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Burman, P.; Casar-Borota, O.; Perez-Rivas, L.G.; Dekkers, O.M.

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Mini-Review

Aggressive Pituitary Tumors and Pituitary Carcinomas: From Pathology to Treatment

Pia Burman,[1] Olivera Casar-Borota,[2,3] Luis Gustavo Perez-Rivas,[4] and Olaf M. Dekkers[5]

[1]Department of Endocrinology, Skåne University Hospital, Lund University, 205 02 Malmö, Sweden
[2]Department of Immunology, Genetics, and Pathology; Uppsala University, 751 85 Uppsala, Sweden
[3]Department of Clinical Pathology, Uppsala University Hospital, 751 85 Uppsala, Sweden
[4]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ludwig-Maximilians-Universität München, 80804 Munich, Germany
[5]Department of Internal Medicine (Section of Endocrinology & Clinical Epidemiology), Leiden University Medical Centre, 2333 ZA Leiden, The Netherlands

Correspondence: Pia Burman, MD, PhD, Associate Professor, Department of Endocrinology, Skåne University Hospital, Lund University, Jan Waldenströms gata 24, 205 02 Malmö, Sweden. Email: pia.burman@med.lu.se.

Abstract

Aggressive pituitary tumors (APTs) and pituitary carcinomas (PCs) are heterogeneous with regard to clinical presentation, proliferative markers, clinical course, and response to therapy. Half of them show an aggressive course only many years after the first apparently benign presentation. APTs and PCs share several properties, but a Ki67 index greater than or equal to 10% and extensive p53 expression are more prevalent in PCs. Mutations in *TP53* and *ATRX* are the most common genetic alterations; their detection might be of value for early identification of aggressiveness.

Treatment requires a multimodal approach including surgery, radiotherapy, and drugs. Temozolomide is the recommended first-line chemotherapy, with response rates of about 40%. Immune checkpoint inhibitors have emerged as second-line treatment in PCs, with currently no evidence for a superior effect of dual therapy compared to monotherapy with PD-1 blockers. Bevacizumab has resulted in partial response (PR) in few patients; tyrosine kinase inhibitors and everolimus have generally not been useful. The effect of peptide receptor radionuclide therapy is limited as well.

Management of APT/PC is challenging and should be discussed within an expert team with consideration of clinical and pathological findings, age, and general condition of the patient. Considering that APT/PCs are rare, new therapies should preferably be evaluated in shared standardized protocols. Prognostic and predictive markers to guide treatment decisions are needed and are the scope of ongoing research.

Key Words: Ki67- index, TP53, ATRX, temozolomide, immunotherapy, bevacizumab, PRRT

Abbreviations: 5-FU, 5-fluorouracil; ACTH, adrenocorticotropin; APT, aggressive pituitary tumor; CAPTEM, capecitabine and temozolomide; CNS, central nervous system; CR, complete response; CT, computed tomography; ESE, European Society of Endocrinology; GH, growth hormone; HPF, high-power field; ICI, immune checkpoint inhibition; IHC, immunohistochemistry; MGMT, O^6-methylguanine-DNA methyltransferase; MMR, DNA mismatch repair; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin; NET, neuroendocrine tumor; PC, pituitary carcinoma; PD, progressive disease; PET, positron emission tomography; PitNET, pituitary neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; PR, partial response; PRL, prolactin; RT, radiotherapy; SCT, silent corticotroph tumor; SD, stable disease; TKI, tyrosine kinase inhibitor; TMZ, temozolomide; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

When to Suspect an Aggressive Pituitary Tumor?

- Corticotroph invasive macroadenomas, especially in men
- Macro/giant prolactinomas initially not responding to high doses of cabergoline, or losing sensitivity to dopamine agonists
- Somatotroph invasive macroadenomas progressing on treatment with somatostatin analogues
- Nonfunctioning invasive macroadenomas switching to functioning tumors, especially silent corticotroph tumors (SCTs) becoming adrenocorticotropin (ACTH) secreting
- Rapid relapse/progression after surgical removal
- Tumors progressing after radiotherapy (RT)
- Tumors with high proliferative markers (eg, Ki67 > 10% and/or high mitototic count) and extensive p53 expression
- Tumors harboring *TP53* or *ATRX* mutations

Pituitary tumors typically grow slowly and can be controlled by surgery and/or standard medical therapies; RT may be needed to arrest tumor growth. These tumors are generally considered clinically benign. A small subset (1), demonstrates progressive/recurrent tumor growth not controlled by repeat surgery, RT, and/or medical therapy (dopamine agonists, somatostatin analogues). They are here referred to as aggressive pituitary tumors (APTs) (2). Pituitary carcinomas (PCs) are defined by the presence of metastases, within or outside the central nervous system (CNS), and are also denominated metastatic pituitary neuroendocrine tumors (PitNETs) (3). In this review, we discuss the epidemiology, the clinical and pathological characteristics, known genetic aberrations, the treatment options and the prognosis in patients with APT/PC.

Epidemiology

In studies from nontreated nonfunctioning pituitary tumors, growth is reported in 1 out of 5 patients (1). In line, 10 years after surgical treatment up to 50% of the tumors showed signs of regrowth (4). Moreover, 13% of patients show signs of a

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second radiological regrowth even after surgery and RT (5). These numbers show that growth is not a rare feature in clinically benign pituitary tumors; however, the vast majority do not display a course that fulfills the criteria for APT or PC. The incidence of PC is around 0.1% to 0.5% (6-8), APT being 2 to 3 times more common than PC (1, 6). However, the exact incidence of APT is not well established for 3 reasons: lack of a uniform definition, APTs are often not reported separately in studies on pituitary adenomas, and different published series have different inclusion criteria, which hampers the epidemiological picture. Rough estimation suggest that less than 1% of all macroadenomas will display a truly aggressive course (1). It has to be acknowledged that if 2b tumors (eg, invasive and proliferative) are considered as APTs as well, reported incidences are clearly higher (7).

Clinical Characteristics at First Presentation (Size, Invasion, Tumor Subtype)

APTs/PCs most often affect patients in their mid-40s (median age 45; range, 3-79 years at diagnosis) (6, 8). Overall, 60% are men, with exception of the growth hormone (GH)-secreting subtype, which seems more (8), or at least equally common, in women (9). Invasion into the cavernous sinus and/or erosion of the clivus or sellar floor was observed in 80% of the 121 APTs and 50 PCs reported to the second European Society of Endocrinology (ESE) survey (8). Twenty-two percent of all tumors were giant (≥ 4 cm in diameter), 75% macroadenomas, and only a small proportion, mostly ACTH-secreting tumors, presented as microadenomas (8). In clinically benign lactotroph tumors, the proportion of giant tumors is estimated to be 2% to 4% (10) but among the aggressive lactotroph tumors the giants accounted for 34% (8). Most giant lactotroph tumors respond to treatment with dopamine agonists. In a study of 84 giant lactotroph tumors reported to the Swedish Pituitary Registry in 1991 to 2018, 2 demonstrated an aggressive course over a median 8.7 years (G Himonakos, personal communication).

Compared to benign pituitary tumors, the ACTH-secreting subtype is overrepresented in APTs/PCs (8, 11-14) (Fig. 1). Gonadotroph tumors account for approximately 66% of pituitary tumors in surgical series (15) but only 5% to 33% in the largest series of APTs/PCs, indicating that this subtype is less prone to become aggressive (8) (see Fig. 1).

Clinical Course

APTs/PCs display a highly variable course. More than half of them follow an aggressive path from the outset, whereas others present as clinically benign and subsequently develop aggressive features, as illustrated in Fig. 2. In the ESE survey (8) a shift from an apparent clinically benign to an aggressive course was observed after a median 5.5 years from diagnosis (Fig. 3). Whether such changes represent de novo transformation to a malignant tumor, or results from slow progression of a tumor predisposed to aggressive behavior, is the subject of debate.

Dedifferentiation with loss of hormone secretion is uncommon in APTs/PCs, while an apparent gain in function occurs. Such examples are the evolution of a dopamine-sensitive lactotroph microadenoma into a giant GH-secreting APT harboring a *GNAS* gene mutation (16), cosecretion of GH occurring in parallel with rapid growth of a lactotroph APT, and cosecretion/overt secretion of GH coinciding with the appearance of metastases in a lactotroph and a somatotroph PC (17).

Benign nonfunctioning tumors occasionally shift to hormone-secreting tumors. This occurs in about 5% of SCTs (18-20) but rarely in silent somatotroph tumors (21). In 4 initially benign SCTs, tumor expression of prohormone convertase 1/3, which converts proopiomelanocortin to ACTH, was higher after having become functioning (19). This phenomenon seems more common in APT/PC (6, 8) and was observed in 5 of 13 SCTs and 2 of 6 silent somatotroph tumors (8). Thus, a change from a silent to functioning state may occur in concert with aggressiveness, and should alert the clinician.

