**AGGRESSIVE PITUITARY TUMORS AND PITUITARY CARCINOMAS**

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**Abstract**

Aggressive pituitary tumors (APT) refer to pituitary adenomas exhibiting rapid growth, resistance to conventional treatments and/or early/multiple recurrences, with abandonment of the previous term ‘atypical pituitary adenoma’. Pituitary carcinomas (PC) are defined by non-contiguous craniospinal or distant metastasis. Whilst PC is exceedingly rare, comprising only 0.1-0.2% of all pituitary neoplasms, APT may account for up to 15% of all pituitary neoplasms, depending on the definition used. Typically evolving from known pituitary macroadenomas, APT/PC is most commonly diagnosed in the fifth decade of life with corticotroph and lactotroph neoplasms predominating. Diagnosis relies on MRI, hormonal studies and histological assessment including proliferative markers and immunohistochemistry for pituitary hormones and, most recently, transcription factors. Structural and molecular mechanisms have been proposed in the pathogenesis of APT/PC, although there appears to be no contribution from known familial pituitary tumor syndrome genes such as *MEN1*. Treatment is multimodal, ideally delivered by an expert team with a high-volume caseload. Surgical resection may be performed with the aim of either gross total resection or tumor debulking. Radiotherapy may be administered either as fractionated external beam radiation or stereotactic radiosurgery. Standard pituitary medical therapies such as somatostatin analogues have limited efficacy in APT/PC, whereas temozolomide yields a clear survival benefit. Evidence is emerging for the use of peptide receptor radionuclide therapy, tyrosine kinase inhibitors, VEGF inhibitors, and immunotherapy. Avenues for further research in APT/PC include molecular biomarkers, nuclear imaging, establishment of an international register, and routine pituitary tumor biobanking.

**INTRODUCTION AND DEFINITIONS**

Pituitary adenomas (PA) are benign, typically slow-growing neoplasms originating from cells of the adenohypophysis (1). Aggressive pituitary tumors (APT) refer to PAs demonstrating rapid growth, resistance to conventional treatments and/or early/multiple recurrences (2,3). In the absence of reliable pathological predictors of tumor behavior (2), APTs lack specific diagnostic criteria and are instead best considered a clinical composite of various pituitary neoplasms exhibiting clinically aggressive behavior. Efforts should be made to be as objective as possible in diagnosing APTs (2). Postoperative recurrences should only be considered to be APTs when surgery was performed by an expert neurosurgeon with a high-volume caseload (2). Whether resection was intentionally limited because of reduced surgical fitness may also need to be considered. Intrinsic tumor resistance to medical therapy should be distinguished from inadequate dosing or poor compliance as well as drug toxicity, which is increasingly recognised in the setting of dopamine agonist (DA) treated prolactinomas (4). Progression or recurrence after radiotherapy is more compelling than resistance to only surgical and medical therapy (5-7).

APT is distinct from the term ‘atypical pituitary adenoma’, which was defined by the earlier 2004 World Health Organization (WHO) classification of endocrine tumors as PAs with a Ki-67 labelling index >3%, an elevated mitotic index, and extensive p53 nuclear immunostaining (8). The Ki-67 labelling index is assessed by MIB-1 immunohistochemistry (IHC). As Ki-67 is a nuclear protein with suggested roles in ribosomal RNA transcription and chromosome separation (9), MIB-1 stains cells in the S (DNA synthesis) phase of the cell cycle and thereby represents the rate of cellular proliferation (1). Immunopositivity for p53 reflects nuclear accumulation of p53 (9). In other tumors, p53 immunostaining is related to *TP53* mutations that prolong the half-life of p53 and result in nuclear accumulation, although *TP53* mutations are very rare in p53-immunopositive pituitary neoplasms (10). A threshold of >2 mitoses per 10 HPF was also included in the 2004 WHO classification as this portends a greater risk of recurrence (2). The intent of the 2004 WHO framework was to identify more aggressive tumors warranting more intensive management and follow-up. However, the term ‘atypical pituitary adenoma’ was omitted in the 2017 WHO classification of endocrine tumors as these criteria have not been clinically validated (2,3,11). Although some data show correlations between the 2004 WHO criteria and tumor behavior, the criteria do not consistently and independently predict tumor behavior in individual patients, with one study showing no difference in recurrence risk and disease-free survival in atypical PAs versus other PAs (12).

Although most APTs are invasive (13,14), invasiveness alone is insufficient to define APTs (2), partly because invasion is often subjective with variability between radiological, operative, and histological assessments (3). Moreover, highly invasive prolactinomas may respond well to DA therapy rather than following an aggressive clinical course. However, invasiveness is still considered a key component of aggressiveness. Compared to non-invasive, non-proliferative PA (Grade 1a), the relative risk of persistent disease is 8.0 for invasive but non-proliferative PA (Grade 2a) versus 3.1 for non-invasive but proliferative (at least two of: Ki-67 ≥3%, p53 staining with >10 strongly positive nuclei/10 HPF, mitotic count >2/10 HPF) PA (Grade 1b) (14). The impact of invasiveness and proliferation on tumor aggression is synergistic. Invasive and proliferative PAs (Grade 2b) carry a 25-fold higher risk of persistent disease and a 12-fold higher risk of tumor progression compared to non-invasive, non-proliferative PA (14). Progression-free survival is also more influenced by the effect of invasiveness than that of proliferation (15), with a relatively greater prognostic effect from invasiveness in lactotroph and corticotroph PAs than other subtypes (14).

At the extreme end of the spectrum, pituitary carcinoma (PC) is defined by non-contiguous craniospinal or distant metastasis. Apart from histological confirmation of the pituitary origin of suspected metastases, PC is a clinical diagnosis with no defining histopathology and remains as a distinct category in the 2017 WHO classification (8).

**EPIDEMIOLOGY**

Because of the lack of definitive diagnostic criteria, the prevalence of APT is unclear (2). A study incorporating radiological and histological assessments of aggressiveness found ‘grade 2b’ (invasive and proliferative) tumors in 15% of patients, although this was not a consecutive series with many patients excluded due to insufficient data and others selected to balance patients with and without persistent disease (14). Aggressiveness was also not invariable in grade 2b tumors (16). Tumor recurrence and persistence, which are generally representative of APT, are more frequently seen in younger rather than older adults (14,17,18). PAs are overall uncommon in children but tend to be more aggressive in the pediatric setting, with 26% of prolactinomas demonstrating DA resistance (19). Some (17) but not all data (15,18) show greater risks of recurrence and progression with larger PAs. As highlighted in Table 1, APT/PC development is more likely in certain tumor subtypes, namely, silent corticotroph PA, Crooke’s cell PA, plurihormonal PIT-1 positive PA (formerly ‘silent subtype 3 PA’), sparsely-granulated somatotroph PA, and lactotroph macroadenomas in men (3,20-24).

