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Mirela Diana Ilie, Emmanuel Jouanneau, Gérald Raverot

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#### ARTICLE TITLE

Aggressive pituitary adenomas and carcinomas

#### AUTHOR NAMES AND DEGREES

Mirela Diana Ilie, MD MSc<sup>1</sup>, Emmanuel Jouanneau, MD PhD<sup>2</sup>, Gérald Raverot, MD PhD<sup>3</sup>

#### AUTHOR AFFILIATIONS

1. Endocrinologist-in-training, Endocrinology Department, "C.I.Parhon" National Institute of Endocrinology, Bucharest, Romania
2. Professor of Neurosurgery, Neurosurgery Department, Reference Center for Rare Pituitary Diseases HYPO, "Groupement Hospitalier Est" Hospices Civils de Lyon, "Claude Bernard" Lyon 1 University, Lyon, France
3. Professor of Endocrinology, Endocrinology Department, Reference Center for Rare Pituitary Diseases HYPO, "Groupement Hospitalier Est" Hospices Civils de Lyon, "Claude Bernard" Lyon 1 University, Lyon, France

#### AUTHOR CONTACT INFORMATION

1. Endocrinology Department II, "C.I.Parhon" National Institute of Endocrinology Romania, 34-36 Aviatorilor Boulevard, 011863 Bucharest, Romania ; [mireladiana.ilie@gmail.com](mailto:mireladiana.ilie@gmail.com); @the\_hormone\_doc
2. Neurosurgery Department, Groupement Hospitalier Est, Hôpital Pierre Wertheimer, 59 Pinel Boulevard, 69677 Bron, France; [emmanuel.jouanneau@chu-lyon.fr](mailto:emmanuel.jouanneau@chu-lyon.fr)
3. Fédération d'Endocrinologie, Groupement Hospitalier Est, Hôpital Louis Pradel, 59 Pinel Boulevard, 69677 Bron, France; [gerald.raverot@chu-lyon.fr](mailto:gerald.raverot@chu-lyon.fr) ; @GeraldRaverot

#### CORRESPONDING AUTHOR

Gérald Raverot

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#### KEY POINTS

- a subset of pituitary tumors present an aggressive behavior that remains difficult to predict, and in very rare cases, they metastasize
- from 2018, we have guidelines for the management of aggressive pituitary tumors and carcinomas, but several issues remain unaddressed due to the scarcity of available data
- we define "clinically relevant tumor growth" based on signs and symptoms, while "unusually rapid tumor growth rate" when the tumor increases by 20% in under 6 to 12 months
- temozolomide and the Stupp protocol might have a place earlier in the management of aggressive pituitary tumors and carcinomas, and not only as a "salvage therapy"
- despite temozolomide efficacy in about 40% of cases, a need for alternative therapies exists, and immunotherapy should be considered

#### SYNOPSIS

A subset of pituitary tumors present an aggressive behavior that remains difficult to predict, and in very rare cases, they metastasize. The current European Society for Endocrinology (ESE) guidelines for the management of aggressive pituitary tumors and carcinomas provide valuable guidance, but several issues remain unaddressed due to the scarcity of data available in the literature. In this review, we present key clinical aspects regarding aggressive pituitary tumors and carcinomas, and we also discuss some of the unanswered questions of the ESE guidelines, focusing on both diagnosis (most notably on how to define “clinically relevant tumor growth” and “unusually rapid tumor growth rate”) and treatment (most notably on the potential place of temozolomide and of the Stupp protocol earlier in the management of these tumors).

## **Introduction**

Pituitary adenomas and carcinomas are neoplasms derived from the endocrine cells of the adenohypophysis. The vast majority are benign, and either they remain clinically inapparent<sup>1</sup> or they are easily treatable with the currently available conventional therapies (medical treatments, surgery, and in some cases radiotherapy)<sup>2</sup>. However, some of these tumors exhibit an aggressive behavior that is difficult to predict, and in very rare cases, they metastasize<sup>3</sup>. The prevalence of pituitary adenomas and carcinomas is presented in Figure 1<sup>4,5</sup>. Both aggressive pituitary adenomas and carcinomas are difficult to manage and are responsible for increased morbidity and mortality. The recently published European Society of Endocrinology (ESE) guidelines<sup>2</sup> provide valuable guidance, but at the same time leave some unaddressed issues due to the scarcity of the data available in the literature. Here, we present key clinical aspects from definition to diagnosis, treatment and follow-up. We also discuss some of the unanswered questions of the ESE guidelines (for example how to define a “clinically relevant tumor growth”) and the potential place of temozolomide (TMZ) earlier in the management of aggressive pituitary tumors and pituitary carcinomas, instead of using it only as a “salvage therapy”.

