

Review

Challenges and Gaps in the Management of Aggressive Pituitary Tumours: A Narrative Review

Ruwanga V. G. D¹, Muthukuda D. T¹, Buddhika P. G¹, Seneviratne M. B. S², Jayantha B³, Asha H. S⁴

¹ Sri Jayewardenepura General Hospital, Sri Lanka

² Department of Pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka

³ General Sir John Kotelawala Defence University, Sri Lanka

⁴ Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore

Abstract

An Aggressive Pituitary Tumour (APT) is defined as a tumour showing unusually rapid tumour growth with invasion into surrounding structures evidenced on imaging, or clinically relevant tumour growth despite optimal standard therapies. Almost all of APTs are macroadenomas at clinical presentation accounting for up to 15% of all pituitary neoplasms. No single marker can accurately predict the behaviour of a tumour. Ki-67 index >3%, mitotic count >2 mitoses per 10 HPF and the presence of p53 expression along with imaging showing features of invasion have been the most reliable diagnostic methods. Intrinsic characteristics of the tumour determine the rapidity of tumour growth rate of recurrence and the degree of resistance to conventional treatments. Invasiveness is a major determinant of incomplete tumour resection. APTs are resistant to current available treatment options including surgery, standard medical therapy, and radiotherapy. Multimodal approach in the management comprises re-do surgery, with medical therapy including chemotherapy and radiotherapy. Temozolomide, a chemotherapeutic agent can be used in those with documented tumour growth despite optimal standard therapy. Though medical therapy alone is not effective in controlling tumour growth in APT; it helps in controlling hormone hypersecretion to some extent. Peptide receptor radionuclide therapy (PRRT), targeted therapies and immune checkpoint inhibitors are emerging treatment modalities. Lifelong follow up is required with periodic imaging and hormonal evaluation to assess treatment response, adverse effects of medications and evolution to pituitary carcinoma. Future studies are needed to identify prognostic indicators of future aggressive behaviour of pituitary tumours and biomarkers to assess treatment response.

Keywords: pituitary tumour, immunohistochemistry, Ki-67 index

Correspondence email: dinithiruwanga84@gmail.com

ORCID ID: <https://orcid.org/0009-0005-5663-017X>

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Introduction

Pituitary neuroendocrine tumors (PitNET) is a benign tumour which is slow growing in nature. Approximately 10% to 15% of intracranial neoplasms are pituitary adenomas [1]. Pituitary adenomas can be categorized as aggressive or non-aggressive and invasive or non-invasive, based on their histological findings, imaging findings and/ or clinical behaviour. An aggressive pituitary tumours (APT) are tumours that require multiple surgeries, have a high likelihood of recurrence, and are resistant to standard treatments.

Pituitary tumours have a wide range of clinical behaviours; with a large proportion clinically silent initially due to indolent growth; though some are invasive; and a small proportion exhibit rapid growth. Radiological and clinical behaviour do not always correlate with the proliferation index of the tumour on histopathology [2]. Functioning tumours are recognized earlier due to symptoms related to excess hormonal secretion. Tumour recurrences occur in 30% of patients

with pituitary tumours between 0.4 – 37 years following surgery and the risk is high when there is a residual tumour [3]. The pathways regulating development, progression, and invasion of these tumours are still poorly understood.

MRI brain, hormonal analysis, histological evaluation using proliferative markers and immunohistochemistry for pituitary hormones and, more recently, transcription factors are all used in the diagnostic process. Even though research had been done on biological markers of aggressive behaviour of pituitary adenomas, none of these have been individually proven to be causative.

Management of APTs is very challenging because of their rapid growth, invasiveness, and high recurrence rate [4]. Most pituitary tumours can be managed with either surgery or medical treatment with some cases requiring radiotherapy. As APTs do not respond to conventional treatments, there is no standard treatment guideline for APT. Multiple surgeries, either transphenoidal, transcranial, or in combination, may be needed [5]. Complete excision is difficult and considered

as a major factor resulting in postoperative recurrence when pituitary adenomas invade nearby structures and need additional medical treatments and/or radiotherapy [6].

Standard medical treatments have limited efficacy in functional APTs in terms of reducing tumour growth and hormonal hypersecretion. Temozolomide is an oral chemotherapeutic agent which showed efficacy in the medical management of patients resistant to conventional treatment. This is often administered along with radiotherapy which showed improved outcomes [2,5].