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| **Table 1. PA Subtypes with Greater Tendency for APT/PC Development (3,11)** |
| **PA subtype** | **Cell lineage**  | **Transcription factor**  | **Hormone**  | **Cytokeratin pattern**  | **Prevalence of APT/PC**  |
| Crooke’s cell PA | Corticotroph  | T-PIT | ACTH | Ring-like (perinuclear hyaline bodies) | Recurrence in 60%, multiple recurrence in 24%, APT/PC-related mortality in 12% (22)  |
| Silent corticotroph PA | Corticotroph  | T-PIT | ACTH | Diffuse | Multiple recurrences in 57% of recurrent silent corticotroph PA vs. 3% in other non-functioning PA (*P*=0.001) (21) |
| Plurihormonal PIT-1 positive PA (previously silent subtype 3 PA) | Acidophilic  | PIT-1 | GH, PRL, beta-TSH +/- alpha-subunit | Nil  | Postoperative residual in 65% with tumor progression in 53% of these patients (20); greater propensity for invasion and recurrence (3) |
| Sparsely granulated somatotroph PA | Acidophilic  | PIT-1 | GH +/- PRL | Dot-like (fibrous bodies) | Higher frequency of suprasellar extension/cavernous sinus invasion, larger tumors and smaller octreotide suppression test response in sparsely granulated vs. densely granulated tumors (23) |
| Lactotroph macroadenoma in men | Acidophilic  | PIT-1ER-alpha | PRL (+GH in acidophilic stem cell subtype) | Nil (or fibrous bodies in acidophilic stem cell subtype) | Complete DA resistance in 8% men vs. 4% women (24); 57% of DA-resistant lactotroph PAs occur in men (24) |

PC is rare, comprising only 0.1-0.2% of pituitary neoplasms (13,25). The incidence of PC is 4/1,000,000 person-years (26). These figures may, however, be underestimated, as up to 75% of historical PC diagnoses were only made at autopsy (27). PC typically presents in the fourth to sixth decades of life, with a mean age at diagnosis of 44 years (1), but rare pediatric cases have been reported (28,29). Whereas clinically-silent, hormone-staining tumors only account for 7% of all pituitary neoplasms (25), functioning tumors that have evolved from such tumors comprise 25% of APT/PC (30). The commonest PC subtypes are corticotroph and lactotroph neoplasms (13). In a recent review of 72 published PC cases by Yoo *et al*, hormone IHC was positive for ACTH in 35%, PRL in 24%, GH in 14%, TSH in 6%, FSH in 7% and LH in 4%, and 15% were null cell (31). This rate of null cell PC was lower than other reports of 30% (13), possibly relating to the limited availability of prolactin IHC in historical studies (32). Compared to pure PA series, lactrotroph and corticotroph-derived neoplasms are overrepresented and somatotroph and null cell neoplasms are underrepresented in PC (25,30).

The overall epidemiology of APT/PC was recently outlined in a *European Society of Endocrinology* (ESE) survey of clinicians treating APT/PC patients, where APT was defined by the responding clinician. The survey cohort comprised 165 patients (40 PC, 125 APT), forming the largest APT/PC cohort to date. APT and PC were similar in age at diagnosis (43 vs. 45 yr), predominant cell subtypes (corticotroph in 45% vs. 48%, lactotroph in 20% vs. 38%), and functional status (clinically functioning in 58% vs. 63%) but initially silent and later functioning tumors were over-represented in PC (7% vs. 20%) (30). Both APT and PC demonstrated a male predilection (65% vs 63%) (30), in agreement with Yoo *et al* (31), but in conflict with other data showing a slight female predominance (33) or no gender predilection (13).

Clinically relevant germline variants in pituitary tumorigenesis genes are found in up to 20% of PA patients who are young and/or have other personal or family history of endocrine neoplasia (34). The rate of germline mutations specifically in the APT/PC setting is yet to be determined, but germline *AIP* and *SDHx* mutations are typically associated with more aggressive tumor behavior (9,34). PC has been reported in patients with germline mutations, including *SDHB* (35), *MSH2* (36), and *MEN1* (37,38). However, PC appears to be no more common in patients with germline *MEN1* mutations than inpatients with sporadic PAs (39). To the best of our knowledge, there have been no reports of PC in patients with *AIP*-associated familial isolated pituitary adenoma syndrome, multiple endocrine neoplasia syndrome type 4 due to *CDKN1B* mutations, Carney’s complex due to *PRKAR1A* mutations, McCune-Albright syndrome due to *GNAS* mosaicism, or X-linked acrogigantism due to Xq26.3 microduplications involving *GPR101*. APT/PC prevalence is uncertain in *USP8*, a gene where somatic mutations have been implicated in Cushing’s disease. Early data showed *USP8*-mutated corticotrophinomas to be smaller with lower plasma ACTH levels (40), suggesting a milder phenotype. However, subsequent data have shown higher postoperative urinary free cortisol levels in patients with *USP8*-mutated corticotrophinomas compared to wild-type corticotrophinomas, possibly serving as a harbinger for poorer long-term outcomes in these patients (41).

**CLINICAL PRESENTATION**

APT/PC nearly always evolve from pituitary macroadenomas (maximal tumor diameter ≥1cm) (13), but, conversely, many macroadenomas and even giant prolactinomas (≥4cm) respond well to standard treatments and never exhibit aggressiveness (2). Progression of a microadenoma (<1cm) to PC is exceedingly rare (42,43). The time from primary diagnosis with a pituitary neoplasm to presentation with APT/PC is highly variable (2). In APT, aggressiveness can be apparent from diagnosis, or take months to more than a decade to develop (2,44). The course of APTs may be punctuated by periods of radiological and hormonal quiescence (45). One study showed that APTs are more likely to occur following incomplete surgical resection at an odds ratio of 6.3 (17), but another study showed no relationship between APTs and the primary surgical outcome (15). These conflicting results partly reflect the difficulty in distinguishing residual tumor from normal tissue and postoperative changes (17). In PC, the mean latency from primary diagnosis is 6.5-9 years, but can range from months to 35 years (1,6,13,31,33,46,47).

Some symptoms, such as headache and visual field loss, overlap between PA and APT/PC, whilst cranial nerve palsies and obstructive hydrocephalus are more suspicious for APT/PC (33). Patients with Nelson’s syndrome, which is an inherently aggressive neoplasm, often present with mass effects including cranial neuropathies from the growing primary tumor as well as hyperpigmentation from proopiomelanocortin excess; distant metastasis may also occur (48). As in PA, diabetes insipidus is rare in APT/PC (49), and should raise suspicion for sella metastasis from a non-pituitary malignancy (1). Important differential diagnoses are breast and lung carcinomas, which are the commonest primary neoplasms to metastasize to the sella (46). Small cell lung cancer can produce both ectopic ACTH syndrome and sella metastasis, which may be misdiagnosed as a corticotroph PC with distant metastasis (32). PC metastases may lead to other site-specific clinical features, such as hearing loss, ataxia, motor weakness, back pain, neck masses, and liver function derangement (1,9).

Yoo *et al* showed the site of metastases to be craniospinal in 58%, systemic in 32%, and both craniospinal and systemic in 8% of PC cases (31). This is in contrast to an earlier series of 15 PC cases reported by Pernicone *et al* where metastasis was predominantly systemic (47%), compared to craniospinal metastases in 40% and both craniospinal and distant metastases in 13% (13). Common sites of metastasis include the brain (43%), spine (38%), liver (14%) cervical lymph nodes (11%) and bone (10%) (31). Within the CNS, metastases typically involve the cortex, cerebellum and cerebellopontine angle (49). Dural metastases may occur and can be misdiagnosed as meningiomas (33). Rare metastatic sites include the orbit, endolymphatic sac, oropharynx, heart, pancreas, kidney, skin, ovary, myometrium and pelvic lymph nodes (1,13,31,33).