Pituitary Carcinomas

Metastatic spread usually affects only the CNS (brain, spinal cord, dura, leptomeninges) or both CNS and distant organs, such as the skeleton and liver, less often the lungs, and cervical lymph nodes (8, 22, 23). ACTH- and prolactin-secreting tumors seem to more often disseminate to liver and bone (8), and the GH-secreting and nonfunctioning tumors to the CNS (9, 24). Metastases are usually detected 1) during workup of increasing hormone levels without corresponding size increase of the pituitary tumor (Fig. 4); 2) because of symptoms, such as back pain or local compression causing neurological symptoms; and 3) at regular scheduled pituitary imaging (brain lesions) (8). The median time to detection of metastases after pituitary tumor diagnosis is 5 to 9 years (range, 0.5-34 years) (8, 11, 23, 25-27). To our knowledge there are no reports on metastatic lesions preceding the diagnosis of the pituitary tumor.

For detection of metastatic disease computed tomography (CT), magnetic resonance imaging (MRI), and/or functional imaging (positron emission tomography [PET]/CT) is recommended (2). ^{18}F-FDG PET and ^{68}Ga-DOTATATE/^{68}Ga-DOTATOC-PET reflect 2 different aspects of tumor biology: glucose metabolism and somatostatin receptor expression. Overall, FDG-PET seems the most sensitive approach to detect aggressive, highly proliferative neuroendocrine tumors (NETs) (28). ^{18}F-FDG–negative NETs may later become ^{18}F-FDG positive, indicating disease progression (28). There is little information regarding the functional imaging method of choice in PCs. In 3 PCs for which both methods were used, the metastatic lesions had more intense uptakes of ^{18}F-FDG than of ^{68}Ga-DOTATATE in 1 patient (29), and vice versa in the other 2 (30, 31).

Differential Diagnoses—Pituitary Metastases

Metastases to the pituitary gland most commonly originate from breast carcinomas, especially HER2-positive subtypes, and lung carcinomas (32). The lesions usually present in the late stage of cancer but may occur early as single deposits, and even precede discovery of the primary tumor (32, 33). Metastases are mostly located within the sella and the suprasellar region. Unlike primary pituitary tumors, they often extend along the pituitary stalk, displaying an asymmetrical, lobular pattern or a dumbbell shape, although some can be indistinguishable from pituitary tumors on imaging (32). A broad immunohistochemical panel including staining for serotonin, CDX2 (34-36), TTF1 (37), and other organ-

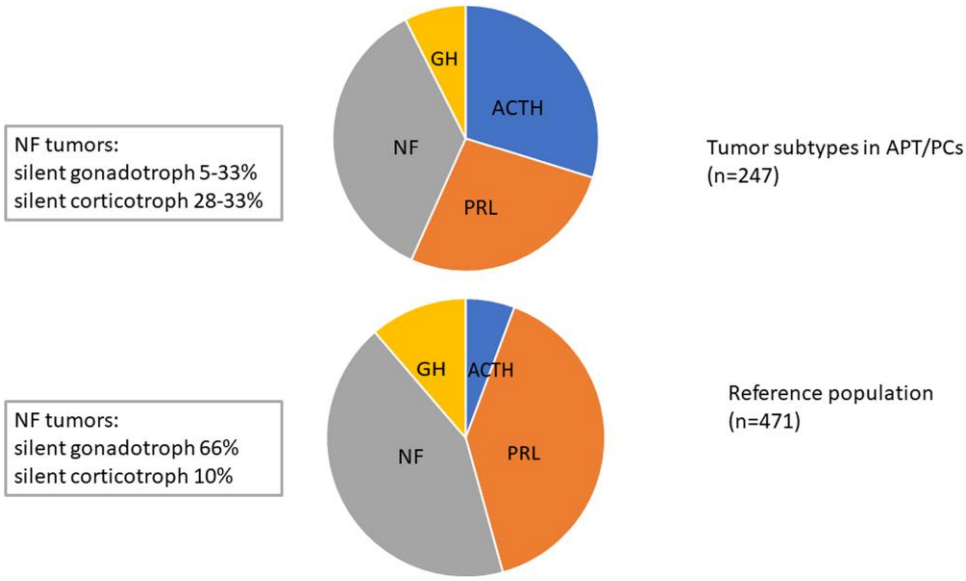

Figure 1. Proportion of tumor subtypes according to hormone secretion in 247 patients with aggressive pituitary tumors (47 PC) in comparison with a reference population. Combined data on APT/PC from the 2 European Society of Endocrinology surveys (6, 8). The reference population from a national study of the prevalence of pituitary tumors (13) and of nonfunctioning pituitary tumors in a surgical series (15).

specific markers is required when diagnosing rare sellar NETs fulfilling criteria of "null-cell adenoma" (negative for adenohypophyseal hormones and/or pituitary-specific transcription factors) (35-38), as illustrated in Fig. 5. Exceptionally, a sudden onset of rapid growth and/or apoplexy caused by a metastasis in a preexisting pituitary adenoma occurs (32, 39).

Proliferative Markers and p53 Immunoexpression in Aggressive Pituitary Tumor/Pituitary Carcinoma

The 2004 World Health Organization (WHO) classification of pituitary tumors introduced the concept "atypical pituitary adenomas" for tumors with uncertain malignant potential (40). "Atypical adenomas" were imprecisely defined by "increased" mitotic activity in combination with Ki67 index of 3% or greater, and/or "extensive" expression of p53. The reported incidence in surgical series ranges from 3% to 18% (41-43).The concept has been abandoned as its prognostic value was not established. Neither the previous (38) nor the current WHO classification of pituitary gland tumors (3) provides cutoff values for Ki67 index or mitotic activity. However, radiologically and/or histopathologically confirmed tumor invasion has emerged as a prognostic factor (3, 7, 38). Certain tumor types, such as lactotroph tumors in men, SCTs, sparsely granulated somatotroph tumors, Crooke cell tumor, and immature plurihormonal PIT1 tumors, are considered "high-risk adenomas" with potentially increased risk for recurrence and invasive growth (3, 38). The first 2 tumor types were overrepresented among APT/PCs in the ESE survey cohort compared to the general picture of pituitary adenomas (see Fig. 1).

The prognostic value of the Ki67 proliferative index in PitNETs remains controversial. PitNETs with a high Ki67 index (> 10%) often demonstrate invasiveness and aggressiveness. In a cohort of 365 unselected pituitary tumors, 3% had Ki67 of 10% or greater (44) compared with 41% in APTs and 61% in PCs in the large ESE surveys (Fig. 6). However, low Ki67 does not exclude the possibility of aggressive behavior and metastatic potential. Although the current WHO classification (3) does not define a mitotic count associated with increased growth potential, the presence of more than 2 mitoses/10 high-power fields (HPFs) rarely occurs in benign pituitary tumors (2, 44).

TP53 is a tumor-suppressor gene and one of the most frequently mutated genes in cancer. Mutations are usually accompanied by high nuclear expression of the encoded p53 protein due to decreased protein degradation, but may also result in partial or complete absence of the protein (45). *TP53* gene mutations may be suspected if a substantial proportion of tumor cells express the protein, but the extent of p53 immunoexpression that could serve as a surrogate marker in APT/PC remains to be defined. In acute myeloid leukemia a threshold of 7% or greater strongly stained cells correlated with the presence of *TP53* mutations (46), whereas in ovarian carcinomas staining of 60% or more cells was indicative of a *TP53* mutation (47). In high-grade gastroenteropancreatic neuroendocrine carcinomas, the cutoff was more than 10% positive cells (48); however, deletions, early frameshifts, or truncating mutations may be inaccurately considered as wild-type phenotype by immunohistochemistry (IHC) (45, 47) Taken together, DNA sequencing analysis is the only reliable method to explore *TP53* mutational status.