### ***1. Current definitions***

- Aggressive pituitary adenomas are defined by the ESE guidelines as radiologically invasive tumors with unusually rapid tumor growth rate or as tumors presenting clinically relevant

tumor growth in spite of optimal use of standard therapies (conventional medical treatments, surgery, and radiotherapy)<sup>2</sup>. However, it is important to note that there is no definition proposed for “clinically relevant tumor growth” or for “unusually rapid tumor growth rate”.

- Pituitary carcinomas are defined exclusively based on the presence of metastases (craniospinal and/or systemic), as so far there are no histological characteristics distinguishing carcinomas from adenomas prior to metastasis<sup>6</sup>. Moreover, clinical and histological data from the ESE survey on aggressive pituitary tumors and carcinomas, due to similarities between the two groups, made Trouillas and colleagues question whether aggressive pituitary tumors and pituitary carcinomas are in fact the two sides of a same coin, and propose that aggressive pituitary tumors be considered tumors with malignant potential. However, despite the similarity between the two groups, pituitary carcinomas showed more frequently a mitotic count >2 per high power field (90% versus 63%) and had higher mortality rate in comparison with aggressive pituitary tumors (43% versus 28%)<sup>5</sup>.

## **2. *Diagnosis***

From a practical point of view, the diagnosis of these tumors should comprise:

- imaging studies,
- full endocrine laboratory evaluation,
- ophthalmological evaluation, and
- histopathological analysis<sup>2</sup>.

### **a) *Imaging studies***

The imaging studies are performed mainly to assess tumor dimension, invasion and growth.

Magnetic resonance imaging (MRI) is the preferred option; thin slices are needed and the

sequences should include sagittal T1-weighted native, coronal T1-weighted native and contrast-enhanced, coronal T2-weighted native +/- axial T1-weighted native sequences. Other than the MRI, computed tomography (CT) scan should be performed when the assessment of bone invasion is needed<sup>2</sup>, and one should screen for metastases as discussed in the “Follow-up” part.

### **Invasion**

Regarding invasion, the ESE guidelines note that invasiveness alone is not synonymous with aggressiveness, but that nonetheless the invasion is a determinant of incomplete resection<sup>2</sup>. Another point concerns the assertion of tumor invasion based on the MRI findings which could be misleading since the extension into the cavernous sinus can result from both tumor invasion and/or tumor expansion<sup>7,8</sup>. It has become common practice to label tumors as invasive when they are classified as Knosp grade 3A, 3B or 4 on the MRI. However, initially, the modified Knosp classification (grades 1, 2, 3A, 3B, and 4) was meant to predict the likelihood of surgically observed invasion into the cavernous sinus (and therefore to predict the surgical outcome) and not to define invasion *per se*. The authors showed important differences in the parasellar invasion found during endoscopic transsphenoidal surgery between grades 3A, 3B and 4 (26.5%, 70.6%, and 100%, respectively). Moreover, tumors classified as Knosp grade 2 were found to be invasive during endoscopic transsphenoidal surgery in 10% of the cases<sup>7</sup>. We recently confirmed the difference in the surgically observed invasion into the cavernous sinus between grade 3A and 3B tumors. In our study the rate of intraoperative invasion of grade 3A tumors was higher (61.5%) than in the original study (26.5%)<sup>7</sup>, but still lower than for grade 3B tumors (78.6%). Moreover, gross total resection was negatively associated with the Knosp grade, with a 56% rate for grade 3A tumors and a 25% rate for grade 3B tumors. It has to be noted that for functioning

pituitary tumors the post-operative remission rate did not differ between grade 3A and 3B tumors, suggesting persistent residual tumor not visible on MRI<sup>9</sup>.