PC subtype may influence the pattern of metastasis. In lactotroph PC compared to corticotroph PC, systemic metastases are relatively more common (71% vs. 57%), and the duration of pituitary neoplasm diagnosis to PC diagnosis is shorter (4.7 vs 9.5 years). In patients with distant metastases, the commonest site is bone in lactotroph PC and liver in corticotroph PC (13).

**EVALUATION**

The principles of APT/PC assessment were recently outlined in the 2018 ESE guidelines for APT/PC management (2). As in PA, the evaluation of patients with suspected or known APT/PC involves radiological, biochemical and histological investigations. Patients with APT should be followed indefinitely as recurrence and progression accumulate with time. In a study of recurrent non-functioning pituitary adenoma (NFPA), the prevalence of recurrent disease rose from 4.4% at 5 years to 10% at 10 years (6). Long-term follow-up also allows monitoring of late treatment-related complications such as radiation-induced hypopituitarism and secondary tumors, and the late development of PC which may occur decades following the initial diagnosis (2). Clinicians should be especially vigilant for metastases in patients with APTs (47), noting that metastasis often occurs insidiously and can involve various craniospinal and distant sites which may be mistakenly attributed to another primary neoplasm (2).

**Radiological Assessment**

The primary imaging modality in all pituitary neoplasms is MRI, ideally with thin (2-3 mm) T1- and T2-weighted slices before and after gadolinium in sagittal and coronal planes (2). T2 sequences are particularly helpful in acromegaly as T2 hyperintensity compared to normal pituitary or grey matter is often seen with sparsely granulated somatotroph PAs which tend to behave aggressively. T2 hyperintensity is also directly correlated with larger somatotroph tumors and blunted octreotide suppression test responses (50). This radiological clue is particularly helpful preoperatively, when the granulation pattern is unknown (50).

MRI should be performed every 3-12 months as guided by previous growth rates, proximity to vital structures and timing of interventions (2). Current images should be compared against baseline and penultimate scans (2) (1). In NFPA, volume doubling time is highly variable, ranging from one to 27 years, but tends to be stable for a given individual with an initially exponential growth pattern followed by deceleration of growth velocity (51). Deviation from this with unusually rapid growth rates are an important marker of APT (2). Rapid corticotrophinoma growth following bilateral adrenalectomy is a specific hallmark of Nelson’s syndrome, which precedes metastasis in over two-thirds of corticotroph PC cases (1).

Patients with APT and either discordant biochemical and radiological findings or site-specific symptoms should be screened for metastasis (2). In the absence of a formal staging system, patients with identified metastatic disease should undergo imaging by one or more modalities to define the extent of metastasis and to evaluate the possibility of a non-pituitary primary neoplasm (49). In patients with pituitary neoplasms and CNS symptoms, neck masses or back pain, pituitary MRI may be extended to include the whole brain and/or spine (1). CT imaging may be useful if bony involvement is suspected or in patients with contraindications to MRI (2). As PC is often hypermetabolic with somatostatin receptor (sst) expression including sst1, sst5 and sst2, nuclear imaging with 18FDG-PET and/or 68Ga-DOTATATE-PET may be valuable in delineating the overall extent of disease (47,52). DOTATATE-PET and FDG-PET may produce discordant but useful findings. The presence of uptake on FDG-PET but not on DOTATATE PET may suggest more dedifferentiated disease. Discordant avidity may also be used to guide the selection of peptide receptor radionuclide therapy versus chemotherapy (2,52).

**Biochemical Assessment**

Pituitary hormones should be measured every 3-12 months, as guided by tumor subtype, clinical features and treatment interventions (2). This is imperative to identify secretory tumors responsive to medical therapies and hypopituitarism requiring hormone replacement (2). Hormone levels are also an invaluable tumor marker to guide treatment response in secretory tumors. Transition to APT/PC may be heralded by conversion of a silent PA to a clinically functioning tumor, loss of response to medical therapies, new or progressive hypopituitarism, or increasing hormonal excess despite radiological stability (1,2,9,32). In particular, an initial response to DA therapy followed by ‘escape’ was documented by Pernicone *et al* in 4/7 (57%) lactotroph PCs (13). Decreased hormone synthesis, reflecting tumor dedifferentiation, may also be a sign of tumor progression with declining serum levels of TSH and alpha-subunit previously reported at the time of metastasis in a thyrotroph PC (53). Another case report described a primary FSH-staining PA followed 15 years later by metastatic disease that stained negative for all pituitary hormones (54). This notion of tumor dedifferentiation may account for the increased aggressiveness of silent corticotrophinomas compared to functioning corticotrophinomas (33).

**Histological Assessment**

ASSESSMENT OF PROLIFERATION

Despite abandonment of the 2004 WHO criteria for atypical PA and the lack of a pituitary neoplasm grading system in the 2017 WHO classification, histopathology may be incorporated with clinical features to predict the trajectories of pituitary neoplasms (1,3,11). The 2018 ESE guidelines recommend performing IHC to evaluate pituitary hormones and the Ki-67 index, at a minimum, in all pituitary neoplasms, with the addition of mitotic count and p53 IHC when Ki-67 is ≥3%; however, it is ceded that the evidence basis for this is very low (2). The ESE guidelines suggest incorporating these histological markers in management decisions, such as the intensity of follow-up regimens and the use of adjuvant radiotherapy in patients with invasive and proliferative postoperative tumor remnants (2). The dominance of Ki-67 in the guidelines reiterates the finding of a Ki-67 index ≥3% being the commonest histological marker of tumor aggressiveness in the recent ESE survey, with this threshold met in 81% of APT and 85% of PC, compared to p53 positivity in 73% APT and 78% PC and mitotic count >2/10 HPF in 63% APT and 90% PC (30). Ki-67 was also the only predictive marker for tumor aggressiveness in other studies comparing various histological and clinical markers (55,56). Ki-67 thresholds of ≥3% and >10% are considered by some experts to indicate APT and PC, respectively (2). However, this is based on limited studies with variable methodologies and a lack of robust long-term data (2). Ki-67 also overlaps between indolent PA, APT and PC. Ki-67 ranges from undetectable to 80% in PC (1,30), and a Ki-67 ≥10% did not discriminate between APT and PC in the ESE survey (30). A mitotic index set at ≥2/10 HPF predicts a greater risk of recurrence (57), but there was again significant overlap between APT and PC in the ESE survey (30). Similarly, p53 immunopositivity, generally defined as >10 strongly positive nuclei per 10 HPF (2), is overrepresented in PC compared to PA, and incremental p53 staining has been observed in the progression from PA to PC (1), but p53 IHC may be negative in PC (58). Even the combination of all three histological markers of proliferation in the ESE survey did not reach statistical significance in differentiating APT versus PC (30). The unreliability of histological markers in predicting tumor behavior probably represents a combination of true biological variability between tumors given the observed variability in clinical features, as well as hampered histological assessment due to intratumoral heterogeneity, different fixation protocols, prior treatment effects, and antibody and interobserver variability (1,49).

MGMT IHC should be considered in suspected or known APT/PC as low expression is another potential marker of aggressive behavior and is predictive of TMZ response; however, these associations are not invariable and the decision to use TMZ should not rest on this result alone (30).