The topic selected for this narrative review article is an entity which is not yet clearly defined and in which the management is still evolving. APTs pose challenges throughout the course of detection and management. In this narrative review article, we have highlighted the key areas including when to suspect APT, how to diagnose, novel molecular markers, strategies suggested in managing a patient with APT in a resource-limited setting, and available treatment modalities etc. in an evidenced based approach. We used a question-and-answer type structure in compiling this article, which we believe would make the manuscript more reader friendly. As our team represent a resource poor setting, we have to admit that there are gaps in the knowledge and practice of this entity in this part of the world, partly because of the rarity and complexity of the APTs. Hence it would be an enlightening article to the relevant parties who are dealing with these patients in similar settings.

Literature review

A literature review was conducted from July 2023 to January 2024 with the intention of including studies that were most applicable to challenges encountered in diagnosing and managing suspected aggressive pituitary tumours. An electronic database (PubMed and Google Scholar) searches of all years of publication using the following search entities were performed: an aggressive pituitary tumour, immunohistochemistry, imaging, surgery, medical treatment, radiotherapy, and temozolomide. We collectively selected the articles, from which we could find the most relevant and up-to-date answers to the questions posed in our article. The selected articles included researches, case reports, reviews and current guidelines written in English language.

The key areas with regard to managing APTs are addressed below;

1.What is an Aggressive Pituitary Tumour (APT)?

According to 2018 European Society of Endocrinology (ESE) guidelines, an APT is defined as a tumour with invasion into surrounding structures evidenced on imaging and unusually rapid tumour growth, or clinically relevant tumour growth despite optimal standard therapies (combining surgery, medical therapy and radiotherapy) [2]. But the term "aggressiveness" has been used interchangeably with "invasiveness" or "atypical," leading to varying interpretations [7]. Therefore, a proper definition for APT is needed as there is no widely accepted consensus definition.

In a residual / recurrence of a functional tumour, persistent hormonal overproduction, despite surgical resection or other treatments, even without further growth can be considered part of the aggressive disease

spectrum, especially if it leads to difficulty in controlling symptoms or requiring ongoing management (e.g., ACTH secretion in Cushing disease, prolactin secretion in prolactinomas) [8].

2.What is the prevalence of aggressive pituitary tumours?

There is lack of uniform definition for aggressive pituitary tumours, and in view of its rarity, the prevalence cannot be accurately determined from literature [9]. APTs account for up to roughly 10-15% of all pitNETs including tumours that show one or more features of aggressive behaviour, but not all necessarily exhibit rapid growth despite standard treatment [10]. Out of all APTs, 75% are macroadenomas, 22% are giant tumours and 30-40% are functioning tumours with corticotroph and lactotroph neoplasms which are being the most common types [11,12,13]. The majority of APT are seen in the fifth decade of life.

3.What are the key features suspicious of an aggressive pituitary tumour?

Although there is no single prognostic marker to predict the aggressiveness of a pituitary tumour; a composite of clinico-pathological behaviour and radiological markers of cavernous sinus invasion Knosp≥3b have been found to be useful in prognosticating aggressive behaviour [14]. The pathological subtypes of pituitary tumours associated with aggressive behaviour include crooke cell adenoma, immature PIT1 lineage tumours, lactotroph tumours in men, sparsely granulated somatotroph and corticotroph (silent corticotroph) tumours [15]. Macroprolactinoma not responding to medical therapy, a non-functioning pituitary adenoma becoming a functioning tumour, progressive tumour growth following radiotherapy, tumours with high Ki-67 index > 10%, a high mitotic count and presence of p53 expression [16], are key features which favour an APT. An ESE survey on 121 aggressive pituitary tumours provides valuable insights into the prevalence of key tumour characteristics associated with tumour aggressiveness [13]. The following chart summarizes the findings (table 1). Here APT was defined as an invasive tumour with an unusually rapid growth rate, or a tumour not controlled by repeat surgery, radiotherapy, and/or demonstrating resistance to medical treatments.

4.How do aggressive pituitary tumours behave?

