ki67 LI</td>
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<tr>
<td>p53</td>
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<tr>
<td>Multimodal classification system</td>
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<tr>
<td>(invasion, proliferation markers)</td>
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FIPA = Familial isolated pituitary adenoma; SDH = succinate dehydrogenase; NCAM = neural cell adhesion molecule.
Adenomas. Only the protein product of MYO5A was more frequently detected with IHC in invasive adenomas, constituting a candidate marker of tumor aggressiveness [40]. MYO5A is a member of the myosin family, and its role in tumor cell invasion and metastasis has recently been described [41].

Germline mutations that cause familial predisposition to pituitary tumors, including multiple endocrine neoplasia (MEN) type 1 (MEN1), MEN4, Carney complex and familial isolated pituitary adenoma, as well as mutations in genes encoding succinate dehydrogenase (SDHB, SDHC and SDHD) [42], have also been linked with a tendency to present with a more aggressive clinical course than sporadic adenomas [43–45].

Several studies have implicated the aberrant expression of miRNAs, small noncoding RNAs that regulate gene expression at the posttranscriptional level, as predictive markers in aggressive pituitary tumors [46]. Lower miR-141 expression has been shown to correlate with postoperative remission in patients with corticotroph adenomas, while downregulation of miR-15a and miR-16-1 has been linked to tumor size in growth hormone (GH)-and PRL-producing adenomas [47, 48].

Downregulation of p27Kip1, an enzyme inhibitor encoded by the CDKN1B gene, has also been linked with invasive and recurrent adenomas and pituitary carcinomas. The encoded protein binds to and prevents the activation of cyclin E-CDK2 [49] and is highly expressed in nontumorous adenohypophyseal cells and adenomas with a low proliferative rate [50], whereas its expression is much lower in invasive adenomas and pituitary carcinomas [51].

Recent studies on oncogene-induced senescence have highlighted the protective role of tumor suppressor genes p16 and p21 in restraining tumor growth and the malignant transformation of pituitary adenomas [52, 53]. Senescent cells show altered cell morphology, including increased lysosomal breakage, causing the lysosomal enzyme β-galactosidase to enter into the cytoplasm [54]. In a recent study, it has been suggested that the senescence pathway, as assessed by β-galactosidase IHC, is more activated in GH-secreting and nonfunctioning pituitary adenomas (NFPAs) [55]. Moreover, a negative correlation was found between Ki67 LI and cytoplasmic staining for both p16 and p21. There are also data on methylation-associated gene silencing involving p16 and other genes such as pRb and DAPK in pituitary tumors which would suggest that methylation profiling might provide a useful biomarker of aggressiveness [56, 57].

A further gene that has been extensively studied and shown to correlate with invasion in several tumor types is the pituitary tumor-transforming gene (PTTG), a member of the securin family, which regulates sister chromatid separation during mitosis [58]. Loss of the PTTG function supresses cell proliferation, diminishing the development of pituitary tumors in retinoblastoma protein-deficient animals [59], whereas increased PTTG expression is expected to lead to tumorigenesis. Concerning human pituitary tumors, PTTG expression was higher in hormone-secreting invasive pituitary adenomas compared to noninvasive ones [60], whereas a PTTG/Ki67 score >2.9 correlated with a clinically aggressive behavior in pituitary adenomas [61].

A recently published study [62] has evaluated the effect that HEPN1 (hepatocellular carcinoma, downregulated 1) gene silencing exerts on the biological behavior of pituitary somatotroph adenomas, presenting a novel candidate tumor suppressor gene. Reduced expression of the HEPN1 gene was more frequently found in invasive human pituitary tumors, whereas loss of HEPN1 function in pituitary adenoma cell lines (GH3 and GT1.1) promoted proliferation and invasiveness of pituitary adenoma cells and inhibited apoptosis.