ASSESSMENT OF CELL LINEAGE

Pathological evaluation is important in identifying the more aggressive subtypes of pituitary neoplasms (Table 1). Hormone IHC is critical in identifying silent corticotroph PAs and plurihormonal PIT-1 positive PA, whilst cytokeratin staining is used to define the dot-like fibrous bodies of sparsely granulated somatotroph PAs as well as patterns specific to Crooke’s cell and silent corticotroph PAs (1). Other histological features of sparsely granulated somatotroph PAs include poorly cohesive cells with sheet-like formation and nuclear polymorphism with weak and focal GH staining (23). Although transcription factor IHC, as recommended in the 2017 WHO classification (11), may assist identification of aggressive pituitary neoplasm subtypes, it does not directly predict aggressiveness (2). Transcription factor IHC is considered most valuable in the differentiation of hormone immunonegative tumors (9). However, the clinical implications of a null cell adenoma that stains negative both for pituitary hormones and pituitary transcription factors are uncertain as the extant literature rarely defines transcription factor status. In a more recent study including 119 hormone immunonegative PAs, only 6 (5%) were also negative for cell lineage transcription factors (59). IHC for T-PIT is attractive given the greater aggressiveness of corticotrophinomas (30), but the availability of reliable T-PIT antibodies has been a concern (9). Nonetheless, the addition of transcription factor IHC is an attempt to overcome the false negative, misleadingly weak or dubious results that may be encountered with hormone IHC (3). Utrastructural analysis is not additive to the contemporary pathological assessment of pituitary neoplasms by morphology and IHC (3).

ASSESSMENT OF PITUITARY CARCINOMA

Like PAs, PCs appear microscopically as well-differentiated neuroendocrine tumors. PCs may demonstrate hypercellularity, nuclear pleomorphism, necrosis, haemorrhage and invasion, with all such features overlapping with PAs (1). Neuronal metaplasia may rarely occur in PC (1).

It is not possible to distinguish PC from PA on histological, immunohistochemical or ultrastructural grounds (1), and there is poor correlation between the histological and clinical features of PC metastases (47). The primary aim in the histological assessment of PC is instead to confirm a pituitary origin of metastases. Biopsy of apparent PC metastases is particularly important where another primary malignancy could explain the metastases, thereby influencing prognosis and management. Tissue diagnosis may be achieved by surgical biopsy or fine needle aspiration (FNA) biopsy of accessible sites such as the cervical lymph nodes, liver, lung or vertebrae (46,47,60). Histological diagnosis based on FNA specimens should be cautious, given its divergence from pituitary histological diagnoses which are virtually always made by craniotomy or trans-sphenoidal surgical resection (46). Key differential diagnoses based on similar cytological appearances include metastasis from renal cell carcinoma, plasmacytoma/multiple myeloma, lymphoma (46), medullary thyroid carcinoma, and other neuroendocrine tumors (47). In PC, metastatic lesions should bear cytological resemblance to the primary pituitary tumor (46,60), noting that proliferative markers, particularly Ki-67, are often higher in metastases (13,33,47). Immunohistochemical stains for neuroendocrine markers such as chromogranin A and synaptophysin aid in the differentiation of PC from non-pituitary neoplasms (1). Hormone IHC is also helpful in suspected metastases from a pituitary neoplasm that is known to be hormone producing (60). To ensure the appropriate use of these histological investigations, the reporting pathologist must be notified of the potential for metastasis from a pituitary neoplasm and aware of the frequent latency between PA onset and PC development. The small possibility of dual concurrent metastatic malignancies should be considered where there is variability in the clinical, radiological or histological features of the metastases (46).

**Genetic Testing**

Currently there are only weak associations between pituitary tumorigenesis genes and development of APT/PC, hence genetic testing for either germline or somatic mutations should not be performed purely on the basis of APT/PC development (2). Germline genetic testing should follow the usual indications as for non-aggressive PAs (2), including young onset and other personal or family history of related neoplasms (34).

**PATHOGENESIS**

As APTs represent a composite of different tumor subtypes, the contributing pathogenic mechanisms are varied. Tumor persistence, recurrence and progression after surgery at least partly relate to greater invasiveness, lowering the chance of gross total resection (15). Resistance to medical therapy in somatotroph APTs may relate to reduced sst2 expression (61) and tumor bulk (23), whilst DA resistance in lactrotroph APTs can occur in cystic tumors and tumors with decreased dopamine D2 receptor and estrogen receptor (ER) expression (2,62). Cell specific feedback sensitivity is also important. The relative indolence of somatotroph PAs with apparent insensitivity of somatotrophs to loss of negative feedback during pegvisomant treatment contrasts sharply with the typically aggressive nature of Nelson’s syndrome following bilateral adrenalectomy with loss of endogenous cortisol feedback in corticotrophs (63). A somatic inactivating mutation in the glucocorticoid receptor gene was found in one such case of Nelson’s syndrome (64). On the other hand, Cushing’s disease requiring bilateral adrenalectomy may reflect intrinsically more aggressive corticotrophinomas that drive the clinical course of disease, rather than adrenalectomy and loss of endogenous negative feedback being the underlying driver of progression (2).

Hypothesized mechanisms of PC dissemination include: hematogenous spread through the anterior pituitary portal system into the cavernous and petrosal sinuses and finally the jugular veins; lymphatic spread via the sphenoid sinus or in the skull base and soft tissues by connections between the intracranial perineural space and lymphatic plexus; and cerebrospinal fluid seeding along the subarachnoid space of the neuroaxis (1,13,47,49). However, there have been no studies comparing the sites of metastases in pituitary neoplasms with cavernous versus sphenoid sinus invasion. Increased matrix metalloproteinase-9 expression in PC and its association with vascular density in PC suggest that extracellular matrix degradation contributes to angiogenesis (65). Matrix metalloproteinase activity may also promote local tumor invasion, including entry into deep brain structures along the Virchow-Robin perivascular CNS spaces, resulting in non-contiguous cranial metastases (47).

Iatrogenesis has been purported in select PC cases with intimately located metastases following trans-sphenoidal surgery (13), craniotomy (66), radiotherapy (47), and ventricular-peritoneal shunt placement (47). Hypotheses for the role of surgery in increasing PC risk include disruption of venous barriers intraoperatively and postoperative formation of friable new blood vessels (47). Radiotherapy has been postulated to increase tumor aggressiveness by inducing genetic mutations, in *TP53* for example (48). However, this theory is controversial and confounded by the fact that surgery and radiotherapy are employed in most patients with APT/PC during the typically protracted progression of PA to APT and finally to PC (1,47). Furthermore, the vast majority of operated and irradiated pituitary neoplasms never develop into PC (1), making iatrogenesis a highly unlikely cause of PC.