There is insufficient information found in the literature to provide a precise and evidence-based definition of "unusually rapid tumor growth rate" or "clinically relevant tumor growth," hence these terms are not defined in the guidelines including ESE guideline [17]. Therefore many studies define significant growth according to the expert opinions. The rapid tumour growth despite standard treatment is defined as tumour growth more than 20% in its maximum diameter, visualised on MRI brain in less than six to twelve months [17]. Clinically significant tumour growth is defined when the tumour has grown to a maximum diameter of more than 20%, which creates new symptoms, or whose location indicates development of new symptoms [17].

APTs are typically diagnosed many years after initial surgery [5]. APTs have a high tendency of recurring or not responding to conventional treatment. They usually have a rapid growth and are larger in size. An ESE survey reported that an apparent clinically benign course changed into an aggressive course after a median of 5.5 years from diagnosis [13].

Table 1: Summary of characteristics at diagnosis of 121 aggressive pituitary tumours (APT) included in ESE survey 2020–2021.

Tumour characteristics	Aggressive Pituitary Tumours (%)
Initial hormone secretion	
Non secretory	33 (27.3%)
Prolactin	38 (31.4%)
ACTH	32 (26.4%)
FSH	1 (0.8%)
GH	12 (9.9%)
TSH	3 (2.5%)
MRI at initial diagnosis	
Microadenoma	5 (4.1%)
Macroadenoma	82 (67.8%)
Invasive at diagnosis Yes/No	
Not invasive	19 (15.7%)
Invasive	76 (62.8%)
Ki67 index (%)–Tumours tested	58/112
Ki-67 <3, n (%)	13 (22.4)
Ki-67 >3, n (%)	45 (77.5)
p53 Positivity- Tumours tested	24/112
<10, n (%)	18 (75)
≥10, n (%)	6 (25)
Mitotic Count -Tumours tested	26/112
n <2, n (%)	18 (69)
n >2, n (%)	8 (31)

Invasiveness is itself not enough to characterize APTs, in part because invasion is frequently arbitrary, with differences between radiological, intraoperative assessment, and histological features^[18]. Eighty percent of the 121 APTs showed invasion into the cavernous sinus and/ or sellar floor^[13]. Twenty five to fifty percent of pituitary tumours invade surrounding structures including the cavernous sinus, blood vessels, nerves and skull bones^[18]. Tumours with parasellar extension and bone erosion are classified as invasive pituitary tumours according to Hardy's classification^[19]. Suprasellar extension of the tumour does not indicate invasiveness of pituitary tumour as non-tumoural tissues line the suprasellar portion of the tumour^[20]. Invasion of the tumour is closely related to extent of surgical resection, recurrence and progression of tumour^[21]. In contrast to microadenomas, macroadenomas typically invade more frequently^[20].

APTs are more likely to be associated with higher surgical complication rates due to several factors, including tumor invasiveness, vascularity, resistance to treatment, and recurrence rates^[2].

The exact proportion of APTs that are functional (hormone-secreting) varies across studies, but certain functional subtypes are more frequently associated with aggressive behaviour. An estimated 10–15% of corticotroph tumours have invasive behaviour^[22]. Furthermore, rather than pursuing an aggressive clinical course, extremely invasive prolactinomas may respond favourably to dopamine agonist therapy, but about 10% of prolactinomas may exhibit aggressive characteristics and be resistant to treatment^[23]. Prolactinoma is more common in females than in males. Nevertheless, prolactinomas in men usually show aggressive behaviour and they do not respond to dopamine agonist therapy^[23]. Occasionally, after many years of observation, previously silent corticotroph tumours may evolve to release ACTH; this change may also portend more aggressive tumour behaviour.

The size of a pituitary tumour at presentation does not always indicate the likelihood of aggressive behaviour, as demonstrated by giant prolactinomas that may respond well to dopamine agonist therapy^[24].

Recurrence and aggressive behaviour of tumours are two different entities as some tumours can recur within 6 months following surgery, while some may recur 10 years after surgery^[2]. Even after surgery and radiotherapy, 13% of patients exhibited regrowth of the tumour^[17].

The majority of pituitary apoplexy occur in non-functional macroadenomas, however aggressive pituitary tumors (APTs) include risk factors for apoplexy, such as rapid tumour growth, and invasion into vascular structures. There is insufficient data to conclude that APTs are substantially more likely than other macroadenomas to experience apoplexy overall^[2].

5.Is it possible to differentiate APT from pituitary carcinoma (PC)?