### **Tumor growth**

How we should measure and classify the tumor growth in order to assess the treatment response is an important issue. Imber *et al.* recently showed that although pituitary tumors are irregularly shaped (especially after treatment), a 1D approach (*i.e.*, the longest diameter, as governed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline 1.1, used in most cancers outside of the central nervous system<sup>10,11</sup>) was in general adequately correlated with the volumetric assessment. The authors warn that in particular cases of pituitary tumors, like multiloculated pituitary tumors, multifocal and bony invasive tumors, small recurrences, and small areas of residual tumor, the 3D volumetric assessment might be more accurate than the 1D assessment and add value, but this appeared to be true especially in diagnosing partial remission versus stable disease, and not in cases of tumor progression<sup>12</sup>.

RECIST 1.1 define progressive disease as a 20% increase in the sum of the longest diameters (in comparison to the smallest sum of the longest diameters recorded since a particular treatment was started), with a 5 mm absolute increase in the sum required, and/or as the apparition of new lesions. The term “sum of diameters” is used to account for the multiple lesions that may be present. The 5 mm absolute increase in the sum is in order to avoid over-diagnosing progressive disease when the sum of the longest diameters is very small and a 20% increase would be within measurement error. It is also important to note that RECIST guideline is based mainly on CT scans and, for consistency and ease, it recommends to measure the longest diameter on the axial plane (even though the true longest diameter may be on another plane); moreover, to be considered measurable, a lesion must be initially  $\geq 1\text{cm}$ <sup>10,11</sup>.

However, in the case of pituitary tumors, given the fact that the lesion is unique (and therefore there is a sole longest diameters and not a sum of diameters), increases of less than 5 mm might be accurately measured, depending also on how well delineated is the tumor and on the MRI machine, sequence and slice thickness. We suggest that it should be discussed with the radiologist within each pituitary team what represents the smallest accurately measurable increase, but that a 20% increase in the longest diameter should usually suffice to call it progressive disease.

Returning to the definition of an aggressive pituitary tumor, the guidelines don't define "clinically relevant tumor growth" or "unusually rapid tumor growth rate" because not enough data exists in the literature to allow for a clear and evidence-based definition. Therefore, studies looking at this matter are most needed, but until these will be available, based on our own experience, we propose the followings. For the first term, in the case of pituitary tumors, due to their location, even when a tumor does not show progressive disease (*i.e.*, increasing its longest diameter by 20%), it may still show "clinically relevant tumor growth". These situations include a tumor starting to approach or to compress the optical chiasm, aggravation of the optical field defects and compression of the cranial nerves bypassing the cavernous sinuses. In these cases, as the name states, it is really the signs and symptoms (present, or anticipated if the tumor is in contact with the optical chiasm) that should put the diagnosis of a "clinically relevant tumor growth" independent of the absolute or relative increase in the tumor diameters (especially since it may not be the longest diameter that causes the complications). Alternatively, a tumor should be considered as progressive when its longest diameter increases by more than 20% even if the growth is not clinically relevant (for example tumors expanding in the sphenoid sinus). "Unusually rapid tumor growth rate" is more difficult to define. Normally, pituitary tumors grow

slowly and one needs to compare the last imaging study not only with the penultimate one, but also to older imaging studies in order to evaluate the tumor growth, as recommended by the ESE guidelines<sup>2</sup>, and as illustrated in Figure 2. Therefore, if the tumor increases by 20% in under 6 months (or even in under 12 months if we have available only an annual MRI), we classify the growth rate as unusually rapid. Figure 3 illustrates a rapidly growing pituitary tumor.

#### **b) Histopathological analysis and prediction of aggressiveness**

The aggressive behavior may manifest even >10 years after the primary diagnosis of a pituitary tumor, and so far no single marker is capable to accurately predict it<sup>2</sup>. This would be of particular importance because it would allow for an earlier and more intensive management of these tumors. Currently, the ESE guidelines recommend at a minimum to perform immunohistochemistry for pituitary hormones and to determine the Ki-67 index, and state that the mitotic count and p53 immunodetection should be envisioned at least in cases with a Ki-67 index  $\geq 3\%$ <sup>2</sup>. The European Pituitary Pathology Group (EPPG), on the other hand, has proposed very recently a standardized diagnostic approach for these tumors, in which both the Ki-67 index and the mitotic count are listed to be performed systematically, with a cut-off for the mitotic count of >2 mitoses per high-power field<sup>13</sup>. For the prediction of aggressiveness, the EPPG also suggested the introduction in the routine clinical practice of the five-tiered classification of Trouillas and colleagues (1a: non-invasive and non-proliferative, 1b: proliferative and non-invasive, 2a: invasive and non-proliferative, 2b: invasive and proliferative, 3: pituitary carcinoma)<sup>14</sup> given that its ability to predict the risk of progression and recurrence after surgery was validated by multiple independent studies<sup>13,15-17</sup>.