**Molecular Mechanisms**

Competing molecular models of APT/PC pathogenesis include a hyperplasia-adenoma-carcinoma sequence with accumulation of molecular alterations, versus clonal evolution of a subclone with genetic/epigenetic changes favoring cell survival, proliferation and ultimately metastasis (1,47,67). As most patients present with a long history of pituitary neoplasm (13,32), *de novo* malignant transformation of normal adenohypophyseal cells seems unlikely. There are, however, rare reported cases of rapid progression from pituitary neoplasm diagnosis to death (43,68). The frequent transition of PC from PA via an APT stage (1,47) suggests that pathogenic mechanisms may be shared between PAs, APTs and PCs. Although, whilst some genes like *PTTG* are overexpressed in PAs compared to normal pituitary tissue and in APTs compared to other PAs (69), other genes such as the *RAS* gene only appear to be implicated in APT/PC (70,71). Whilst there is some overlap between genetic changes in APT/PC and the genes underlying more common solid organ malignancies, mutations in classic oncogenes and tumor suppressor genes are relatively uncommon (33). Certain molecular events may be specific to the different elements of APT/PC pathogenesis. A transcriptomic analysis of lactotroph pituitary neoplasms found different genetic changes in purely invasive tumors (upregulation of *ADAMTS6* and *CRMP1;* downregulation of *DCAMKL3*) compared to tumors that were invasive and aggressive (upregulation of *ADAMTS6*, *CRMP1*, *PTTG*, *ASK*, *CCNB1*, *AURKB* and *CENPE*; downregulation of *PITX1*). Upregulation of *Pttg*, *Aurkb*, *Cenpe* and *Crmp* and absent *Pitx1* expression in malignant lactrotoph tumors in rats recapitulated these findings, and there is a functional basis to the involvement of these genes with *ASK*, *PTTG*, *AURKB*, *CCNB1* and *CENPE* involved in the cell cycle, *ADAMTS6* in the extracellular matrix, *CRMP* in cellular migration, and *PITX1* in pituitary differentiation (72).

Copy number variation (CNV) at the chromosomal level is the most frequent genetic aberration in pituitary neoplasms (73). CNV is particularly common in functioning neoplasms, especially prolactinomas, as well as neoplasms with high proliferative indices (73-75). The mean number of chromosomal imbalances per tumor is 1.6 in initial PAs, 3.4 in recurrent PAs and 8.3 in PC (74,75). Aneuploidy was observed in all but one of the 15 PC cases reported by Pernicone *et al* (13). The degree of genomic disruption is directly proportional to the Ki-67 (73). This progressive increase in CNV supports an adenoma-carcinoma sequence, as observed in other endocrine tumors such as pancreatic and adrenocortical neoplasms (75). Recurrent chromosomal aberrations in APT/PC include gains in chromosome 4q, 5, 13q and 14q and losses of chromosome 1p, 2, 8q, 10, 11, 12q, 13q and 15q (6,74,75). These chromosomes contain multiple genes implicated in APT/PC pathogenesis, as listed in Table 2, although the underlying evidence for the causal involvement of these genes is limited owing to the rarity of PC and variability in genomic technologies.

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| **Table 2. Selected Genes Implicated in APT/PC Pathogenesis** |
| **Gene**  | **Locus**  | **Function** | **Alteration in APT/PC** |
| ***Oncogenes*** |
| *PTTG*, pituitary tumor transforming gene | Chr 5q33.3\* | Securin protein in spindle checkpoint machinery, responsible for error-free mitosis | Overexpression associated with increased risk of PA recurrence, strong correlation with Ki-67 (69) |
| *VEGFA*, vascular endothelial growth factor A (also referred to as VEGF) | Chr 6p21.1 | Induces angiogenesis by promoting endothelial cell survival and proliferation | Increased VEGF staining in PC (76); PC stabilised by VEGF inhibition (bevacizumab) (77) |
| *EGFR*, epidermal growth factor receptor | Chr 7p11.2  | Receptor tyrosine kinase contributing to tumor progression by increasing proliferation, decreasing apoptosis, and inducing angiogenesis and invasion | Increased EGFR expression in APT/PC (78)  |
| *HRAS*, V-HA-RAS Harvey rat sarcoma viral oncogene homolog | Chr 11p15.5\* | Promotes cellular proliferation and differentiation  | Rare activating mutations in APT/PC (70,71) |
| *CCND1*, cyclin D1 | Chr 11q13.3\* | Promotes transition at the G1-S phase cell cycle checkpoint | Germline *CCND1* genotype associated with locally invasive and malignant pituitary neoplasms (79); increased CCND1 staining in APT vs other PA and normal pituitary (80) |
| *ERBB2*, V-ERB-B2 avian erythroblastic leukemia viral oncogene homolog 2 (also referred to as HER2/neu) | Chr 17q12  | Induces cell survival and proliferation | Increased expression in PC (43) |
| *TOP2A*, topoisomerase DNA II alpha | Chr 17q21.2  | Enzyme modifying topological state of DNA, involved in DNA transcription and mitosis | Increased topoisomerase II alpha immunostaining in invasive PA, silent type 3 PA and PC; mixed results regarding correlation with Ki-67 (81) |
| ***Tumor Suppressor Genes*** |
| *MSH6*, MutS E. coli homolog of 6 | Chr 2p16.3\*  | Mismatch repair protein, removes DNA base mismatches caused by errors in DNA replication or by DNA damage | Loss of MSH6 in progression from atypical PA to PC, loss of MSH6 +/- MSH2 in TMZ-resistant atypical PA/PC (44,82); inactivating *MSH6* mutations in PC (83) |
| *MGMT*, methylguanine-DNA methyltransferase | Chr 10q26.3\*  | DNA repair enzyme, removes alkylating adducts in DNA | Decreased MGMT expression in APT/PC, correlates with activation of genes in DNA damage response and DNA repair pathways and genes involved in transcription (84) |
| *CDKN1B*, cyclin-dependent kinase inhibitor 1B (encoding p27Kip1) | Chr 12p13.1  | Binds cyclin/cyclin-dependent kinase complexes, regulates transition at the G1-S phase cell cycle checkpoint | Loss of normal p27 expression in PC (85) |
| *RB1*, retinoblastoma 1 gene | Chr 13q14.2\*  | Regulates cellular proliferation  | *RB1* loss of heterozygosity in highly invasive and malignant pituitary neoplasms (86) |
| *TP53*, tumor protein p53 | Chr 17p13.1  | Induces cellular senescence or apoptosis in response to DNA damage | Increasing cellular accumulation in APT/PC, rare inactivating mutations in APT (48) |
| *BCL2*, B-cell CLL/lymphoma 2 | Chr 18q21.33 | Anti-apoptotic  | Decreased Bcl-2 expression in PC, correlates with higher rates of apoptosis in PC vs. PA (87) |
| ***Other***  |
| *PTGS2*, prostaglandin-endoperoxide synthase 2 (encoding COX2) | Chr 1q31.1  | Cyclo-oxygenase involved in angiogenesis | Increased Cox-2 expression in PC (88) |
| *LGALS3*, lectin galactoside-binding soluble 3 (encoding GAL3) | Chr 14q22.3\*  | Galactose-binding lectin regulating cyclin-E-associated kinase activity | Increased Gal-3 immunopositivity in corticotroph and lactotroph PC (89) |
| *HIF1A*, hypoxia-inducible factor-1alpha | Chr 14q23.2\* | Transcription factor mediating cellular responses to hypoxia | Increased HIF1A expression in PC (90) |

*Abbreviations: \* chromosomal loci that are frequently gained or lost in APT/PC*

A particular gene of interest in the pathogenesis of APT/PC is *MGMT*, which maps to 10q26.3. Low MGMT expression is a common feature in APT/PC (30,84). It is also overrepresented in patients with plurihormonal PIT-1 positive PA, Crooke’s cell PA, Nelson’s syndrome and recurrent NFPA, all of which exhibit more aggressive behavior (84). Low MGMT expression is in turn associated with upregulation of genes involved in transcriptional activity, DNA damage response and DNA repair (84). Interestingly, in pituitary neoplasms low MGMT expression does not correlate with *MGMT* promoter hypermethylation as it does in glioblastoma, suggesting that *MGMT* is inactivated by alternative, currently unknown mechanisms (2,7,84).