Growth factors such as epidermal growth factors (EGFs), vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGFs) and their receptors (EGFR, VEGFR and FGFR, respectively) have also been found to be involved in pituitary tumor aggressiveness [63, 64]. FGF-2 is overexpressed in pituitary tumor cells with higher levels in more aggressive tumors [65]. A truncated form of the FGF receptor-4 (FGFR4 or ptd-FGFR4) has been shown to induce pituitary tumor invasion in vitro and in vivo animal models. This constitutively activated protein is found in approximately 60% of tumors (mostly GH-, ACTH- and FSH-/LH-producing adenomas) and correlates with Ki67 LI [66]. The ability of pituitary tumors to invade surrounding tissues depends on the presence of matrix metalloproteinases (MMPs) that break down membranes and connective tissue. Expression of MMP9 and MMP2 was found to correlate with the degree of invasion, adenoma phenotype and a high radiological grade of invasiveness in some but not all studies [32, 67–69]. Expression of the polysialylated form of neural cell adhesion molecule has also been associated with tumor aggressiveness [70].

A further recent study has elucidated the role of galexin-3, a β-ganglioside-binding lectin involved in cell adhesion, growth, differentiation and apoptosis encoded by the LGALS3 gene, as a possible predictive marker of ag-

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gressive tumor behavior in 92 ACTH- and PRL-secreting adenomas [71]. LGALS3 IHC was found in more than 30% of neoplastic cells and along with LGALS3 mRNA positivity they were more important markers than Ki67 LI, for predicting progression or recurrence. However, the reliability of genomic and molecular markers remains to be assessed in large prospective studies, alone or as part of multimodal prognostic models.

Diagnosis

Clinical Features

The initial clinical features of aggressive pituitary adenomas do not differ from nonaggressive typical adenomas and are mainly attributed to pressure effects to surrounding tissues and/or to the effects of excessive hormonal secretion. Being by definition more invasive than their typical and benign counterparts, symptoms such as visual impairment, presenting either as visual field loss or a reduction in visual acuity and/or cranial nerve palsies, usually dominate the clinical picture. In several cases, the presence of relatively unusual symptoms/signs not commonly encountered in benign pituitary tumors, such as hearing loss, ataxia, and/or motor impairment, cerebrospinal fluid leak or hydrocephalus, may point to the presence of an aggressive/invasive tumor [1, 72]. However, the most common clinical presentation of aggressive pituitary tumors is early recurrence after initial pituitary surgery, and rapid local growth and tumor extension. Most aggressive pituitary tumors were initially considered to be hormonally active, which is in line with the significantly higher Ki67 LI found in secreting compared to nonsecreting adenomas [73, 74]. However, a critical analysis of the well-documented published series of atypical adenomas (table 2) has revealed that approximately half of these tumors are nonfunctioning, whereas atypical GH-secretting adenomas appear more frequent than atypical ACTH or PRL tumors. Symptoms related to hormonal hypersecretion usually do not differ from those encountered in patients with benign adenomas, and there are no hormonal level cutoffs that differentiate aggressive from benign or malignant macroadenomas, although higher pro-opiomelanocortin levels may be associated with a more aggressive course in patients with Cushing’s disease [75]. Very high levels of PRL, ACTH, and/or GH despite apparent surgical clearance of the tumor should raise suspicion for the presence of more aggressive or potentially malignant pituitary tumors. Similarly, worsening of the secretory status due to partial or complete sec-

Imaging

Current imaging diagnostic modalities, mainly magnetic resonance imaging, exert high sensitivity in detecting aggressive pituitary tumors which in their great majority are macroadenomas, but currently there are no reliable features distinguishing aggressive from apparently ‘benign’ adenomas. In the series of atypical adenomas reported by Zada et al. [20], 17 out of 18 atypical adenomas (94%) were macroadenomas, and radiological invasion was evident in 15/18 (83%) compared to 45% of typical adenomas (p = 0.004). Ten lesions (56%) showed infrasellar invasion with clival or sellar floor erosion, 9 (50%) showed suprasellar invasion and 6 (33%) invaded at least 1 cavernous sinus; in 5 patients (28%), invasion of all 3 regions was noted.

Application of Knosp’s and Hardy’s radiological classification systems (fig. 1 and 2, respectively) could help evaluate the extent and type of invasion of these tumors, although there is no strong evidence relating each grade with the clinical course. However, the radiological proof of invasiveness in combination with proliferation markers and adenoma classification may help predict the clinical behavior [10].