Genetic Alterations in Aggressive Pituitary Tumor/Pituitary Carcinoma

TP53 and *ATRX* (alpha thalassemia/mental retardation syndrome, X-linked) are the most consistently altered genes detected in APT/PC. Until recently, somatic *TP53* mutations were described in only 5 APTs/PCs (49-52). Several recent publications have reported that *TP53* mutations are frequent in corticotroph APTs/PCs, to a lesser extent in aggressive tumors of Pit-1 lineage (53-58). In a study examining *TP53* status in 86 corticotroph tumors (including 24 APTs), mutations

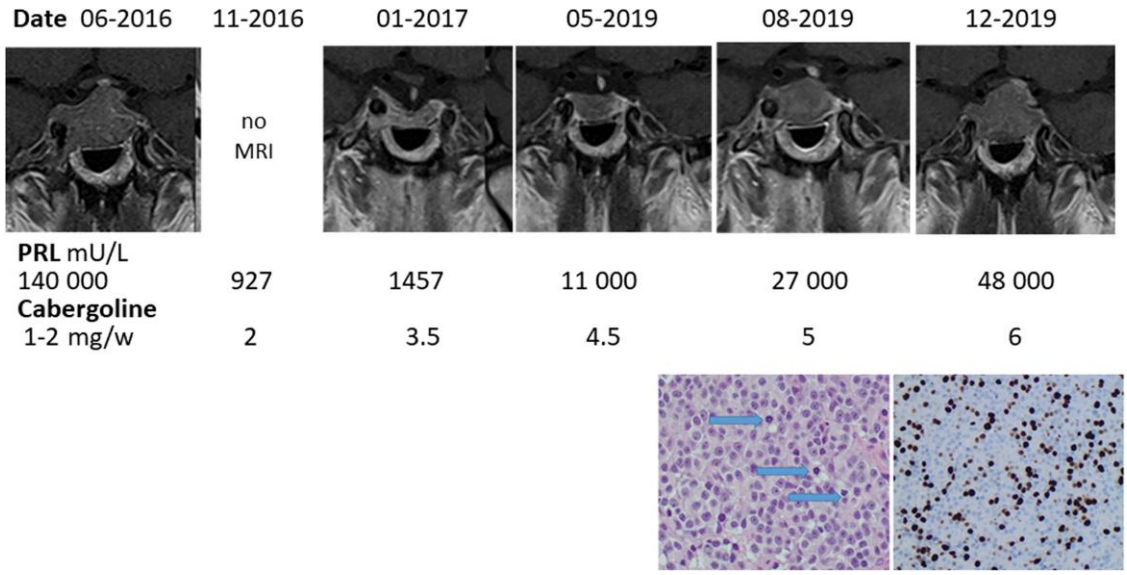

Figure 2. A 74-year-old man with an invasive lactotroph macroadenoma and high prolactin (PRL) levels responding to cabergoline. Subsequently, the tumor changed its behavior and progressed despite increasing doses of cabergoline. After developing headache and ophthalmoplegia, the patient was referred to our clinic for pituitary surgery. Upper, Response to cabergoline (mg/wk) over time, imaging and PRL levels (mU/L). Lower, Pathology showed a highly proliferative tumor. (Left) mitotic count 41/10 high-power magnification fields (reference ≤ 2); mitoses, arrows, (right) Ki67 30% (reference < 3%).

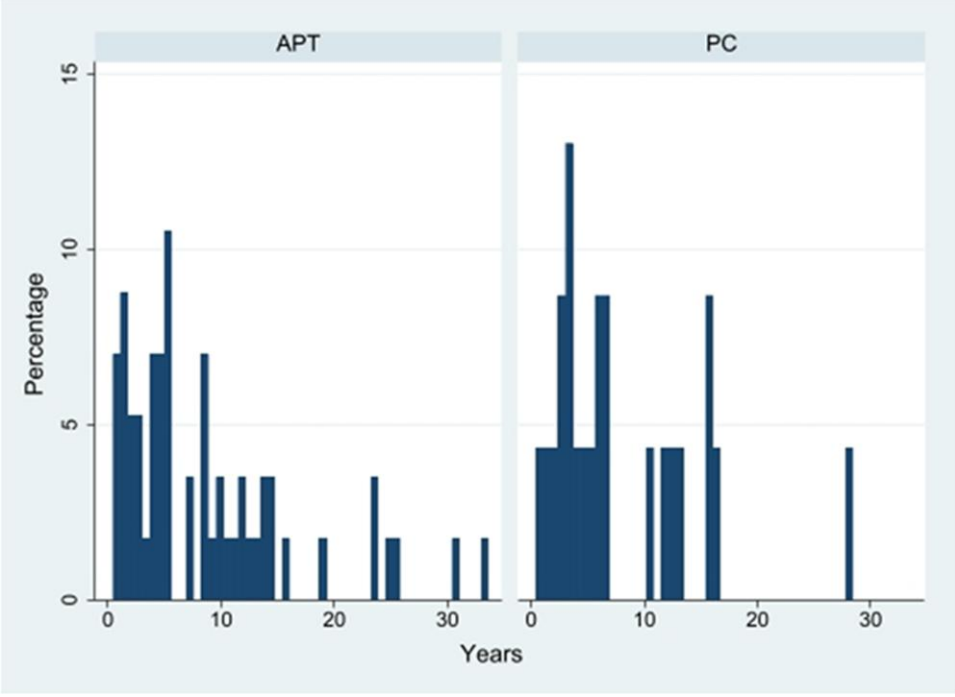

Figure 3. Time from diagnosis to clinically aggressive behavior in 97 patients with APT/PC. Data from (8).

were found in 9 cases and linked to more aggressive features and worse outcome (55). *ATRX* mutation with a lack of *ATRX* immunolabeling was first described in a patient with a corticotroph carcinoma, but was not found in a large cohort of PitNETs (34). Subsequent IHC screening of 48 aggressive PitNETs (18 PCs) revealed a lack of immunolabeling in 9 tumors (53), 7 of 22 corticotrophs, and 2 of 24 of the Pit1 lineage. Loss-of-function *ATRX* gene alterations of different types were confirmed in all 9 *ATRX*-immunonegative tumors. The mutations were more frequent in PCs vs APTs: 5 of 18 vs 4 of 30. It is worth noting the coexistence of *TP53* and *ATRX* alterations in 6 of the tumors (53), as well as in 5 other APT/PC cases in the literature (57, 59-61). The detection of concomitant *PTEN*, *TP53* and/or *ATRX* alterations, or *TP53* and *DAXX* mutations (54, 58, 61, 62, 63; Supplementary Table S2), emphasizes the role of p53, ATRX/DAXX, and

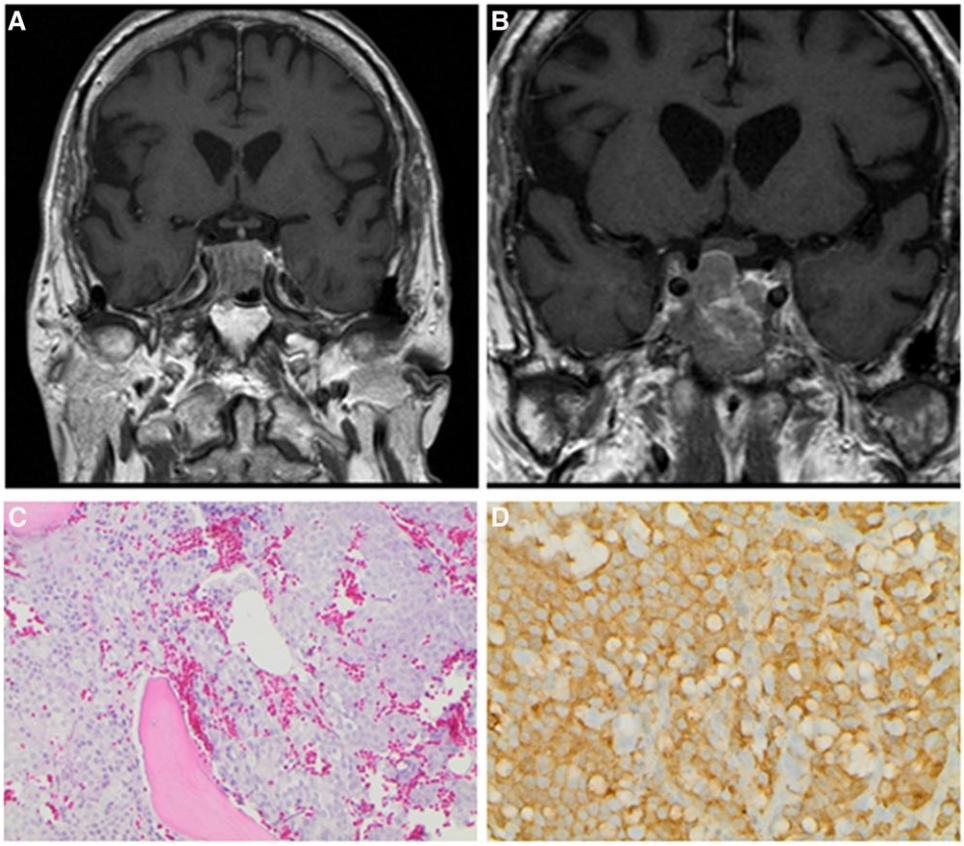

Figure 4. A, A 63-year-old man diagnosed 2007 with Cushing syndrome, UFC 5.4 × ULN, adrenocorticotropin (ACTH) 16 (reference < 10 pmol/L), and an invasive macroadenoma (Ki67 1%, focally 5%-7%, no "atypical" features). B, The tumor 4 years later (Ki67 5%-6%) after 3 pituitary surgeries, radiotherapy, and adrenalectomy. During the last year, ACTH was reported as above the upper level of assay measurement (> 400 pmol/L). The patient developed anemia and was referred to the university hospital. ACTH was 15 060 pmol/L after dilution of the serum; a bone marrow biopsy showed widespread infiltration of tumor cells (C, hematoxylin-eosin, magnification 200×) staining for ACTH (D, ACTH, 400×).

mechanistic target of rapamycin (mTOR) pathways in the pathogenesis of APTs/PCs.