The conversion of PA to APT/PC does not appear to be explained by the genes causing sporadic (e.g. *USP8*, *GNAS*) and/or familial (e.g. *AIP*, *MEN1*, *CDKN1B*, *PRKAR1A*, *SDHx*) PAs (2). In a study of 52 patients with somatotroph PA, *GNAS* mutations were found in 53% of tumors but there was no difference between the more common densely granulated subtype and the more aggressive sparsely granulated subtype, and Ki-67 index, invasiveness and diameter did not differ between *GNAS* mutated and wild-type tumors (23). By contrast, a known activating *GNAS* mutation was reported to coincide with conversion of a lactotroph PA into a somatotroph APT (91). This suggests that the conversion to hormone production in APT/PC may sometimes relate to acquired genetic mutations with a true gain of secretory function. An alternative explanation is simply increased tumor bulk with increased hormonogenesis (30).

A myriad of other molecular changes has been observed in APT/PC. As in other cancers, a role for telomerase in facilitating cellular immortality has been suggested with both Ki-67 and telomerase activity shown to increase with sequential resections of a lactotroph PC, whereas telomerase activity was absent in PAs (92). Increased immune tolerance may also be contributory with reduced T-cell concentration, *HLA-B* downregulation and upregulation of genes involved in T-lymphocyte suppression shown in plurihormonal PIT-1 positive PAs (93). The role of T-lymphocytes in pituitary immune tolerance is underscored by the high rates of hypophysitis with the use of ipilimumab in other malignancies (94), and the recent successful use of combined anti-CTLA4/PD1 therapy in a corticotroph PC (83). Changes have also been observed in microRNA, which are small non-coding RNAs that bind the 3’-untranslated regions of target mRNAs, thereby regulating post-transcriptional gene expression (95). In a study of lactotroph neoplasms, miR-183 was downregulated in APTs versus non-aggressive PAs and this was associated with increased expression of *PCLAF*, a gene inhibiting p53 and p21 mediated cell cycle arrest. miR-183 and *PCLAF* also correlated with Ki-67 and p53 expression (95). In a case of a non-functioning PC with multiple intracranial metastases, miR-20a, miR-106b and miR17-5p were upregulated in the metastases compared to the primary neoplasm, in association with decreases in the tumorigenesis genes, *PTEN* and *TIMP2*, which are downstream targets of these microRNAs (96). Another study showed upregulation of miRNA-122 and miRNA-493 in PC versus PA, with miRNA-493 shown to interact with the *LGALS3* and *RUNX2* genes which have been implicated in pituitary cellular proliferation (97).

**MANAGEMENT**

The key principle in the management of patients with APT/PC is for care to be directed by an expert multidisciplinary team. Multimodal treatment strategies are most commonly required. Surgery, radiotherapy and medical therapies all have a role in the management of APT (Figure 1). Tumor location and size, the presence of single or widespread metastatic disease (in PC), prior surgery and extent of resection(s), previous radiotherapy and cumulative doses, optimisation of standard medical therapies, past oncological treatments and patient comorbidities are all important considerations in formulating management plans.

**Figure 1. Treatment options in APT/PC**



**Surgical Management**

Patients with APT frequently require repeated neurosurgical procedures. In the ESE survey cohort, patients underwent a mean of 2.7 operations while 29% had four or more pituitary operations over the course of their disease (30). Multiple studies now demonstrate improved outcomes and lower complication rates when pituitary surgery is performed by high-volume neurosurgeons (98-101). The likelihood of achieving gross total resection is consistently reduced in the presence of tumor invasion, particularly of the cavernous sinus, even in the most experienced hands (102,103). Endoscopic endonasal surgical techniques utilising angled endoscopes and wide exposure may facilitate safe and more extensive surgical resection compared with transsphenoidal microsurgical approaches (104-106). In some circumstances where tumor extends to a significant degree into suprasellar or other extrasellar regions, a transcranial approach may be favored. However, the degree of resection may be limited by the risk of morbidity, depending on tumor location.

Surgical resection, even as a debulking procedure, should be considered in patients with APT as it may offer significant relief of compressive symptoms, particularly when there is visual disturbance (107,108). In patients with isolated metastatic deposits (either craniospinal or systemic disease) complete surgical excision may result in long-term disease-free progression particularly when followed by adjuvant radiotherapy (109-111). Repeat surgical resections of recurrent metastases may also prolong survival (13).

**Radiotherapy**

The use of radiotherapy should be considered in patients with APT as it may assist in long-term control of tumor growth (112). Radiotherapy is recommended in the setting of clinically significant tumor growth despite surgery, and in the case of functional tumors where standard medical therapy has been ineffective (2). In patients with PC, palliative radiotherapy may be delivered to sites of metastatic disease but there is no evidence that it prolongs survival (112). Discussion about radiotherapy should take place within a multidisciplinary setting involving an expert radiation oncologist (2). The role of further debulking surgery prior to radiotherapy should be discussed. Radiotherapy applied to a smaller tumor volume is more effective, and removing tumor in close proximity to the optic apparatus may allow safer and improved radiotherapy delivery (2,113). In previously irradiated patients, consideration must be given to the cumulative radiation dose applied to the target region. In patients with invasive tumor remnants following surgery *and* where histological markers indicate the potential for aggressive tumor behavior (high Ki-67, particularly ≥ 10%; elevated mitotic count; increased p53 immunostaining), adjuvant radiotherapy should be considered (2). In the case of evident aggressive tumor behavior, combination radiotherapy and chemotherapy with temozolomide (TMZ) may yield improved outcomes (30).

Fractionated external beam radiation therapy (EBRT) and stereotactic radiosurgery (SRS, delivered as single dose or in fractions) are both highly effective in the management of PAs. In one study of NFPAs, routine use of postoperative radiotherapy was associated with a doubling of 10-year progression-free survival compared with patients who did not undergo radiotherapy (93% vs. 47% ) (114). Success rates vary across studies because of different modalities (linear accelerators, Gamma Knife, proton beam irradiation) and variable techniques, doses and imaging protocols used between centers (115). In APT, there are limited data on the effectiveness of radiotherapy. In a series of 50 patients with persistent or recurrent adenomas despite prior radiotherapy, further focal SRS was effective in the majority of cases, although a large number of cases were treated for persistent GH excess rather than radiologically aggressive tumors (116,117). The response to radiotherapy may only be transient in more aggressive tumors or even ineffective, particularly in cases demonstrating progression despite salvage chemotherapy (30).

The choice of radiotherapy technique and modality is ultimately based on safety considerations (e.g. proximity to optic chiasm), volume of disease, and local center availability (2). Adverse effects of radiotherapy delivered to the pituitary, such as hypopituitarism or risk of secondary tumors, has rationalized the modern day use of radiation therapy for pituitary tumors. However, considering the morbidity and excess mortality associated with APT, these adverse effects, particularly given their significant latency, should not hinder the prompt use of radiotherapy in APT.