A small percentage of pituitary tumours that exhibit multiple recurrences with locally destructive activity (APT), as well as rare cases of metastasis (pituitary carcinoma), do not respond to conventional treatment^[2]. Pituitary carcinoma (PC) is defined as pituitary tumours which have cerebrospinal and/or systemic metastases, but APTs lack distant metastasis^[25]. The differentiation between APT and pituitary carcinoma, particularly in cases where there is potential for metastasis but no actual metastasis, is a subject of ongoing debate and it is still unclear if they represent different conditions or different aspects of the same spectrum^[8].

Pituitary carcinoma are rare tumours which account to 0.1% to 0.2% of pituitary tumours^[18]. There is debate over whether or not a pituitary tumour's invasion qualifies as an additional requirement for carcinomas^[26]. The majority of PC cases begins with aggressive clinical courses^[27].

Both types of tumours share features of aggressive behaviour, including rapid growth, and local invasion, it can be challenging to distinguish locally aggressive pituitary adenomas from pituitary carcinomas since metastases are uncommon at the time of their first presentation^[28].

It should be highlighted that APTs and carcinomas cannot be distinguished from one another by histological characteristics alone. In an attempt to forecast tumour behaviour and distinguish between APT and pituitary carcinoma before recognizing metastatic disease, efforts have been made to characterize the morphologic characteristics and genetic markers linked to these two conditions^[29]. These include detecting the level of mitotic activity, cytologic atypia, analyzing proliferation markers like Ki-67 with the MIB-1 antibody, and looking at cell-cycle molecular markers such as p27 and galectin-3 and MGMT, gene expression of p53, and MMP-9 genes^[29,30].

6.How should a patient suspected of having an APT be assessed?

While some APTs initially appear as clinically benign and later develop aggressive features, more than half of them take an aggressive course from the beginning^[24]. It signifies that diagnosis of some APTs have to be made in retrospect. Imaging, hormonal assessment and histological evaluation of the tumour should be performed in all these patients. Intra-operatively observed tumour extension is also useful in predicting aggressiveness^[31]. Neurological and visual field assessment should be done periodically. MRI brain should be done 3 months post-operatively to assess for residual tumour which would serve as the baseline to

assess for tumour growth on future imaging.^[32] Lack of distinction between continuous growth of a tumour even after surgery and true recurrence on pituitary imaging is a challenge. Knosp grading on MRI brain is used to evaluate and grade cavernous sinus invasion. Knosp classification grades III and IV show cavernous sinus invasion^[14]. The specimen retrieved during surgery should be sent for immunohistochemistry for the assessment of pituitary hormones, transcription factors, proliferative markers like Ki-67 proliferative index, mitotic count and p53 expression. They help to identify the type of adenoma, and those with higher risk of aggressive behaviour. Ki-67 $\geq$ 3% and/or increased mitoses and/ or p53 expression are frequently, but not always observed in APTs^[2,33].

Pituitary hormonal analysis should be done at 3-12 monthly intervals following surgery for early identification of relapse of functioning pituitary tumours and to identify hormonal deficiency due to regrowth of tumours compressing on the normal adenohypophysis^[2]. The transformation of a non-functioning pituitary adenoma into a clinically secretory tumour, non-responsiveness to medical treatment, the onset of new or progressive features of hypopituitarism, or rising hormones despite radiological stability can all be signs of transitioning to an APTs.

7. What are the immunohistochemical markers of APT? Do they represent the aggressiveness of the pituitary tumour?

In 2017 WHO classification of pituitary tumours, grading system of pituitary tumours was not included. Instead, histopathological features correlated with clinical symptoms were used to predict tumour behaviour^[33]. All pituitary tumours need histological assessment at least with Ki-67 proliferative index and immunodetection of pituitary hormones according to the ESE guideline 2018^[2]. When Ki-67 proliferative index is more than 3%, p53 expression and mitotic count should be assessed^[2]. The Ki-67 proliferative index, an indicator of cellular proliferation, shows the proportion of cells stained with MIB-1 antibody and it differentiates proliferating cells from quiescent cells^[34]. In addition to predicting aggressive tumour behaviour, Ki-67 index of more than 3% has 97% specificity and 73% sensitivity in differentiating between invasive adenoma from non-invasive adenomas^[34]. However, there is lack of consensus on its utility to predict relapse^[2]. Pituitary tumours with Ki-67 proliferative index more than 10% show characteristics of aggressive and invasive behaviour^[34].