### **3. Treatment**



### **a) Temozolomide**

TMZ is an oral alkylating agent that led to a remarkable improvement in the five-year overall and progression-free survival rate in patients with aggressive pituitary tumors and carcinomas that respond to TMZ<sup>18,19</sup>. TMZ monotherapy is now recommended by the ESE guidelines as the first-line chemotherapy after the failure of standard therapies and following documented tumor growth<sup>2</sup>. However, in the largest series to date, a radiological response was seen in only about 40% of cases treated with a first course of TMZ, with clinically functioning tumors showing a better response to TMZ than the non-functioning ones (the formers were 3.3 times more likely to regress). Moreover, after TMZ was stopped, 25 to 48% of tumors progressed after a median of one year follow-up<sup>20</sup>, and the response to a second course of TMZ was rarely effective<sup>20,21</sup>. Therefore, other treatment options are clearly needed.

Due to insufficient data in the literature, the ESE guidelines only suggest, in patients with rapid tumor growth in whom maximal doses of radiotherapy have not been previously reached, the use of the Stupp protocol<sup>2</sup> (*i.e.*, radiotherapy with concomitant and adjuvant TMZ<sup>22</sup>). However, it is important to note that in glioblastomas, in which the Stupp protocol was first validated (before the Stupp protocol, newly diagnosed glioblastoma was treated by surgical resection, followed by adjuvant radiotherapy), adding to radiotherapy concomitant and adjuvant TMZ resulted in a survival benefit with minimal additional toxicity<sup>22</sup>. In aggressive pituitary tumors and carcinomas, data from the ESE survey on 157 patients treated with TMZ as first-line chemotherapy, of which 14 patients received concomitant radiotherapy, showed that first-line TMZ plus concomitant radiotherapy was associated with an increased response rate (complete or partial radiological response in 71% of the cases) compared to TMZ monotherapy (complete or partial radiological response in 34% of the cases). While the authors state that there were no

evident clinico-pathological differences between these two treatment groups, they also note that the majority of patients treated with first-line TMZ plus concomitant radiotherapy hadn't received radiotherapy previously<sup>20</sup>, and therefore this increase in the response rate may also reflect a selection bias. Nonetheless, TMZ was shown to have radiosensitiser properties *in vitro* and *in vivo*<sup>23</sup>, and in an Italian study in which 27 patients with aggressive pituitary tumor or carcinomas were treated with radiotherapy, the tumor recurred after the last radiotherapy in all but 3 patients who were given TMZ concomitantly with radiotherapy or one month thereafter<sup>24</sup>. In our clinical practice, we tried the Stupp protocol in two patients not previously treated with radiotherapy, and achieved partial response in both cases (a male patient with a prolactinoma described in<sup>25</sup> and a male patient with a silent corticotroph carcinoma). We think that in selected cases of pituitary tumors, the Stupp protocol may represent an option instead of using radiotherapy alone. But doing so not only implies using a Stupp protocol instead of TMZ monotherapy, it also implies using it before the failure of radiotherapy alone. This leads us to a second point, that of using TMZ solely as a "salvage therapy" (*i.e.*, after the failure of all conventional therapies). So far, this is how TMZ was mainly used, and how it is recommended by the ESE guidelines. However, there are several authors who argue that TMZ might have a place earlier in the management of aggressive pituitary tumors<sup>26-28</sup>. As long as the benefits are evaluated to be greater than the risks (the most commonly described side effects of TMZ when used in pituitary tumors were fatigue, nausea/vomiting, and cytopenias, but other side effects including abnormal liver function, headache, hearing loss, edema, hypotension, and adrenal crisis have also been noted<sup>2,20</sup>; in other cancers, although rarely, secondary hematological malignancies have been described<sup>29</sup>), we agree that TMZ might be worth trying earlier in the management of

selected cases, and not only as a salvage therapy, but a stronger level of evidence would be welcomed.