Analysis of serial samples from individual patients revealed *TP53* or *ATRX* mutations already at the first surgery (50, 53, 55, 58), suggesting that molecular events predisposing for malignant behavior in PitNETs occur early during tumorigenesis. Next-generation sequencing studies have demonstrated high variant allele fractions for most *TP53* and *ATRX* mutations (53, 54, 57, 58), which supports a clonal origin of those alterations. Thus, *TP53* and *ATRX* may act as tumorigenesis drivers, and could be useful biomarkers for early identification of patients at higher risk for developing APT and PC (Fig. 7).

USP8 is the most frequently altered gene in corticotroph tumors (62-64). Although *USP8* mutations are common in non-APT (65-68), they have been detected in a few APT/PC cases as well (55, 58, 69). *USP8* and *TP53* mutations are mutually exclusive (55, 58) and may define 2 different molecular corticotroph tumor entities. *SF3B1* is, so far, the only recurrently mutated gene in lactotroph tumors (70), including few APTs and 1 PC (70, 71), and has been associated with shorter disease-free survival (70).

Several other genes have been reported in small series or in isolated APT/PC cases; these are listed in the Supplementary Table S1 (72). They are either equally identified in non-APT, appear in combination with *TP53*, *ATRX*, or *SF3B1* variants, or are extremely rarely reported. Finally, some authors have investigated the association between chromosomal rearrangements and aggressive features in pituitary tumors. Genomic rearrangements seem not to be specific for recurrence or aggressiveness (65), but rather of tumor type (65, 73). In children with Cushing disease, chromosomal instability is associated with larger, invasive tumors (74). In adults, a higher degree of aneuploidy, copy number variation, and microsatellite instability was observed in *TP53* mutant corticotrophs (58), while losses of chromosome regions 1q and 11p were linked to recurrence in nonfunctioning, and aggressiveness in lactotroph tumors, respectively (75, 76).

Standard Therapeutic Options (Surgery, Radiotherapy, Medical Therapy)

APT/PC patients mostly undergo multiple surgical procedures (6, 8, 26). While repeat surgery may be necessary for decompression of the optic chiasm, the potential benefit of subtotal resections must be weighed against the risks, especially damage to the surrounding brain/nerve tissues. In PC patients with single or few metastases, gross total resection or debulking of the lesions seem reasonable.

In the ESE surveys, about 90% of patients treated with temozolomide (TMZ) had received RT earlier in the disease course (6, 8). Of 143 patients treated with RT, 45% had tumor regression, but all tumors progressed later on. A second RT was given to 55 patients after a median time of 5.4 years, and resulted in a similar response (8). The benefit of RT

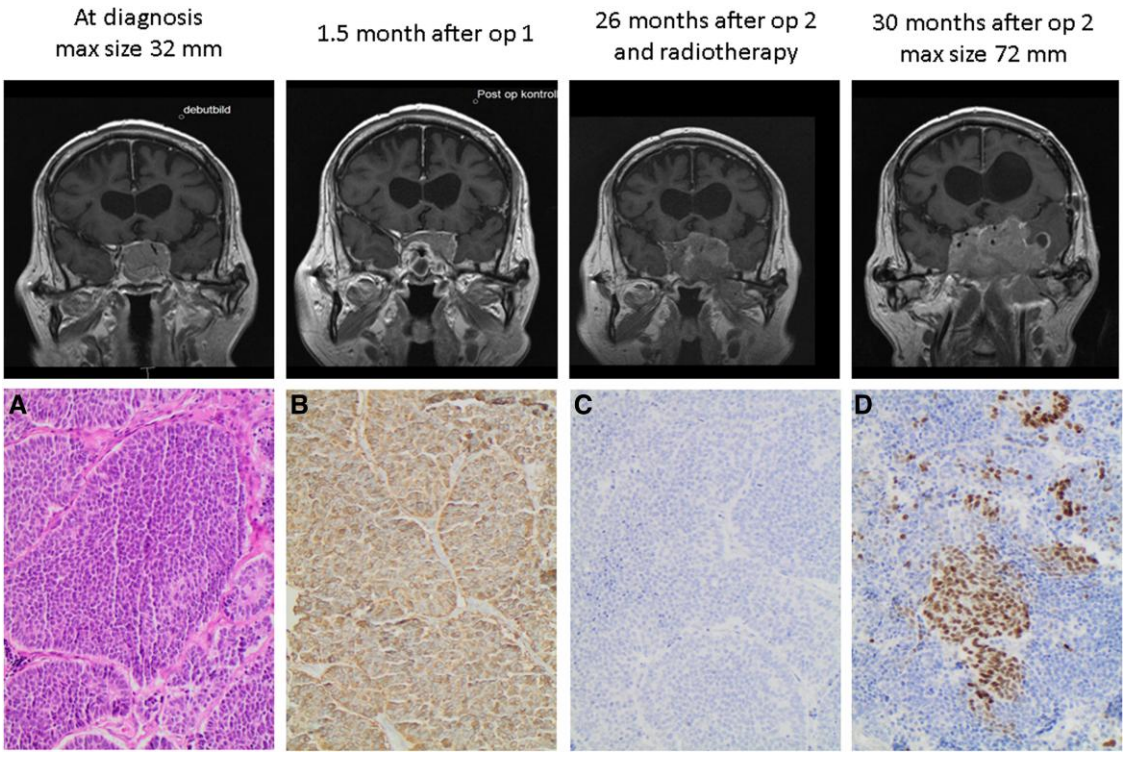

Figure 5. A 61-year-man was referred in 2010 because of panhypopituitarism (not diabetes insipidus). Upper, Pituitary imaging showed a macroadenoma, largest diameter 32 mm. Histopathology was compatible with hormone-negative pituitary adenoma. A, Hematoxylin-eosin staining, and B, chromogranin A was expressed; staining for pituitary transcription factors could not be performed at that time. The tumor was not controlled by 2 surgeries and radiotherapy. Temozolomide had no effect. Octreotide scintigraphy showed strong uptake in the pituitary tumor, not elsewhere. Treatment with octreotide led to relief of headache but the tumor continued to grow; the largest diameter increased to 72 mm 2.5 years after diagnosis. ^{177}Lu DOTATATE was given but the patient died shortly afterwards. At reexamination of the tumor, pituitary transcription factors (Pit-1, TPIT, SF-1) were negative (T-PIT staining presented in C). D, A subset of the tumor cells spread throughout the tumor stained for CDX2, suggesting that the tumor represents a metastasis from another neuroendocrine tumor, in the first place from the gastrointestinal tract, although other primary locations cannot be excluded (34, 35). At reevaluation of the octreotide scintigraphy, there was a faint uptake in the right pulmonary hilus, possibly a lymph node metastasis. All microphotographs taken at 200× magnification.

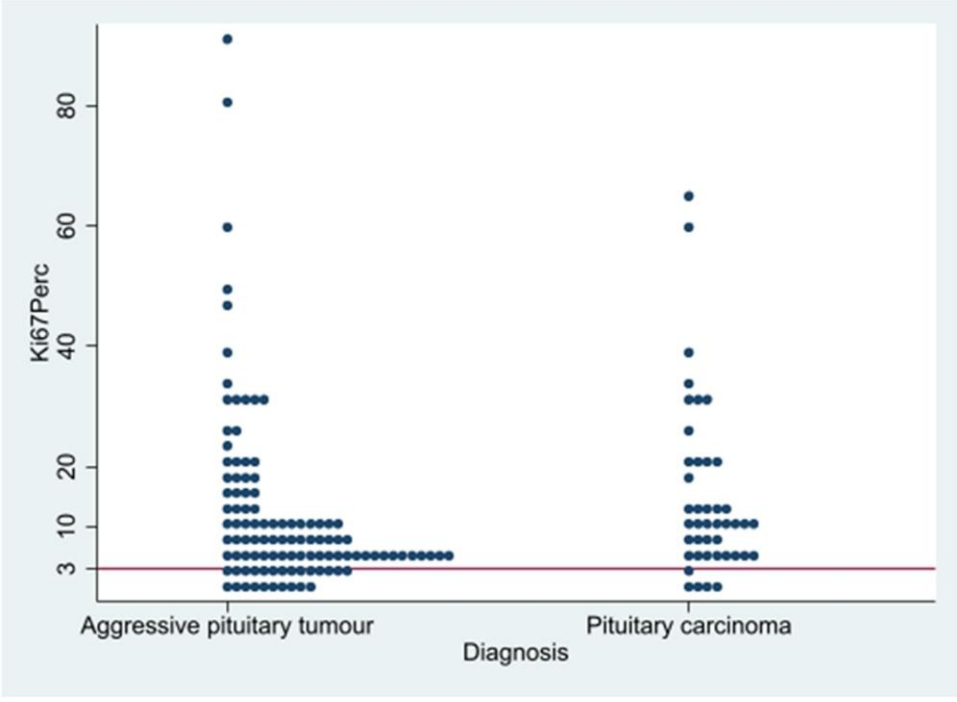

Figure 6. Ki67 indices at first surgery in 150 patients with aggressive pituitary tumors. Combined data from the 2 European Society of Endocrinology surveys (6, 8).