P53 protein, tumour antigen involved in cell cycle regulation, can be seen in APT and invasive adenomas^[35]. P53 expression was identified in 15.2% in invasive adenomas and 100% in pituitary carcinomas and not identified in non-invasive pituitary adenoma^[35]. However, its utility in the diagnosis of APT remains unclear at this time. Mitotic count greater than two mitoses per HPF indicates a higher probability of tumour recurrence^[33].

Ki-67 proliferative index $>3\%$ was found in 81% of APTs and 85% of PC, p53 positivity in 73% of APT and 78% of PC and mitotic count >2 mitoses per 10 HPF in 63% of APT and 90% of PC^[2]. There is lack of evidence to suggest which pituitary tumours may progress to more aggressive forms by using current molecular markers, Ki-67 index and p53 expression. Ki-67 index $> 3\%$, mitotic count > 2 mitoses per 10 HPF and the presence of p53 along with imaging showing invasion are considered as predictors of APT^[21].

However, these molecular profiles of histology from repeated surgeries can be monitored and high expression of these markers may be helpful in deciding management options such as adjuvant radiotherapy in patient with a residual tumour^[21].

8. What are the novel molecular markers of APT ?

There is no single molecular marker identified that may accurately predict the tumour behaviour^[21]. Fibroblast growth factor receptor-4 (FGFR4), transmembrane receptor tyrosine kinase, detected in tumour cell biopsy, has been demonstrated to promote the invasion of pituitary tumours in vivo on animal models and metalloproteinase 9 has been shown at higher concentration in invasive pituitary tumours^[36,37]. In prolactin secreting tumours, ASK, CCNB1, AURKB1 and PTTG, were shown to be associated with proliferation of the tumours and ADAMTS6, CRMP1 and DCAMKL3, were associated with invasiveness of the tumours^[38]. These markers primarily assessed through mRNA expression and protein expression in tumour cells^[38].

Many growth factors have been studied in an attempt to determine the aggressiveness of pituitary tumours, but none has been shown to be a good biomarker. GH-producing adenoma cells express vascular endothelial growth factors (VEGFs), epidermal growth factors (EGFs), and their receptors (VEGF and VEGFR, respectively). The levels of EGFs and VEGFs are associated with the aggressiveness of pituitary tumours^[39]. A combination of novel molecular markers and immunohistochemical markers may enhance the prediction of aggressiveness of these tumours, but these has not been tested so far^[40]. The following chart summarizes key areas discussed above from 1-7 (table 2).

9. What are treatment options for managing patients with an APT?

APTs are resistant to currently available conventional treatment options including surgery, standard medical treatment and radiotherapy. A multimodal approach is essential for the management of a patient with an APT and this basically consists of multiple surgeries, medical therapy including chemotherapeutic drugs like temozolomide, and repeated cycles of radiotherapy^[41] (figure 1).

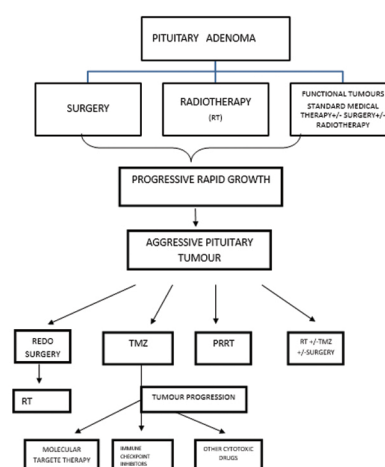


Figure 1: Suggested approach for the management of aggressive pituitary tumours. TMZ, temozolomide; PRRT, Peptide Receptor Radionuclide Therapy can be given instead of TMZ in patients who have a positive somatostatin receptor PET/CT; Molecular targeted therapy: bevacizumab (an anti-VEGF antibody), tyrosine kinase inhibitors (TKIs), everolimus (an mTOR inhibitor); Immune check point inhibitors: nivolumab (Anti-PD-1/PD-L1 antibodies), ipilimumab (anti CTLA-4 antibodies); Other cytotoxic drugs: fluorouracil (5-FU), adriamycin, cisplatin, carboplatin, procarbazine, mitotane, etoposide, vincristine, doxorubicin- some of these have been used at earlier steps in some case reports