Another point when it comes to TMZ is the duration of treatment. The ESE guidelines recommend that in responders TMZ to be administered for at least 6 months, and that longer duration of treatment should be considered in the case of continued therapeutic benefit<sup>2</sup>. It is not currently known if continuing the treatment for a longer period improves the chances of a sustained remission in responders<sup>2</sup>, but it is known that after stopping TMZ, an important percentage of responders show progressive disease and that the response to a second course of TMZ is poor<sup>20</sup>. On the other hand, an argument in favor of a shorter duration of treatment is the cumulative bone marrow toxicity caused by TMZ, especially that patients with pituitary tumors are more probable long-term survivors<sup>26</sup>. Therefore, prospective studies analyzing the optimal duration of treatment with TMZ would be most welcomed. In our practice, we usually continue TMZ for as long as an anti-tumoral and hormonal effect is observed and the treatment is tolerated. However, we try to decrease TMZ to half-dose after 24 cycles in order to limit the potential cumulative toxicity.

#### **b) Other treatment options**

The main other treatment options have been recently reviewed by our team<sup>30</sup> and involve a limited number of patients: 20 patients treated with peptide receptor radionuclide therapy (PRRT)<sup>28,19,31,20,32-37</sup>, 12 treated with bevacizumab (a vascular endothelial growth factor receptor-targeted therapy)<sup>2,20,38-42</sup>, 10 treated with tyrosine kinase inhibitors<sup>20,43,44</sup>, 6 treated with everolimus (a mammalian target of rapamycin inhibitor)<sup>20,45-47</sup>, and two patients treated with immune checkpoint inhibitors<sup>48,49</sup>. Not enough data is available to draw any definitive

conclusion, but based on the radiological response, the therapies currently showing the most promise are bevacizumab, PRRT, and immune checkpoint inhibitors<sup>30</sup>. Figure 4 shows the radiological response of these 50 patients on the aforementioned treatments<sup>30,49</sup>.

#### **4. Follow-up**

Imaging (usually MRI) and full endocrine evaluation are recommended every 3 to 12 months, depending on the location of the tumor, the previous growth rate and the clinical context. The follow-up should be lifelong, because the acceleration of the growth rate and metastasis may appear many years after the diagnosis of an aggressive pituitary tumor<sup>2</sup>.

The average latency period from the primary diagnosis of a pituitary tumor to metastasis was 9 years in a recent review of 72 cases of pituitary carcinomas. The metastases were most frequently intra-cranial and spinal, followed by liver, cervical lymph nodes and bone metastases (lung, endolymphatic sac, and orbit metastases were rare)<sup>50</sup>. In patients with aggressive pituitary tumors, it is currently recommended to screen for metastases either in case of discordant biochemical and radiological findings (*i.e.*, when hormone levels increase without a corresponding increase in tumor dimension) or in case of site-specific symptoms (neck pain, back pain and/or neurological complaints). In these cases, the guidelines recommend both structural – MRI and CT scans, and/or functional imaging studies – fluorodeoxyglucose (FDG)- and/or Somatostatin receptor (SST)- Positron Emission Tomography (PET)-CT scans, as appropriate. Regarding the treatment of metastases, the same guidelines suggest loco-regional therapies in case of isolated metastases/localized and low metastatic disease burden<sup>2</sup>.

## **Conclusion**

Especially given the rarity of aggressive pituitary tumors and carcinomas, and the scarcity of available data, the ESE guidelines are of tremendous help, providing the clinician with vital guidance in the management of such tumors. However, several important points regarding both diagnosis (how to classify the tumor growth velocity, how to predict an aggressive behavior etc.) and treatment (should TMZ be used earlier in selected cases of aggressive tumors, should a Stupp protocol be sometimes used instead of radiotherapy alone etc.) remain unanswered or only partially answered. Studies on these matters are therefore urgently needed in order to enable evidence-based answers and recommendations, and would be of most help to the patients bearing such tumors and to the clinicians caring for them.

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### **Figure legends**

Figure 1. Prevalence of pituitary adenomas and carcinomas.