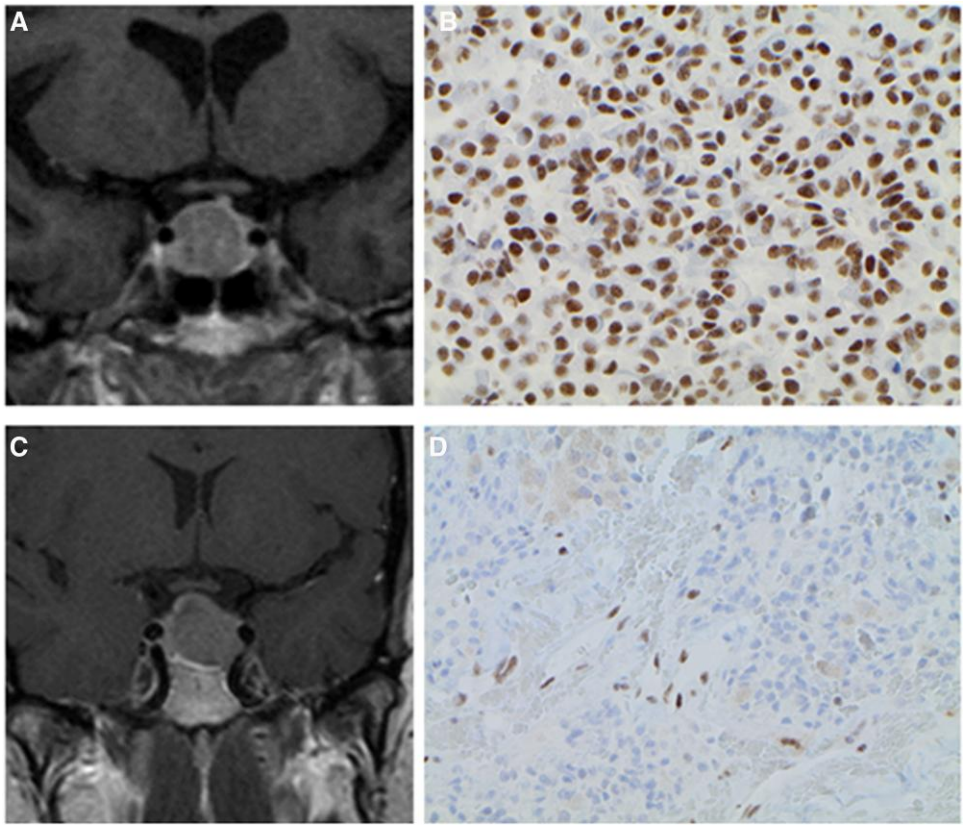

Figure 7. Evolution of corticotroph tumors in 2 women with initially similar features but different *ATRX* status: a 33-year-old woman, 3 op + radiotherapy (RT). At the first op KI67 was 2.5%, mitotic count less than 2/10 high-power field (HPF), p53 neg. A, Magnetic resonance imaging (MRI) and B, immunohistochemistry with positive ATRX staining (retained expression) in the tumor cells. At follow-up 10 years later she seems cured. A 38-year-old woman, 3 op + RT + bilateral adrenalectomy. C, MRI of the pituitary tumor at diagnosis. At first op Ki67 was less than 1%, in a hot spot 7%, mitotic count less than 2/10 HPF, p53 neg. D, immunohistochemistry was negative for ATRX (loss of expression) in the tumor cells. Metastases were confirmed 7 years after the first surgery. Both microphotographs taken at 400× magnification. Illustrations for the ATRX-negative case, lower row, are provided by courtesy of Dr Britt Edén Engström, Uppsala University Hospital, Uppsala, Sweden.

outweighs the long-term risk of severe side effects, such as stroke (77) and second brain tumors (78). In patients with PC, locoregional RT of metastases with or without concurrent chemotherapy can be useful for controlling local disease (79).

As regards medical therapy, dopamine agonists and somatostatin analogues may reduce hormone secretion. In case of severe headache, octreotide may offer pain relief in spite of not causing tumor regression (P.B. unpublished). In patients with hypercortisolism, adrenal glucocorticoid inhibitors should be used to ameliorate the catabolic state and decrease thrombosis risk and the risk of opportunistic infections. Bilateral adrenalectomy has often been required to control hypercortisolism. This procedure is known to promote growth of the corticotroph tumor in about 40% of patients with Cushing disease (80). It is conceivable that aggressive corticotroph tumors could be more prone to progress, but this has not been established and should be weighed against the detrimental effects of glucocorticoid excess (8).

Temozolomide–Mechanism of Action

TMZ is an oral alkylating drug with good penetration into the brain and acts by attaching a methyl group to guanine bases. The modified guanine base is misread as adenine and paired with thymine during the DNA replication (81). The mispairing triggers the DNA mismatch repair system (MMR), resulting in energy-consuming cycles with thymine excision, replacements by cytosine, and reinsertions of thymine until thymine is depleted (82). This ultimately causes double-strand breaks in the genome, which stimulates apoptosis. The tumoricidal effect of TMZ can be counteracted by O^6-methylguanine DNA methyl-transferase (MGMT), a DNA repair enzyme, which, by removal of the O^6-methyl group, restores the guanine base to its native form (81). MGMT is consumed during this process and requires de novo synthesis for replenishment. Therefore, low tumoral content, usually defined as less than or equal to 10% immunolabeled nuclei, seems beneficial for a drug effect; conversely, high MGMT content may confer resistance to TMZ.

Effects of Temozolomide in Aggressive Pituitary Tumor/Pituitary Carcinoma

An effect of TMZ in APT/PC was first published in 2006 (83-85), followed by small series reporting tumor regression in 38% to 69% of patients (12, 17, 86, 87). A treatment effect is usually observed after 3 to 6 months. The biochemical response may precede the radiological response and is often more marked (2, 17).

TMZ monotherapy is recommended as first-line chemotherapy in the management of APT/PC (2). In the first ESE survey, the overall response rate (complete response [CR] or

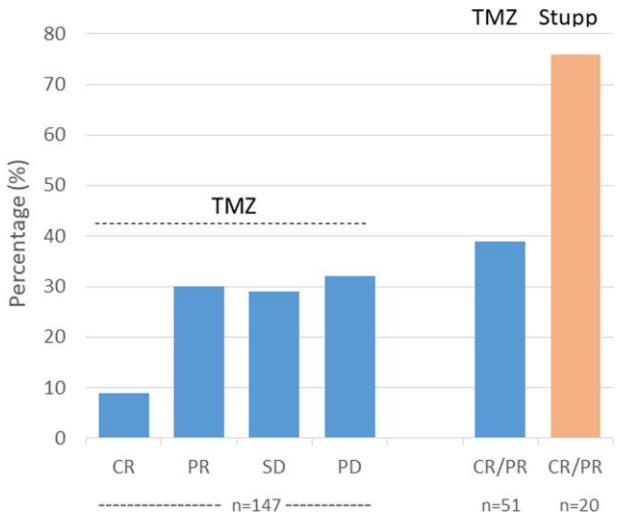

Figure 8. Outcome of temozolomide (TMZ) monotherapy and of TMZ concurrent with radiotherapy (Stupp). CR, complete regression; PD, progressive disease; PR, partial regression; SD, stable disease. Data on TMZ monotherapy (8) and on the Stupp protocol (6, 8).

Table 1. Experience of a second course of temozolomide in 37 patients with aggressive pituitary tumor/pituitary carcinoma

Effect of 1st TMZ	Time to rechallenge after stop of 1st TMZ, mo	Effect of 2nd TMZ
CR, n = 3	Median 96	PR
CR, n = 2	30, 3	SD (on 24 and 12 cycles, in 1 case CAPTEM)
PR, n = 4	Median 31	PR
PR, n = 5	Median 24	SD (on 3, 3, 10, 12, and 1 ongoing cycles)
PR, n = 7	Median 12	PD
SD, n = 2	12, unk	PR
SD, n = 4	Unk	SD (on 3,12, 20, 26 cycles)
SD, n = 6	Median 6.5	PD
PD, n = 1	Unk	SD (on 10 cycles)
PD, n = 3	Unk	PD (in 1 case CAPTEM)

Table is based on references (6, 8, 89, 109-111).
Abbreviations: CAPTEM, capecitabine and temozolomide; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TMZ, temozolomide; Unk, unknown.