Treatment

In general, aggressive pituitary tumors are by definition notoriously difficult to manage due to their size, invasiveness, rapid growth and high frequency of recurrence. Treatment options include surgery, external radiotherapy, medical treatment and peptide receptor radionuclide therapy (PRRT). Since clear-cut definition and reliable prognostic markers are lacking, aggressive pituitary tumors are difficult to be identified at initial presentation, and therefore the primary therapeutic approach is no different compared to other pituitary tumors depending on the type of adenoma.

Initial Treatment after Diagnosis

Apart from patients with prolactinomas, all other patients with pituitary tumors should be offered curative or debulking transphenoidal surgery unless comorbidities are present that increase the perioperative risk. Prolactinomas are initially treated with dopamine agonists, main-
ly cabergoline, which is efficient in controlling tumor growth and PRL levels in most cases [76]. Resistance to dopamine agonists presenting as escalating PRL levels and/or tumor growth can be an early indicator of aggressiveness, but this may not always be the case, as some ‘benign’ prolactinomas may show resistance due to polymorphisms in the dopamine receptor [77]. For prolactinomas refractory to medical treatment, maximizing cabergoline dosage beyond conventional doses has been proposed, as long as adverse effects are tolerable [76]. In patients with invasive GH-secreting macroadenomas and giant adenomas, preoperative use of long-acting SSAs may achieve preoperative tumor shrinkage, although studies evaluating improvement of surgical outcomes have produced controversial results [78–80]. Patients failing to be cured surgically or recurring after initial cure are treated with the long-acting SSAs lanreotide and octreotide, either alone or in combination with the GH receptor antagonist pegvisomant; resistance to these agents heralds a more aggressive course. Sparsely granulated GH-producing tumors have also been reported to be resistant to medical treatment with SSAs compared to the densely granulated type [81].

Aggressive ACTH adenomas causing Cushing’s syndrome are usually invasive macroadenomas, and surgery achieves low remission rates ranging between 22 and 65% [82, 83]. Repeated debulking surgeries can be applied along with medical agents including inhibitors of steroidogenesis, dopamine agonists, glucocorticoid receptor blockers, the novel SSA pasireotide [84] or drugs currently under investigation such as LCI699 [85]. Bilateral adrenalectomy is also effective in controlling cortisol excess; however, removal of cortisol-mediated negative feedback on the pituitary tumor may serve as a growth stimulus to corticotroph tumors, especially aggressive ones, increasing the risk of developing Nelson’s syndrome [86].

Gonadotropin-producing pituitary adenomas, categorized by the WHO as NFPA, are often discovered late as invasive macroadenomas, and medical treatment is ineffective and currently not indicated. Very few data exist for the rare TSH-secreting tumors (TSHomas), most of which are diagnosed as macroadenomas with frequent suprasellar extension or sphenoidal sinus invasion [87]. In addition, these tumors may frequently be aggressive, locally invasive, involving the cavernous sinus, internal carotid artery or other structures, may present marked fibrosis, possibly related to a high expression of FGF-2 [88] or dense calcification [89], thus rendering complete resection of the tumor either impractical or dangerous.

Treatment with SSAs is highly effective, controlling TSH secretion in most and inducing tumor shrinkage in 40% of patients [90], while resistance and escape phenomenon have been described in a minority of cases [91].

Surgical Therapy

All medical treatments in patients harboring aggressive pituitary tumors are often ineffective in controlling hormonal hypersecretion and/or tumor growth. Hence, resurgery appears a feasible treatment option for aggressive and/or recurrent tumors, although remission rates after repeated transsphenoidal surgery are much lower [92–94]. In cases where tumors extend significantly into the suprasellar region, the transcranial approach may still be advantageous but the transsphenoidal or endoscopic surgical approaches are also valid and can be used depending on the surgeon’s experience [14]. Near-total surgical resection with no apparent remnant in imaging postoperatively can rarely be achieved as aggressive pituitary tumors tend to be infiltrative and recur over a relatively short time [95]. Repeated pituitary tumor debulking surgeries can be performed to remove further emerging tumor tissue albeit with less success and increasing rate of complications such as worsened visual field, optic nerve palsy, meningitis, anterior pituitary deficiencies and diabetes insipidus [96], and can be combined with other therapeutic modalities such as systemic and/or radiological therapies to achieve tumor control.