**Peptide Receptor Radionuclide Therapy (PRRT)**

Pituitary neoplasms express somatostatin receptors and have demonstrated 68Ga-DOTATATE uptake on PET/CT, stimulating interest in the use of PRRT in the management of APT (118,119). There is only limited experience with PRRT reported in the literature to date in patients with APT. A variety of radionuclides have been utilised including 111Indium-DPTA-octreotide, 177Lutetium DOTATATE, 177Lutetium DOTATOC and 90Yttrium-DOTATOC (2,120). Of 14 cases, only two patients (one giant lactotroph PRL-secreting adenoma, one GH-secreting macroadenoma) have demonstrated a reduction in tumor size, one without a concomitant hormonal response (121,122). Stable disease was reported in three cases while nine patients progressed with PRRT (2).

**Standard Medical Therapy**

APTs typically display resistance to the standard medical therapies commonly used in the management of functional PAs. Use of maximally tolerated DA treatment should be attempted in lactrotroph APTs given occasional reported responses (123,124). Cabergoline (3.5-11mg per week) is more effective than bromocriptine or quinagolide (2). Tamoxifen has been unsuccessfully used in lactotroph PC (2). In rare cases of somatotroph PC, use of DA treatment has been associated with GH and IGF-1 reductions and symptomatic improvement, but without tumor shrinkage (27,125). Similarly, the use of first generation SSAs in somatotroph APTs is largely ineffective, whereas pasireotide may improve biochemical control although data in APT are scarce (126). Resistance to first generation SSAs (octreotide, lanreotide) due to downregulation of sst2a expression has been described among *AIP* mutation positive individuals with somatotroph tumors, but expression of sst5 is often preserved and thus response to second generation broader-spectrum SSAs, such as pasireotide, may be more effective (127). Temporary benefit from high dose octreotide has been described in a case of thyrotroph PC (53).

Aggressive corticotroph tumors represent a particular challenge, and these patients often require medical therapy to reduce hypercortisolism, a common direct cause of death (112). Adrenal glucocorticoid inhibitors, such as ketoconazole or metyrapone, are frequently used in such cases. Pasireotide has been reported in 15 cases of aggressive corticotroph tumors, including nine with Nelson’s syndrome, but with only one case exhibiting a hormonal and radiological response (2,128).

**Chemotherapy**

WHEN TO INITIATE CHEMOTHERAPY

In patients with PC, the decision to start systemic chemotherapy is clear and associated with improved survival (2,129,130). In patients with isolated metastases, loco-regional therapies such as hepatic chemoembolisation for low-bulk liver metastases may offer temporary tumor control (131). For APT, in cases of documented tumor growth, other treatment options may be explored first, such as further surgery or radiotherapy if appropriate, and histological parameters such as Ki-67 or tumor subtype, may play a role in decision making. However, it is increasingly recognised that apart from the presence of metastases, there is little that distinguishes APT from PC (16). Most importantly, time to death following diagnosis of pituitary tumor is similar between APT and PC (30). Prior to the recognition of TMZ efficacy in APT, chemotherapy was typically reserved as salvage therapy because of poor response rates. The mean survival rate in the pre-TMZ era for PC was 1.9 years (49). APT and PC treated with TMZ are now reported to have 5-year overall survival rates of 57.4% and 56.2% respectively (132). In the large French cohort, median survival was 44 months in patients who responded to TMZ compared with 16 months in non-responders (133). While TMZ is still most commonly used as a last resort therapy, it has been successfully employed during or prior to radiotherapy (30,134). In fact, the 2018 ESE guidelines suggest, in patients with rapid tumor growth where maximal doses of radiotherapy have not been reached, TMZ may be combined with radiotherapy as per the Stupp protocol used for glioblastoma (2,135). As new therapeutic modalities emerge in the coming years, clinicians will likely employ TMZ earlier in the treatment algorithm for APT. Decisions must be made within an expert multidisciplinary team setting where risk-benefit ratios are carefully deliberated, taking into account the morbidities of repeated surgery or radiotherapy as well as the potential for rare long-term consequences of chemotherapy such as hematological malignancy (2).

TEMOZOLOMIDE

TMZ is recommended as first-line chemotherapy for patients with APT and PC, with more than 200 cases now reported in the literature including the recent ESE survey (2,30). The overall response rate is 37-47% across the larger cohorts, with complete responses (both biochemical and radiological) seen in approximately 5% of cases (2,30). However, if stable disease is considered a clinically beneficial outcome, as it frequently is in oncological studies, then rates of progression-free survival are 50-87.6% in APT and PC (30,130). Clinically functioning APT are 3.35 times more likely to respond to TMZ compared with non-functioning APT (30). APT are just as likely to respond to TMZ compared with PC, although progression may be more frequent among tumors with a Ki-67 ≥10% (30).

TMZ is a second-generation imidotetrazine alkylating agent which, when hydrolysed, forms toxic methyl adducts with DNA bases resulting in ineffective DNA repair and ultimately cellular apoptosis (136). TMZ is given as an oral outpatient-based chemotherapy, most commonly as monotherapy. Some centers advocate use of capecitabine pre-treatment (CAPTEM) because of *in vitro* data in neuroendocrine tumor cell lines suggesting synergistic effects with this regimen, although evidence supporting its superiority in APT is lacking (137). Similarly, it has not yet been demonstrated that TMZ in combination with any other drug(s) has enhanced efficacy (2). However, where maximal doses of radiotherapy have not been given to a patient, there is suggestion of improved response when TMZ is given concurrently with radiotherapy (2,30,138). Experimental data strongly support a radiosensistizing effect of TMZ (139,140).

The TMZ doing regimen given for APT is 150-200mg/m2 for 5 consecutive days every 28 days. It is generally well tolerated, although mild to moderate fatigue, nausea and myelosuppression are common side effects, occurring in roughly half of patients but leading to TMZ discontinuation only in a minority (2). A dose reduction or delay in treatment cycles can allow patients to continue TMZ when myelosuppression occurs. Regular monitoring of hematological and liver function profiles is required during treatment. Hemorrhage into cerebral metastases has been described in a patient with PC who developed severe thrombocytopenia (141). Hepatoxicity has been reported when TMZ was used concurrently with ketoconazole therapy, and cholestatic hepatitis has also been reported in association with TMZ treatment in the wider literature (142,143). TMZ-induced hearing loss has been described among two pituitary cases and other rare side effects in non-pituitary literature include hypersensitivity pneumonitis, Stevens-Johnson syndrome and hematological malignancies (2). Prophylactic trimethoprim-sulfamethoxazole to protect against *Pneumocystis* pneumonia should be considered, particularly in hypercortisolemic patients receiving concurrent radiotherapy and TMZ and patients who develop significant lymphopenia during TMZ therapy (2).