Table 2: The summary of key areas discussed above from 1-7

Feature	Key points
1. Key features suspicious of APT	Macroprolactinoma not responding to medical therapy A non-functioning pituitary adenoma becoming a functioning tumour Tumours with high Ki-67 index > 10% High mitotic count and presence of p53 expression The pathological subtypes of pituitary tumours e.g. crooke cell adenoma, immature PIT1 lineage tumours, lactotroph tumours in men Progressive tumour growth following radiotherapy
2.Prevalence of aggressive pituitary tumours	15% of all pituitary tumours (difficult to determine due to lack of uniform definition)
3.Behaviour of aggressive pituitary tumours	Rapid tumour growth High tendency of recurring Not responding to conventional treatment Invasion into the adjacent vital structures Non functional tumour may evolve into functional tumours Most APTs take an aggressive course from the beginning
4.Differentiation between APT and pituitary carcinoma (PC)	Presence of distant metastases is a key differentiating factor for PC (but metastases are uncommon at the time of their first presentation) Pre-operative - Clinical features of hormone excess/neurological and visual field assessment Imaging-MRI brain (invasion into adjacent vital structures/ Knosp grading) Hormonal assessment (functional/non-functional)
5.Assessment of suspected APT	Post-operative - Imaging- MRI brain (residual tumour/ tumour growth/ Knosp grading) Histological evaluation of the tumour - immunohistochemistry for the assessment of pituitary hormones, transcription factors, proliferative markers like Ki-67 proliferative index, mitotic count and p53 expression Novel molecular markers
6.Immunohistochemical markers of APT	Predicting aggressiveness of pituitary tumours - Ki-67 index >3% Mitotic count >2 mitoses per 10 HPF Presence of p53 expression Predicting invasion of pituitary tumours - Fibroblast growth factor receptor-4 Metalloproteinase 9 ADAMTS6, CRMP1 and DCAMKL3 - In prolactin secreting tumours
7.Novel molecular markers of APT	Predicting proliferation of pituitary tumours - ASK, CCNB1, AURKB1, PTTG

Important factors to take into account in the management include the size and location of the tumour, presence of metastasis, the extent of any prior resections performed, the prior radiotherapy doses, the optimal dosage of standard medical therapies, previous oncological treatments, and patient co morbidities. However, it is difficult to treat APT because of large size, tumour invasion into surrounding structures, rapid growth, and high recurrence rate.

The combination of TMZ and radiotherapy is recommended to a patient who is on maximally tolerated dose of radiotherapy for a rapidly growing APT [2]. Based on its synergistic effects with radiotherapy invitro and in experimental trials, TMZ is regarded as a radiosensitizer [42]. There were few case reports describing favourable outcomes in patients with APT who had received TMZ with stereotactic radiotherapy [43]. Twenty patients who had high Ki-67 proliferative index and p53 mutation in 2 ESE surveys received combination therapy with TMZ and radiotherapy. Compared to patients who received only TMZ, 75% of patients who received combination therapy reported favourable outcomes. In comparison, patients receiving only temozolomide (TMZ) had favourable outcomes in 37% of cases. This difference was statistically significant ($p = 0.007$) [44].

10.What are the factors that affect resistance of APTs to current available treatment modalities?

Tumour biology, genetics, epigenetic and tumour microenvironment play a role in treatment resistance of APTs. High levels of O6-methylguanine-DNA methyltransferase (MGMT) reduce the efficacy of temozolomide (TMZ) by repairing the DNA damage it causes [45]. Defects in MMR genes (MLH1, MSH2, MSH6, PMS2) can lead to TMZ resistance [45]. Alterations in P53 contribute to tumour progression and therapy resistance [46]. Larger tumours or those near critical structures may receive suboptimal radiation doses. Hypoxia reduces radiotherapy and drug effectiveness [47].

Loss of dopamine receptors reduces response to cabergoline in prolactinomas [48]. Variability in SSTR2/5 expression affects response to somatostatin analogues. Increased vascularization can lead to poor drug penetration and resistance [49].