Radiation Therapy

Radiation therapy (RT) for aggressive pituitary tumors that recur, continue to grow or are not biochemical controlled despite medical and/or surgical therapy is a further therapeutic option. Conventional external RT has been used in adjuvant settings to prevent tumor regrowth in large or partially removed pituitary tumors and for local control of expanding tumors, some of which were later proven to be aggressive pituitary tumors. RT efficacy ranges in several studies from 67 to 100% depending on the selection of cases [97]. Conventional radiotherapy has been shown to reduce recurrence of NFPA remnants, particularly if administered immediately during the postoperative period [98], but its efficacy is often limited in aggressive tumors. While a tumorstatic effect is the most common outcome regarding tumor growth control, in rare instances tumor shrinkage has been reported [99]. Stereotactic radiosurgery with delivery of high-dose radiation in a single visit or fractionated RT (smaller fractions of radiation given over a period of 4–6 weeks) can also be applied if the tumor is adjacent to radiation-sen-
tive normal tissues. Techniques such as Gamma Knife surgery, linear accelerator or CyberKnife can provide more precise targeting of the adenoma, offering better control of the dose of radiation received by adjacent structures, such as the pituitary stalk, pituitary gland, optic chiasm and cranial nerves in the cavernous sinus. Retrospective series with new radiosurgery methods published to date have shown similar results as conventional RT [100] with a tendency to achieve their effect slightly faster and with less frequent side effects, mainly pituitary deficiency [101]. In contrast to repeated surgical debulking, the amount of radiation treatment that can be administered is limited by the risk of optic neuropathy, necrosis in the temporal lobe and other brain areas and the rare possibility of developing a secondary brain tumor. There has also been concern regarding the possible role of radiotherapy in the transformation or progression of pituitary adenomas to carcinomas following reports of sarcomatous changes induced by RT on pituitary adenomas [102]. However, this is unlikely to be a general process in view of the large number of irradiated pituitary tumors and the small number of pituitary carcinomas [103]. Reirradiation using stereotactic linear accelerator or Gamma Knife radiosurgery can be considered as a salvage/palliative choice in selected previously irradiated patients to achieve local growth control with acceptable complication rates, given the lack of options that may be available otherwise; however, this approach did not control hormonal hypersecretion in one study [104]. Use of Gamma Knife surgery in patients who had previously undergone conventional RT led to an accelerated fall in GH excess and stabilization of NFPAs in the majority of cases [105], while no significant side effects were observed in a median follow-up of 36 months, except for a 43% incidence of new pituitary failure.

Peptide Receptor Radionuclide Therapy
PRRT has recently been proposed as a potential treatment option for aggressive pituitary adenomas based on the avid uptake of normal pituitary and adenoma tissue on positron emission tomography with gallium-labeled octreotide ($^{68}$Ga-DOTATATE PET/CT). The theoretical rationale relies on the delivery of a toxic dose of radiation to specific neoplastic cells expressing somatostatin receptors and is achieved using radiolabeled SSAs with agents such as $^{90}$Yttrium or $^{177}$Lu-Lutetium. PRRT has been used with great success in neuroendocrine neoplasms, particularly gastroenteropancreatic [106]. Although experience with PRRT in pituitary tumors is limited, a significant tumor shrinkage and clinical improvement following admini stration of a course of $^{111}$Indium-DTPA-octreotide in a patient with a recurrent giant prolactinoma resistant to conventional treatment have been described [107]. Symptomatic improvement and long-term control (8 years) were also reported in a patient with an atypical NFP treated with $^{177}$Lu-DOTATOC [108], whereas in a small case series of 3 patients treated with $^{177}$Lu-DOTATATE, only 1 patient obtained a clinically useful response [109]. Larger prospective studies with dosimetric evaluation of absorbed dose and assessment of toxicity to surrounding normal brain tissue are required to establish the usefulness of this promising therapeutic modality.