WHEN TO STOP TEMOZOLOMIDE

Response to TMZ will be evident after 3 months of therapy (144). Treatment should cease in the event of progressive disease while receiving TMZ, or if serious adverse events occur. It is recommended to continue with treatment for at least 6 months, but therapy is often extended if there is ongoing clinical benefit (2). In the ESE survey, median treatment duration was 9 months and the longest course was 36 months (30). In this patient cohort, treatment with TMZ was initiated prior to the publication of management guidelines for APT. Hence, duration of therapy was often prescribed by oncology teams at the outset and was based on experience with TMZ clinical trials in glioblastoma (135). Following cessation of TMZ treatment in APT and PC, there is frequently a period of sustained remission. Time to tumor progression is variable, and whether longer treatment courses or degree of initial response improves progression-free survival is not currently clear. The median time to progression after cessation across patients in the ESE survey cohort was 12 months (range 1-60). Two patients exhibiting the longest time to progression were PC cases with complete response to TMZ (30). In the French multicenter cohort, patients receiving more than 12 months of TMZ achieved a median relapse-free survival of 57 months compared with 18 months in those receiving less than 12 cycles (133). However, response rates were 100% in those receiving longer treatment courses versus 75% in the shorter treatment group. Nevertheless, long-term treatment has been reported to be associated with improved progression free survival of 61% compared to 16% for short term treatment (132).

DETERMINANTS OF RESPONSE TO TEMOZOLOMIDE

The most well recognised biomarker of the likely response to TMZ is expression of O(6)-methylguanine DNA methyltransferase (MGMT). An endogenous DNA repair protein, MGMT is responsible for removal of the methyl group induced by TMZ therapy. In the absence of MGMT, unrepaired methylated guanine (O6-MeG) lesions incorrectly pair with thymine, triggering activation of the mismatch repair pathway (MMR). Intact MMR results in futile attempts at repair via incorrect reinsertion of thymine opposite the O6-MeG lesion. Cycles of ineffectual repair eventually result in DNA strand breaks which lead to cell cycle arrest followed by either apoptosis or cellular senescence. If MMR function is lost, then paradoxically cells can survive. However, even in the presence of intact MMR, MGMT can facilitate cell survival by direct repair of O6-MeG, targeting it for ubiquitination and degradation (Figure 2)(145).

Low expression of MGMT, as determined by IHC, is associated with a high response rate, around 75%, while tumors with high MGMT expression are unlikely to respond (30,136). Evaluation of MGMT status by IHC should be performed by a neuropathologist with expertise in APT (2). Lack of standardized IHC technique, use of different expression criteria across centers, poor fixation methods, and tumor heterogeneity are among the challenges in assessment of MGMT IHC. MGMT promoter methylation analysis has not been associated with response to TMZ in pituitary neoplasms (136,146).

DNA mismatch repair proteins such as MSH6, MLH1, MSH2 and PMS2 may also play a role in response to TMZ. Loss of MSH6, in the presence of low MGMT, has been described as a mechanism responsible for the development of resistance to TMZ (147). The overexpression of multidrug resistance proteins and activity of the Sonic hedgehog signalling pathway may also contribute to TMZ resistance (130).

**Figure 2. Temozolomide Cytotoxicity and Mismatch Repair Pathway**



TREATMENT OPTIONS BEYOND TMZ

There is a pressing need to identify alternative effective oncological therapies for patients progressing on TMZ or following an initial successful course of TMZ treatment. Given the paucity of treatment options, a second 3-cycle trial of TMZ treatment may be considered in patients who develop recurrence after a previous response to TMZ (2). However, a second treatment course has rarely been reported to be successful in such cases (2). If there is rapid tumor progression on TMZ treatment, a trial of other systemic cytotoxic therapy is recommended based on historical reports of transient regression and/or stabilization with some regimens (2). Lomustine (CCNU) and/or 5FU have most commonly been employed, but multiple other drugs, alone or in combination, including cyclophosphamide, doxorubicin, adriamycin, carboplatin/cisplatin, etoposide and vincristine have also been reported, with variable results (2,30).

Use of targeted therapies offer some promise, but data on clinical effectiveness are lacking. *In vitro* data demonstrating upregulation of Raf/MEK/ERK and PI3K/Akt/mTOR pathways in pituitary tumors have thus far not translated into clinical success in APT (30,148,149). There has been limited use of tyrosine kinase inhibitors (lapatinib, sunitib, erlotinib), with just one case report of a partial response with lapatanib in a lactotroph APT (150). VEGF-targeted therapy with bevacizumab, as monotherapy or in combination with TMZ, has resulted in partial response or stable disease in a few cases, although progressive disease has also been reported (30,77).

Finally, there is emerging interest in the potential use of immunotherapy for the treatment of APT. Pituitary neoplasms, particularly APT, have been shown to express programmed death ligand 1 (PD-L1), a T-cell immune checkpoint biomarker, along with tumor infiltrating lymphocytes (151,152). Combination treatment with ipilimumab and nivolumab has recently been reported to result in marked tumor shrinkage and hormonal response in a patient with a hypermutated corticotroph PC (83).

**PROGNOSIS**

Morbidity and mortality are increased in APT even in the absence of progression to PC (2,16). This is particularly true in functioning corticotroph APTs, where morbidity and mortality are further increased in relation to cortisol excess (2).

In the ESE survey, mortality was higher in PC (43%) compared to APT (28%) (16), but median survival from initial diagnosis of pituitary tumor was similar (11 years in APT vs. 12 years in PC) (30). The time to death from PC diagnosis ranged from seven days to eight years in the study by Pernicone *et al*, with a 66% 1-year-survival (13). The mortality rate reported by Yoo *et al* was 55% with an average time to death after PC diagnosis of just 10 months (31). Amongst all endocrine carcinomas, PC demonstrates the strongest decline in survival with advancing age (26). Prognosis is also poor in patients with corticotroph PC, systemic metastases, or progression during TMZ therapy (1,13,30,153). By contrast, patients who respond to TMZ experience a clear survival benefit (133). Exceedingly long-term survival over several years has been observed in selected cases (6,13), even without TMZ (153), but predictive markers for such survival remain unknown (47).

**FUTURE DIRECTIONS**

Comprehensive molecular studies will hopefully identify better biomarkers for PAs that are destined to become APT/PC. In addition to molecular biomarkers, the growing sphere of nuclear medicine may prove useful in the assessment of PC, which currently lacks a standard method of staging. 11C-methionine, a tracer with specific avidity for neoplastic pituitary tissue, has shown superior sensitivity to 18F-FDG-PET in localising functioning PAs (154). Though yet to be studied in PC, 11C-methionine holds promise in better delineating metastatic disease. Integration of molecular, functional and clinical data may ultimately assist clinicians in better identifying tumors with the potential for more aggressive behavior. This will allow earlier and more proactive management in affected patients with the goal of improving prognosis.

Because of the rarity of PC and the diverse subtypes of APT, current data are plagued by small sample size driven by case reports or series, heterogeneous case mix, short follow-up and clinical rather than histological diagnoses of PC metastases, with heavy reliance on expert opinion and local practice and a dearth of randomized controlled trials. Calls by the ESE to form an international register for APT/PC should help address the multiple evidence gaps in these rare disorders (2). As APT/PC are almost invariably diagnosed retrospectively, routine pituitary tumor biobanking with methodical storage of tissue in media that circumvent formalin-induced DNA damage will be critical in studying pathogenesis. Waiting for metastasis before labelling a pituitary neoplasm as PC is particularly problematic, given the similar time-to-death from initial pituitary tumor diagnosis between patients with APT versus PC (16). The recent suggestion to replace the term ‘pituitary adenoma’ with ‘pituitary neuroendocrine tumor’ (PitNET) is hoped to emphasise the malignant potential of a subset of these neoplasms and expand treatment intensity (9,155); however, as with all changes in nomenclature, this risks a disconnect between existing literature and contemporary clinical practice.

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