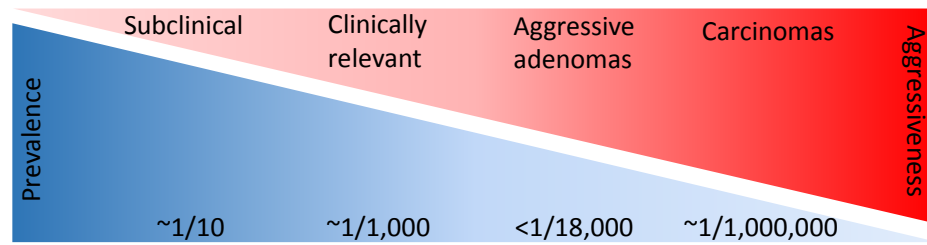
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Figure 2. Radiological follow-up of a slowly growing pituitary tumor, demonstrating the need to compare the last imaging study not only with the penultimate one, but also to older imaging studies in order to evaluate the tumor growth. Top panel: Coronal T2-weighted native MRI sequences. Bottom panel: coronal T1-weighted contrast-enhanced MRI sequences.

Figure 3. Radiological follow-up of a rapidly growing pituitary tumor. Top panel: Coronal T2-weighted native MRI sequences. Bottom panel: coronal T1-weighted contrast-enhanced MRI sequences.

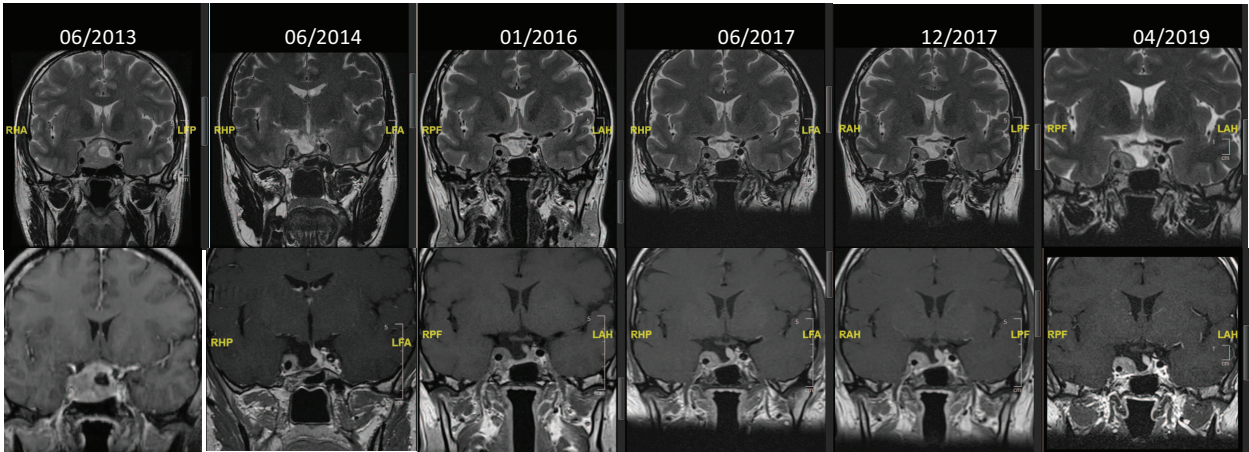
Figure 4. Radiological response of the aggressive pituitary tumors and carcinomas treated so far with peptide receptor radionuclide therapy (PRRT), bevacizumab, tyrosine kinase (TK) inhibitors, everolimus, and immune checkpoint (IC) inhibitors. It should be noted that some of these patients were previously treated with temozolomide, and that in some patients the mentioned treatment was administered concomitantly with other treatments (including temozolomide). Regarding the two cases treated so far with IC inhibitors, partial response was seen in a case of a corticotroph carcinoma treated with combined ipilimumab and nivolumab, while progressive disease in a case of an aggressive corticotroph adenoma treated with pembrolizumab. Complete response = no visible tumor, partial response = >30% decrease in tumor size, stable disease = <10% increase and <30% decrease in tumor size, progressive disease = new metastases or >10% increase in tumor size.

Data from Ilie MD, Lasolle H, Raverot G. Emerging and Novel Treatments for Pituitary Tumors. *J Clin Med.* 2019; 8(8):1107:1-17 and Caccese M, Barbot M, Ceccato F, et al. Rapid disease progression in patient with mismatch-repair deficiency pituitary ACTH-secreting adenoma treated with checkpoint inhibitor pembrolizumab: *Anticancer Drugs.* 2020; 31(2):199-204.



Pre-operative

Post-operative



Pre-operative

Post-operative