Chemotherapy
Aggressive pituitary adenomas have relatively low proliferation indices and seem to retain certain aspects of well-differentiated tumors, thus responding poorly to standard chemotherapy regimens [110]. The same rule applies to pituitary carcinomas despite their relatively higher proliferation indices; however, due to the rarity of these tumors, no randomized prospective studies of systemic chemotherapy have been conducted. Different cytotoxic chemotherapy protocols including procarbazine-etoposide-lomustine (cyclo-hexyl-chloroethyl-nitrosourea or CCNU) [111] and lomustine-doxorubicin [112] have been used in individuals with aggressive pituitary tumors, achieving mostly transient tumor growth and hormonal responses. In a small series of 7 patients, of whom 3 had aggressive pituitary tumors and 4 carcinomas, combination therapy with lomustine and 5-fluorouracil showed an overall poor response rate in terms of tumor shrinkage, although temporary clinical responses were noticed in some patients [110]. Furthermore, observational data suggest that prolonged survival in some patients with pituitary carcinomas is associated with chemotherapy received prior to the appearance of distant metastases. Therefore, early use of chemotherapy may be of value in some patients with recurrent highly aggressive tumors as long as these patients can be readily selected based on markers that are currently missing from clinical practice [1].

Temozolomide
Since 2006, temozolomide (TMZ), originally approved for use in refractory glioblastoma multiforme, has been used to successfully treat pituitary carcinomas and aggressive pituitary adenomas (table 4). TMZ is an orally administered second-generation alkylating agent, an imidazotetrazine derivative that is rapidly converted at physiological pH to methyl-triazeno-imidazole-carbox-
amide, which is the active drug. It exerts its action by attaching a methyl group to the O\text{6} position of guanine bases causing mispair with thymine bases, DNA damage, proliferation arrest and cell death (apoptosis). O\text{6}-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that counteracts the effects of TMZ by removing alkylating adducts from DNA. TMZ can readily cross the blood-brain barrier, and its action is not cell cycle specific, thus inhibiting all stages of tumor cell growth, even in slow-growing tumors, such as pituitary tumors.

To date, 32 cases of aggressive pituitary tumors and 29 cases of pituitary carcinomas have been treated with TMZ in the literature (table 4). The overall clinical and radiological response rate was initially reported to be approximately 69% in carcinomas and 60% in aggressive adenomas [96]. However, these response rates were based on published case reports that were successfully treated introducing a positive reporting bias. Combined data from 4 studies of small cohorts [113–116] reveal a mean tumoral response (partial response) in 55.5% (10/18) of patients with carcinomas and 41% (7/17) with aggressive adenomas. If stabilization of the tumor (stable disease) is also considered as a favorable outcome, TMZ efficacy rises up to 72% (13/18) for carcinomas and 70.5% (12/17) for aggressive adenomas (table 4). Nevertheless, responses were frequently short lasting, and subsequent progression developed following an initial response to treatment. Some authors have also reported changes in histopathological and morphological features of tumors after TMZ treatment based on findings from reoperated patients. Tumor softening and friability were noticed, facilitating

Table 4. Reported patients with aggressive pituitary tumors and carcinomas treated with TMZ