11. What is the role of surgical treatment in the management of APT?

A multidisciplinary team approach including the input of the endocrinologist, neurosurgeon, radiologist and oncologist is needed for optimal decision making on repeated surgery. Almost all APTs need multi-step surgeries because of its pathological complexity. According to the ESE survey, 80.5% of pituitary carcinomas and 77.4% of APTs had undergone at least two surgical treatments [50]. The goals of primary surgery in predicted APTs preoperatively are maximal safe resection to delay tumour regrowth, reduction of complications due to mass effects like cranial nerves palsies and optic chiasmal compression, improvement of effectiveness of adjuvant therapy like radiotherapy and obtaining of a definitive histopathological diagnosis with immunohistochemical markers which could predict aggressiveness of the tumour. Redo surgery for tumours that have already demonstrated aggressive behaviour, may be required in a case of tumour regrowth despite prior surgery to relieve neurological symptoms, failure of medical and radiotherapy, functional APT with severe hormones hypersecretion despite standard treatments.

Transcranial approach is a better option when the tumour has suprasellar extension and trans-sphenoidal approach is better when the tumour has parasellar extension [2]. Gross-total resection (GTR) rates for redo surgeries ranged from 46.6% to 53.5%, while primary surgeries had GTR rates between 69% and 71%, according to a systematic review and meta-analysis [51]. Higher risk of complications due to scarring and altered anatomy, failure to resect the tumour completely, risk of hypopituitarism, CSF leakage and vascular injuries are major challenges faced in redo surgeries.

A high-volume neurosurgeon with expertise in pituitary surgery achieves better surgical outcomes with less complication rates [52]. Even in the most skilled hands, the probability of obtaining GTR is consistently decreased in the presence of tumour invasion, especially of the cavernous sinus.

Recurrence following surgery depends on tumour invasion into surrounding structures which is difficult to dissect, expertise of the neurosurgeon and intentionally limited surgery due to limited surgical fitness of the patient. It is difficult to differentiate between residual tumour following suboptimal surgery and true recurrence evident on MRI.

Invasiveness and size of the tumour are major determinants of incomplete tumour resection which increase the tumour recurrence and risk of morbidity [53]. A GTR rate of 58.5% was recorded in a study on endoscopic endonasal reoperations, with greater success in situations where cavernous sinus invasion was absent [51]. Invasion of tumour is based on the findings of radiological images, intraoperative findings and histology.

Size of the tumour at presentation does not always correlate with aggressive behaviour of a tumour. For example, a large prolactinoma may show excellent response to medical treatment with dopamine agonists [20]. A macroadenoma has a high propensity to invade adjacent structures compared to a microadenoma [18].

Surgery remains a key pillar of APT management, but debulking surgery is often combined with adjuvant treatments like radiotherapy and systemic chemotherapy due to high recurrence rates [54].

12. What is the place of radiotherapy in the management of APT?

Radiotherapy is recommended to reduce the tumour growth in non-functioning APT despite surgery, when the complete resection of the tumour is not possible, and in functioning APT where the hormonal hypersecretion is not controlled by surgery and standard medical treatment [2]. Patients with clinically relevant invasive tumour remnants with pathological markers favouring aggressive behaviour also could be considered for adjuvant radiotherapy to prevent tumour recurrence [2].

According to the ESE survey, at least two radiotherapy courses were administered to patients with pituitary carcinoma (42.9%) and patients with APTs (25.9%) [41]. When selecting radiotherapy, safety considerations especially if the tumour abuts the optic chiasm, size of the tumour and available modes of RT should be considered.

Stereotactic radiosurgery (SRS) and external beam radiotherapy (EBRT) which deliver high dose radiotherapy, are radiation delivery modalities in

patients with APTs [2]. EBRT is typically administered at 45-54 Gy and SRS at 12-25Gy [2]. Radiation sensitivity varies between the tumour and the surrounding normal structures. Delivering a precise radiation dose to the tumor while limiting exposure to nearby normal tissues is the aim of EBRT [54]. SRS intends to destroy specific target tissue with a comparatively low exposure to nearby normal tissue [54]. It is difficult to evaluate the response to radiotherapy and its effectiveness as many studies have used different techniques and dosages [55]. Smaller tumours respond well to radiotherapy and the risk of developing hypopituitarism is less [55]. When a pituitary tumour continues to grow after receiving radiation therapy, it is important to consult an expert radiation oncologist to determine if more doses are needed to the area of tumour regrowth.