≥ 30% regression) was 37% in 156 patients; 33% had stable disease, and in 30% the tumors progressed (6). In the second survey, 40% achieved radiological response (Fig. 8) with similar effects in APTs and PCs (8). Eventually most tumors will progress, but sustained treatment effects for 5 to 11 years have been reported (6, 88, 89). In the second ESE survey the mean time between TMZ discontinuation to the next therapeutic intervention of any kind (new surgery, RT, alternative medications) was 6.4 years after CR, 3.3 years after partial response (PR), and 1.4 years, in patients who had stable disease (SD) during the first course of TMZ (8).

Is There a Case for Earlier Use of Temozolomide in Aggressive Pituitary Tumor?

TMZ may be considered before RT, or, in select cases, even before reoperation (88, 90-92). An example could be a young patient with an aggressive, dopamine agonist–resistant giant lactotroph tumor threatening the vision. The more rapid onset of the TMZ effect compared to RT could argue for a 3-month trial of TMZ in such a case. Moreover, RT of the brain may impair cognitive functions (93), with the brain in children being especially vulnerable (94). In giant tumors, focused RT is often not an option and the total irradiated volume can be large. The higher risk of surgical complications in large multilobulated tumors must also be taken into account.

Can the Response to Temozolomide Be Predicted?

O^6-Methylguanine DNA Methyl-Transferase

In glioblastomas, epigenetic silencing of *MGMT* by methylation of the promoter region is associated with a better response to TMZ and better survival (95-97). In contrast, the prognostic significance of MGMT expression determined by IHC remains controversial. In one study of glioblastomas there was a good correlation between *MGMT* promoter status and MGMT protein expression (98), but in APT/PC (99, 100), as well as in another series of glioblastomas (101), the 2 methods were not in agreement, partly because of interobserver variations with IHC (101).

The clinical value of measuring MGMT before commencing TMZ in APT/PC was recently discussed (92). Inconsistent results with antibodies toward MGMT hamper the use of IHC in routine diagnostic work. Overall, APTs/PCs with low MGMT respond better (17, 99, 102-105). Complete tumor regression has been achieved only in tumors with low content, but there are examples of PRs in tumors with intermediate or even high MGMT levels. On the other hand, not all tumors with low levels respond well, and currently a treatment trial of 3 months regardless of MGMT status is considered reasonable (2).

DNA Mismatch Repair System

Low expression of MSH2 and MSH6, 2 MMR proteins, can promote pituitary tumor growth (106). MMR-deficient cells are 100-fold less sensitive to methylating drugs like TMZ (107). This finding is supported by the poor response to TMZ in malignant brain tumors harboring *MSH6* mutations (108), and by escape from the TMZ effect concomitantly with loss of MSH6 expression in an aggressive lactotroph tumor (50). Somatic MMR gene mutations seem uncommon in APTs/PCs naive to TMZ treatment. It is expected that optimized methodology of MGMT detection will improve the use of MGMT status in guiding treatment decisions.

When to Discontinue Treatment?

TMZ is recommended to be discontinued if radiological progression is demonstrated after 3 cycles (2). In responding cases, the ESE guideline proposes to continue treatment for at least 6 months with consideration for longer duration if continued benefit is observed. Since the safety profile is good, one could argue for continuing TMZ until no further decrease in hormone levels/tumor size is observed. A second course of TMZ is generally less effective than the first one, but could be tried in case of a good response to the first course and a late relapse/progression after discontinuation of TMZ (6, 8, 89, 109-111) (Table 1).

Table 2. Experience of treatment with capecitabine and temozolomide in 20 patients with aggressive pituitary tumor/pituitary carcinoma

Tumor (reference)	MGMT IHC	CAPTEM cycles	Outcome	Adverse events
APT, ACTH (117)	Low (< 15%)	30	SD for 2 y	Thrombocytopenia grade 3
APT, ACTH (117)	Low (< 15%)	16	CR at 10 cycles	Lymphopenia grade 3
APT, SCA (117)	Low (< 15%)	27	CR	Lymphopenia grade 2
PC, SCA (118)	Weak	12 + 7 at progression	PR PR	—
APT, SCA (118)	Weak (low)	12	PR	Nausea
APT, PRL (119)	40% weak	10	CR	
PC, ACTH (17)	0%-60%	TMZ only 5, CAPTEM 3	Initial PR—PD PD	—
APT, PRL (119)	50% strong	TMZ only 5, then op → CAPTEM 10	PD SD	Hand-foot syndrome
APT, GH (120)	> 50%	CAPTEM 3	PR	
PC, ACTH (17)	95%	TMZ alone 7, CAPTEM 4	PD PD	—
APT, ACTH (123)	NR	4	PR after 2 cycles, then PD	—
APT, ACTH (124)	NR	4	Stable 8 mo then PD	—
PC, ACTH (124)	NR	6	PD	Severe thrombocytopenia
APT, PIT 1 (116)	NR	3	PD	—
APT, PRL (6)	NR	18	PD	
PC, ACTH (121)	High (liver mets)	3 2 when liver mets	PR (PIT tumor), after 2 y PD	Thrombocytopenia, acute renal failure, pulmonary embolus
APT, ACTH (6)	NR	12	PR	—
APT, ACTH (8)	NR	TMZ 5 at recurrence CAPTEM 12	CR SD	—
APT, ACTH (6)	NR	6	SD	
PC, ACTH (122)	NR	7	SD	Stopped for intolerance

Abbreviations: ACTH, adrenocorticotropin; APT, aggressive pituitary tumor; CAPTEM, capecitabine and temozolomide; CR, complete response; GH, growth hormone; IHC, immunohistochemistry; MGMT, O^6-methylguanine-DNA methyltransferase; mets, metastasis; NR, not reported; PC, pituitary carcinoma; PD, progressive disease; PIT, pituitary neuroendocrine tumor; PR, partial response; PRL, prolactin; SD, stable disease; TMZ, temozolomide.

Temozolomide Concurrent With Radiotherapy

TMZ is considered being a radiosensitizer based on synergistic effects with RT in vitro and in experimental studies (112, 113). TMZ given concurrently with RT (the so-called "Stupp protocol") is the standard treatment of glioblastomas (95). Besides a few cases reporting a successful outcome in APTs/PCs, TMZ concurrent with stereotactic reirradiation has been given in 21 patients with relapsing APTs (114). Low MGMT was associated with good radiological response. Fourteen of the 21 patients had previously received TMZ, but the outcome in previous TMZ nonresponders was not specified.

In the 2 ESE surveys, 20 patients with high-proliferative tumors, Ki67 greater than 10%, or p53 expression received TMZ combined with RT. A response was achieved in 75% compared with 40% in patients treated with TMZ monotherapy (see Fig. 8). According to the ESE guideline, the Stupp protocol can be considered in patients with rapidly growing tumors for which maximal RT has not been given (2). A trial to determine whether RT combined with TMZ is more effective than RT alone is ongoing in patients with refractory pituitary tumors (Clinicaltrials.gov No. NCT04244708).

Temozolomide Combined With Capecitabine

Capecitabine is converted to 5-fluorouracil (5-FU) in tissues, especially in tumors. The rational of combining TMZ and capecitabine is based on synergistic proapoptotic effects in neuroendocrine cells when capecitabine (5-FU) is administered before TMZ (115). Capecitabine (14 days with addition of TMZ 5 days [CAPTEM]), has been tried in advanced neuroendocrine pancreatic tumors. The regimen has not offered a clear clinical advantage in APTs/PCs (6, 8, 17, 116-125) (Table 2).

Other Chemotherapy

Chemotherapy, most often lomustine with/without combination with 5-FU, but also adriamycin, cisplatinum, carboplatin, procarbizine, mitotane, etoposide, vincristine, and doxorubicin in various combinations, has been used in a smaller number of patients. The effects are modest (126), but occasional patients have appeared to attain disease control or even partial regression (127-130). In the ESE surveys (6, 8) 10 patients were treated with chemotherapy. Two had PR (on lomustine monotherapy, and cisplatin + adriblastin, respectively).