<table>
<thead>
<tr>
<th>No.</th>
<th>First author</th>
<th>Year</th>
<th>Adenoma type</th>
<th>Response to TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Syro [130]</td>
<td>2006</td>
<td>PRL + (PR)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Neff [132]</td>
<td>2007</td>
<td>PRL + (PR)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Kovacs [134]</td>
<td>2008</td>
<td>Silent subtype 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>corticotroph –</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Debono [135]</td>
<td>2008</td>
<td>ACTH (Nelson’s) +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(SD)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Moyes [137]</td>
<td>2009</td>
<td>ACTH (Crooke’s cell) +</td>
<td>(PR)</td>
</tr>
<tr>
<td>6</td>
<td>Hagen [139]</td>
<td>2009</td>
<td>ACTH (Crooke’s cell) +</td>
<td>(PR)</td>
</tr>
<tr>
<td>7</td>
<td>Hagen [139]</td>
<td>2009</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>McCormack [140]</td>
<td>2009</td>
<td>GH –</td>
<td></td>
</tr>
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<td>9</td>
<td>Mohammed [142]</td>
<td>2009</td>
<td>ACTH (Crooke’s cell) +</td>
<td>(PR)</td>
</tr>
<tr>
<td>10</td>
<td>Mohammed [142]</td>
<td>2009</td>
<td>ACTH (Crooke’s cell) +</td>
<td>(PR)</td>
</tr>
<tr>
<td>11</td>
<td>Mohammed [142]</td>
<td>2009</td>
<td>NFPA (incidentaloma) +</td>
<td>(PR)</td>
</tr>
<tr>
<td>12</td>
<td>Losa [114]</td>
<td>2010</td>
<td>ACTH –</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Losa [114]</td>
<td>2010</td>
<td>ACTH –</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Losa [114]</td>
<td>2010</td>
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<td>2010</td>
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<td>2010</td>
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<tr>
<td>21</td>
<td>Bush [115]</td>
<td>2010</td>
<td>NFPA + (SD)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Raverot [113]</td>
<td>2010</td>
<td>PRL –</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Raverot [113]</td>
<td>2010</td>
<td>ACTH –</td>
<td></td>
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<tr>
<td>24</td>
<td>Raverot [113]</td>
<td>2010</td>
<td>ACTH + (PR)</td>
<td></td>
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<tr>
<td>25</td>
<td>Murakami [145]</td>
<td>2011</td>
<td>PRL + (PR)</td>
<td></td>
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<td>26</td>
<td>Thearle [123]</td>
<td>2011</td>
<td>ACTH + (PR)</td>
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</tr>
<tr>
<td>27</td>
<td>Dillard [146]</td>
<td>2011</td>
<td>ACTH + (PR)</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Moskow [147]</td>
<td>2011</td>
<td>Silent corticotroph –</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Hirohata [116]</td>
<td>2013</td>
<td>ACTH (Crooke’s cell) +</td>
<td>(PR)</td>
</tr>
<tr>
<td>30</td>
<td>Hirohata [116]</td>
<td>2013</td>
<td>PRL –</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Hirohata [116]</td>
<td>2013</td>
<td>PRL + (SD)</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Hirohata [116]</td>
<td>2013</td>
<td>PRL + (PR)</td>
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</tr>
</tbody>
</table>

Total aggressive pituitary adenomas: PRL 12; ACTH 12; GH 1; NFPA 3; others (null cell, silent) 4; PR: 19 (59.4%); SD: 5 (15.6%); PD: 8 (25%). Total pituitary carcinomas: PRL 10; ACTH 9; GH 0; NFPA 6; others (null cell, mixed) 4; PR: 21 (72.4%); SD: 3 (10.3%); PD: 5 (17.3%). + = Favorable response including disease stabilization (SD) and partial responses (PR); – = tumor progression (PD).
easier resection at reoperation, while TMZ-treated tumors exhibited fewer mitoses, lower Ki67 LI, hemorrhage, necrosis, focal fibrosis and absent MGMT in IHC [117, 118].

The DNA repair enzyme MGMT reverses the methylation caused by TMZ, being the major mechanism of resistance to TMZ treatment. A significant inverse correlation was found between IHC MGMT expression and response to TMZ; however, the absence of MGMT expression was not always predictive of tumor response [113, 115]. On the contrary, studies examining MGMT promoter methylation in pituitary tumors confirmed its poor prognostic value since methylated MGMT promoter was found only in 60% of TMZ-sensitive tumors and 50% of TMZ-resistant tumors [96, 119]. It appears that MGMT IHC but not MGMT promoter methylation status can be used to predict response to treatment in pituitary tumors. A clinically meaningful suggestion has been made by Raverot et al. [113] who have shown that 3 cycles of TMZ identify treatment-responsive patients, whereas after 3 cycles nonresponders do not benefit from additional cycles. Furthermore, recent studies have shown that MGMT may not be the sole molecule determining sensitivity to TMZ in pituitary carcinomas and atypical adenomas, and that loss of MSH6 function (an enzyme involved in the mismatch repair pathway) is associated with poor responsiveness to TMZ treatment [116, 120].

TMZ is generally well tolerated, although patients frequently report fatigue, whereas hematological toxicity may require dose reduction or occasionally drug withdrawal. Certain concerns have been raised regarding the duration of TMZ treatment and optimal dosing. The standard regimen is 150–200 mg/m² of TMZ given daily for 5 days every 28 days, but alternative regimens like ‘dose-dense’ protocols using 150 mg/m² at days 1–7 and days 14–21 of a 28-day cycle and ‘metronomic’ protocols using continuous daily low dose (50–75 mg/m²) have been used [115]. Increased risk of secondary malignancies (particularly leukemia and lymphoma) has been reported with prolonged administration of alkylating agents such as TMZ. It is currently unclear which regimen offers the best efficacy and which is associated with a reduced risk of secondary malignancy [121], whereas there are no data to support whether TMZ can be used alone or in combination with other medications such as pasireotide or capecitabine [122–124].