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogues is recommended as a second-line treatment of well differentiated NETs (131). PET/CT with ^{68}Ga-DOTA peptides enables evaluation of the tumors' expression of somatostatin receptors (SSTR) to select candidates for PRRT. The outcome of PRRT in APTs/PCs has been

Table 3. Experience of treatment with peptide receptor radionuclide therapy in 19 patients with aggressive pituitary tumor/pituitary carcinoma

Tumor-type hormones secreted IHC staining (reference)	Prior therapy	Ki67 index MC, p53	Assessment SUV max or KS	Type of PRRT	Year/cycles	Outcome
APT, PRL (132, 133)	TMZ	ND	Octreoscan: KS ≥ 3	^{111}In-DTPA-octreotide	2009: ×5	PR (84 mo)
APT, NF immunoneg (8)	TMZ	ND	Octreoscan: KS ≥ 3	^{177}Lu-DOTA-TATE	2016: ×2 2017: ×2	PR (> 26 mo)
APT, NF GH, ACTH (8)	TMZ (2×)	10%, MC 10	^{68}Ga-PET: SUV 25	^{177}Lu-DOTA-TATE	2020: x4	PR (8 mo)
APT, GH (134)	ND	ND	Unk	^{90}Y-DOTA-TATE?	?: ×4	PR (follow-up unk)
PC, NF (135)	RT	1%, ND	^{68}Ga-PET: SUV 6.8	^{177}Lu-DOTA-TATE	?: ×3	SD (48 mo)
PC, NF (136)	RT	3%, ND	^{68}Ga-PET: SUV 21.7	^{177}Lu-DOTA-TATE	2010: ×4	SD (40 mo) CR "some mets"
APT, NF ACTH (6)	TMZ	4%, MC 2	Octreoscan KS ≥ 3	^{90}Y-DOTA-TOC	2013: ×2	SD (12 mo)
APT, NF immunoneg (8, 137)	RT	6%, ND	Octreoscan: KS ≥ 3	^{177}Lu-DOTA-TOC	2005: ×3 2015: ×2 2020: ×1	SD
APT, GH, (138)	No RT or TMZ	ND	"Remarkably intensive uptake"	^{177}Lu-DOTA-TATE	2019: ×3	SD, apoplexy 1 y later
APT, NF (133)	RT, TMZ	ND	Unk	^{177}Lu-DOTA-TATE	2015: ×5	PD
APT, PRL (132, 133)	RT	15%, MC 3	Octreoscan: KS ≥ 3	^{177}Lu-DOTA-TOC	2015: ×2	PD
APT, PRL (8)	TMZ + BVZ	25%, MC 13	^{68}Ga-PET: SUV 8	^{177}Lu-DOTA-TATE	2019: ×1	PD
APT, PRL (8)	TMZ (2×)	30%, MC 20	^{68}Ga-PET: SUV 6.9	^{90}Y-DOTA-TOC ^{177}Lu-DOTA-TATE	2016: ×2 2016: ×1	PD
APT, PRL (17)	RT, TMZ	40%, MC10	^{68}Ga-PET: KS = 3	^{177}Lu-DOTA-TATE	2014: ×2	PD
APT, TSH (6)	TMZ	60%, ND	Octreoscan: KS ≥ 3	^{177}Lu-DOTA-TATE	2012: ×2	PD
PC, GH (17)	TMZ	98%, MC 10	Octreoscan: KS ≥ 3	^{90}Y-DOTA-TOC	2008: ×1	PD
APT, GH + PRL (136)	RT ×2	22% p53 pos	^{68}Ga-PET: SUV 34.9	^{177}Lu-DOTA-TATE	2011: ×2	NA, died 1 y later
PC, ACTH (139)	RT ×3	25% p53 pos	Unk	^{90}Y-DOTA-TOC	2006: ×1	NA, died 5 wk later
APT, NF ACTH (136)	RT, TMZ	Ki67 "very high" p53 pos	^{68}Ga-PET: SUV 7.2	^{177}Lu-DOTA-TATE	2011: ×1	PD

Abbreviations: ACTH, adrenocorticotropin; APT, aggressive pituitary tumor; BVZ, bevacizumab; GH, growth hormone; IHC, immunohistochemistry; KS, Krenning score (grade 2, tumor uptake = normal liver, grade 3, uptake > normal liver, grade 4, uptake > spleen or kidney); MC, mitotic count; mets, metastasis; NA, not available; ND, not done; PC, pituitary carcinoma; PD, progressive disease; PET, positron emission tomography; pos, positive; PR, partial remission; PRL, prolactin; RT, radiotherapy; SD, stable disease; SUV, standardized uptake values; TMZ, temozolomide; TSH, thyrotropin; Unk, unknown.

reported in 19 patients, most of which were of the Pit1 lineage (6, 8, 17, 132-139) (see Fig. 9 and Table 3). CR, PR, and SD was achieved in 0, 4, and 5 patients. PD or death within a year after treatment occurred in 10 patients (Fig. 9). Two of 3 tumors with maximum standardized uptake values (SUV max) above 20 had clinically relevant effects, whereas 3 of 3 with values below 10 did not respond. A low Ki67 index was associated with better outcomes (see Table 3).

Everolimus

Everolimus is an oral inhibitor of the mTOR pathway with antiproliferative effects in lactotroph tumor cells (140). Eight patients have been reported; a patient with a lactotroph APT achieved PR sustaining for a year (140). A patient with a corticotroph PC harboring a mutation in the mTOR pathway did not progress over 4 months when the drug was combined with RT (125). There were no effects in another 6 treated patients (6, 109, 116, 141).

Tyrosine Kinase Inhibitors

Lapatinib is an oral small molecule and a dual inhibitor of the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (ErbB2/HER2) tyrosine kinase. Based on an effect of tyrosine kinase inhibitors (TKIs) in vitro and in animal models (142), a 6-month pilot study was performed in 4 patients with aggressive lactotroph tumors.

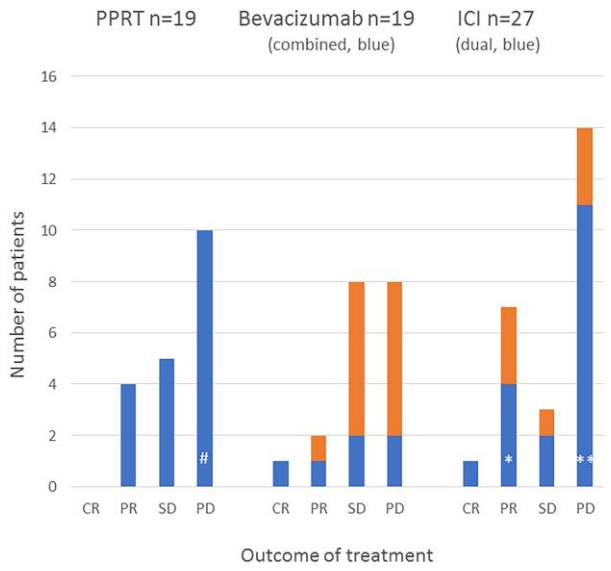

Figure 9. Response to treatment with peptide receptor radionuclide therapy (PRRT), bevacizumab, and immune checkpoint blockade, the overall experience. #Imaging data not reported, died 1 year later, *hormonal CR in 3 patients, **dissociated responses, see Table 4.

Disease stabilization was obtained in 3, while 1 PC progressed (143). There was no effect of erlotinib, an EGFR inhibitor, in a patient with corticotroph APT, whereas a lacto-somatotroph APT treated with gefitinib showed PR (6). Sunitinib, an oral multireceptor TKI, has shown promising results in the treatment of progressive paragangliomas and pheochromocytomas (144), but had no effect in 3 patients with APTs (6, 8, 116). It has been suggested that antiangiogenic drugs can sensitize tumor cells to chemotherapy. A combination of TMZ with apatinib, inhibiting VEGFR-2, led to a marked regression in a single case of a somatotroph APT (145).

Bevacizumab

Vascular endothelial growth factor (VEGF) is a key mediator of endothelial cell proliferation, angiogenesis, and vascular permeability. Bevacizumab is a humanized monoclonal antibody that blocks binding of VEGF and inhibits tumor microvessel formation. Its use in APT/PC has been reported in 19 patients (see Fig. 9). Of 12 patients (4 PCs) given the drug as monotherapy 2 achieved PR (6, 8) and 6 tumor stabilization (8, 71, 146-148), suggesting that the drug may be tried after TMZ failure.

Immune Checkpoint Inhibition

Immune checkpoints, such as CTLA-4 and PD-1, are molecules on immune-competent cells that negatively regulate the immune response and serve to maintain immune tolerance (149). PD-1 is expressed on activated immune cells and inhibits T-cell receptor signaling by binding with its ligands, PD-L1 and PD-L2. Tumors may evade the immune system by upregulating their PD-L1 presentation or by producing factors that increase checkpoint expression on immune cells (150). Immune checkpoint inhibition (ICI) with anti–CTLA-4 antibodies (ipilimumab) and anti–PD-1/PD-L1 antibodies (like nivolumab or pembrolizumab) allow activation of the immune system. ICI have markedly prolonged the survival in some advanced carcinomas although side effects can be severe (151). About 20% of solid tumors respond to the drugs (152).