### Molecular Targeted Therapies

Novel targeted therapies (mTOR inhibitors, anti-VEGF agents) may be warranted for further investigation following a case report of a patient showing disease control for 26 months after administration of the angiogenesis inhibitor bevacizumab [125] and data showing the in vitro effect of everolimus on cell viability in cell cultures from NFPAs [126]. The previously highlighted importance of EGF and its receptor EGFR has also prompted research concerning the use of tyrosine kinase inhibitors, especially the EGFR inhibitor gefitinib, as a targeted medical therapy for ACTH adenomas, demonstrating promising in vitro results [127]. There have also been some promising surgical techniques such as the implantation of Gliadel (carmustine) wafers in patients with aggressive pituitary adenomas showing stabilization or even objective responses in the majority of cases [128].

A proposed treatment algorithm for patients with aggressive pituitary tumors is illustrated in figure 3. Because of the rarity of these tumors, data from randomized controlled studies comparing the efficacy and safety of the various therapeutic modalities are lacking, and the proposed algorithm is based on personal clinical experience and the incorporation of the findings of some of the previously reported studies. The diagnosis of an aggressive pituitary tumor can either be based on histological and genetic biomarkers detected on the adenomatous tissue after surgical removal, or on the distinct clinical course characterized by rapid growth despite the application of appropriate therapy. In case of total or near-total resection of a tumor qualifying as an aggressive pituitary adenoma, it is prudent to apply closer imaging follow-up within 3 months in order to identify early recurrence. Patients with incompletely resected aggressive tumors may require further surgery and additional medical treatment with SSAs and/or cabergoline to control hormonal hypersecretion when present and further tumor growth; however, this is not easily achievable or sustainable. Conventional or targeted RT is considered on an individual basis taking into account patient’s age, anatomical details and histopathological or molecular biomarkers of the tumor; however, no evidence-based criteria are established to identify which patients may benefit from this form of treatment. Further tumor progression should be dealt with resurgery if feasible, particularly in the presence of symptoms/signs of mass effects. Additional RT may also be applied taking into consideration radiation-induced side effects. TMZ can be offered as a palliative/salvage therapy if radiation and surgical treatments have failed to control tumor growth or are associated with increased morbidity. Early use of TMZ cannot be supported on the basis of currently exist-
ing clinical data; however, this treatment can be applied in specialized centers or in the context of well-designed clinical studies. Treatments such as mTOR inhibitors, tyrosine kinase inhibitors and PRRT seem promising but can be offered as a last resort in an investigational setting.

**Conclusion**

Aggressive pituitary adenomas constitute a challenging but not as yet clearly defined entity. Such tumors are diagnosed relatively late, respond poorly to treatment and show an overall poor prognosis. A multimodal approach taking into consideration histopathological, radiological
and novel molecular markers seems to be the most appropriate means to identify tumors that will follow an aggressive clinical course. Registration in comprehensive and detailed databases and multicenter collaboration combined with data from long-term follow-up of patients with pituitary tumors will provide the necessary tools to develop prognostic models of aggressive behavior and apply them in order to identify such tumors. Early diagnosis will offer the chance for prompt application of intensive treatment in an attempt to reduce overall morbidity and possible progression to carcinomas. Traditional treatment agents are usually ineffective, and TMZ is currently the only agent that has shown promising results when used as a salvage therapy, although confirmation from prospective randomized control trials is lacking. Additional research on the role of MGMT and other parameters affecting responsiveness to TMZ is also needed to better predict therapeutic results and select patients who will benefit most. New drugs targeting specific pathways involved in pituitary tumorigenesis are currently under investigation and, together with new modalities of radiotherapy and radionuclide therapy, will hopefully improve outcome of these patients. Better knowledge of the precise molecular derangements in aggressive pituitary adenomas should allow the development of new targeted drugs in the future.

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Aggressive Pituitary Tumors

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