Twenty-seven APT/PC patients have been treated with ICI, 18 corticotroph tumors and 9 of the Pit-1 lineage, mostly lactotroph tumors (8, 71, 121, 122, 153-159) (Table 4). One patient with an APT achieved CR of the pituitary tumor (153); 7 PCs achieved PR (121, 122, 154-157), 3 of these with normalization of hormonal overproduction (122, 154, 155); and 3 patients had SD (122, 155, 158) (see Fig. 6). Dissociated responses were seen in 2 PCs (see Table 4). Fourteen patients had PD, 2 of whose APTs demonstrated an accelerated growth after start of ICI (see Table 4) (71, 159). A clinically meaningful effect, defined as complete/partial radiological regression or tumor stabilization for at least 6 months, was achieved in 9 of 15 PCs and 2 of 12 APTs (see Fig. 9), suggesting that ICI could be tried in patients with PCs.

In other types of cancers, simultaneous inhibition of CTLA-4 and PD-1 pathways resulted in superior effects compared to monotherapy (160). Among the 27 patients with APTs/PCs, 18 received dual therapy and 7 were treated with PD-1 blockade. Five of 18 given dual therapy and 3 of 9 given PD-1 blockade responded to the drugs (see Fig. 9). This may favor the use of PD-1 blockade given that the side effects are fewer compared to dual therapy, but more data are needed.

Can the Response to Immune Checkpoint Inhibition Be Predicted?

High tumor mutation load encoding "nonself" immunogenic antigens (161), marked heterozygosity in human leukocyte antigen class 1 antigens (162), mutations in the MMR proteins (163), the presence of tumor-infiltrating lymphocytes (149), and high PD-L1 expression (164) have been associated with better responses in other types of cancer. Other authors have reported an effect as well in tumors with low levels of PD-1 ligands (165). Nevertheless, none of these biomarkers have invariably predicted the outcome in the APT/PC cohort (see Table 4). In the few APT/PCs in which the mutational tumor burden has been reported, it did not predict response to ICI. Interestingly, the only tumor harboring a somatic mutation in *MLH1*, one of the DNA MMR proteins, achieved CR (153), and another 3 tumors displaying alkylating hypermutational gene profiles post TMZ treatment, including mutations of the MMR proteins MSH2 and/or MSH6, had PR or SD. These observations may indicate that MMR deficiency is beneficial for the drug effect. The discordant effects on the pituitary tumor and metastases in one patient and between metastases in another illustrate differences in tumor properties and/or microenvironments.

Causes of Death and Survival

The prognosis of APT/PC has markedly improved during the last decades. In the largest cohort of APT/PC reported (8) the median survival was 17.2 and 11.3 years, respectively, with the worst outcome in tumors with Ki67 greater than or equal to 10%. Corticotroph tumor patients tended to have a shorter lifespan. In 84% of patients the cause of death was related to the tumor, in 10% to the treatment. Prior to the TMZ era 66% of patients with PCs died within a year of a diagnosed metastasis (11). In comparison, median survival after detection of metastasis was 5.1 years (95% CI, 2.7-7.5) in the 2022 ESE survey, in which a large majority of patients was

Table 4. Treatment with immune checkpoint inhibition, tumor characteristics and outcome in 27 patients with aggressive pituitary tumor/pituitary carcinoma

Tumor type (reference)	MMR mutations	Microsatellite status	Tumor-mutational burden	PD-LI	ICI, dual/PD-1 No. of cycles	Outcome radiology or clinically
APT, SCA (153)	MLH-1	ND	8.8/Mb	ND	Dual, 4 Nivo, 10	CR sustained 7 mo after discontinuation
PC, ACTH (122)	Alkylating hypermutator phenotype MSH2 and 6 (post TMZ)	ND	ND	Neg	PD-1 (pembro), 29	PR (hormonal CR) sustained 42 mo after discontinuation
PC, PRL (154)	Unk	ND	0.9/Mb (mets)	95%	Dual, 4 Nivo, 48	PR (hormonal CR) trx ongoing
PC, ACTH (155)	ND	ND	ND	Neg	Dual, 4 Nivo, 3	PR (hormonal CR) trx ongoing
PC, ACTH (122)	No	Stable	ND	Neg	PD-1, 12	PR sustained 12 mo after discontinuation
PC, silent PIT-1 (156)	IHC pos for MSH2, MSH6	ND	ND	95%	PD-1, 12	PR (> 70%) trx ongoing
PC, ACTH (121)	alkylating hypermutator phenotype MSH6 (post TMZ)	ND	93/Mb	< 1%	Dual, 5	PR while on ICI, PD 6 mo after discontinuation
PC, silent PRL (157)	No	ND	6.8 Mb (before TMZ)	< 1%	Dual, 2 Nivo, 17 2nd dual, 4	PR for 8 mo then PD PD
PC, ACTH (158)	Alkylating hypermutator phenotype, MSH6 (post TMZ)	ND	ND	ND	Dual, 12 ongoing	SD
PC ACTH (122)	No	Stable	"Low"	Neg	PD-1, 6	SD
APT, ACTH (155)	ND	Stable	ND	Neg	Dual,4 Nivo 25	SD
PC, ACTH (71)	IHC neg for MSH6 (post TMZ)	ND	ND	Neg	Dual, 5 Nivo, 21	PD[a] (dissociated response)
APT, ACTH (155)	ND	ND	0.9/Mb	Neg	1) Nivo, 4 2) Ipi, 4	1) SD 2) PD
PC, PRL (155)	ND	ND	ND	ND	1) Dual, 6 2) Nivo, 3 3) Ipi, 1	1) SD 2) PD
PC, ACTH (155)	ND	ND	ND	Neg	Dual, 4 Nivo, 4	Dissociated response; PIT, PR mets, PD
APT, silent PRL pos (155)	ND	ND	ND	10%	1) Dual, 5 2) Nivo 1	PD: (SD on imaging, but clinically PD)
APT, ACTH (155)	ND	ND	ND	5%	Dual, 5	SD on imaging, but clinically PD
APT ACTH (8)	No	ND	22.5/Mb	15%	PD-1, 3	PD
PC, ACTH (8)	No (before TMZ)	Stable	"Low"	ND	Dual, 3	PD
PC, PRL (122)	No	Low before TMZ, intermediate post TMZ	Neg	Neg	PD-1, 2	PD
PC, ACTH (8)	MSH6 (after TMZ)	Stable	2.5/Mb	Neg	Dual, 4	PD
APT ACTH (155)	ND	ND	ND	ND	Dual, 4	PD
APT, PRL (155)	ND	ND	ND	Neg	Dual, 4	PD
APT, ACTH → silent (155)	ND	ND	ND	Neg	Nivo, 5 Ipi, 3	PD
APT, PRL (155)	ND	ND	ND	40%	1) Dual, 4 2) Nivo, 3	1) SD 2) SD on imaging, but clinically PD

(*continued*)

Table 4. Continued

Tumor type (reference)	MMR mutations	Microsatellite status	Tumor-mutational burden	PD-LI	ICI, dual/PD-1 No. of cycles	Outcome radiology or clinically
APT ACTH (159)	IHC neg for MSH2 and MSH6	ND	"Low"	Neg	PD-1, 4	PD (hyper-PD)
APT, PRL (71)	No	Stable	1/Mb	Neg	dual, 2	PD (hyper-PD)

Abbreviations: ACTH, adrenocorticotropin; APT, aggressive pituitary tumor; Dual, ipilimumab + nivolumab; ICI, immune checkpoint inhibition; IHC, immunohistochemistry; Ipi, ipilimumab; MMR, DNA mismatch repair; Nivo, nivolumab; PD-I, pembrolizumab; pembro, pembrolizumab; PRL, prolactin; ND, not done; Neg, negative; SD, stable disease; trx, treatment; TMZ, temozolomide.
[a]Initial regression of pituitary tumor and of preexisting liver metastases but later appearance of a new liver metastasis and progression of the pituitary tumor.

treated with TMZ. In another recent publication, PC patients who had been treated with TMZ-based therapy survived more than 5 years after detection of metastases (23). Besides an effect of TMZ, earlier recognition, locoregional treatment of metastases, and improvements in overall management likely contribute to a better prognosis.

In summary, APTs and PCs have a heterogeneous nature and are challenging to treat. TMZ is the recommended chemotherapy, with response rates of about 40%. ICI has emerged as the second-line treatment in PCs, whereas bevacizumab and PRRT have resulted at best in PR in a limited number of cases. Other treatments have generally not been successful. *TP53* and *ATRX* are the most commonly mutated genes. Predictive markers to guide treatment decisions are needed and are a topic of ongoing research.

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Disclosures

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

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in "References."

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