In highly aggressive tumours, combination of chemotherapy and radiotherapy can be considered. Because APTs require higher radiation doses, wider treatment fields, and are closer to vital structures, they are usually linked to more adverse outcomes than non-aggressive pituitary tumours [56]. Hypopituitarism is the most common long term adverse effect. Radiation induced optic neuropathy, and temporal lobe necrosis are other complications following RT [56]. Therefore, a multidisciplinary team decision including experts in radiotherapy and neurosurgery should be considered when deciding on radiotherapy for APT. Patients should be counselled regarding the long term risk of developing hypopituitarism [57]. Radiotherapy does not relieve the compressive effects on the optic apparatus quickly, and hence is not the first option in those with significant visual compromise.

When surgical options are limited or there is residual tumour after surgery, early radiation may be helpful for some aggressive pituitary tumours. The choice to move on with early RT should be taken case-by-case, taking into account the patient's general health status as well as any potential benefits and risks.

13. What treatments are available for the functioning of APT when the standard medical treatments are not responding?

Standard medical therapy with maximal tolerated doses is recommended depending on the type of tumour [2]. Reducing hormonal hypersecretion in secretory pituitary tumours, reducing or stopping tumour growth and preventing recurrence are the main goals. Management becomes more complicated when APTs do not respond to standard medical treatments (such as steroidogenesis inhibitors for ACTH-secreting tumors, somatostatin analogues for GH-secreting tumors, or dopamine agonists for prolactinomas) in controlling biochemical hypersecretion and/or tumour growth. It is frequently necessary to use multimodal therapy, which includes targeted therapies, chemotherapy, radiation, and surgery. The typical next step in a patient without any other contraindications is to attempt some form of debulking pituitary surgery. In failed medical therapy in prolactinoma, cabergoline can be reintroduced following debulking surgery rather than going for alternative treatment options [58]. A study showed 14 of 56 dopamine resistant tumours responded to dopamine agonists following surgical debulking of the tumours [59].

Hypercortisolism increases morbidity and mortality in patients with corticotroph adenomas. The available data are insufficient for recommendation for or against bilateral adrenalectomy in patients with aggressive corticotroph tumours. Adjuvant pituitary fossa irradiation and/or radiosurgery have been proposed as ways to reduce the risk of tumour growth in patients with

corticotroph adenomas, after bilateral adrenalectomy^[60].

To achieve biochemical control in growth hormone (GH) secreting APTs, multiple surgeries, somatostatin analogues and/or radiotherapy may be needed^[61]. The following chart summarizes available treatment modalities for functional APTs (table 3).

Table 3: Summary of multimodal approach to functional APTs.

Multimodal Approach	Indication
Repeat Surgery	Persistent tumour causing mass effect
Repeated cycles of radiotherapy (SRS/EBRT)	Residual/recurrent tumour after surgery
Temozolomide (TMZ)	First-line chemotherapy for APTs
CAPTEM (TMZ + Capecitabine)	Second-line chemotherapy for refractory cases
Everolimus, Tyrosine Kinase Inhibitors	Targeted therapy for APTs
Immunotherapy (e.g., Pembrolizumab)	Experimental option for resistant APTs
Palliative Care	Symptom management in end-stage disease

14. What is the role of temozolomide in the medical management of APT?

As the first line chemotherapeutic agent for APTs, temozolomide (TMZ), which is recommended by the ESE guidelines, can be used in ongoing tumour progression despite at least one surgery and one RT session, but it is not officially licensed for the treatment of APT^[2,26]. According to certain research and case reports, TMZ has been utilized earlier, even before RT, when the tumour progresses rapidly after surgery or in select cases, even before re-operation^[2]. The recommendation is primarily based on retrospective studies, case series, and expert opinion. There are no prospective studies or randomized controlled trials (RCTs) to provide high-level evidence for its efficacy in these tumours.

Temozolomide causes irreversible DNA damage during DNA replication by methylating DNA^[62] (figure 2). TMZ action is reversed by MGMT and tumours with a lack of MGMT expression has good response to TMZ^[62]. The dose is 150–200 mg/m² per day and repeated on 5 consecutive days per 28 day cycle^[2]. Ideal dosage and duration of treatment have not yet been reported. Expected response to TMZ might vary from tumour shrinkage to stabilization of growth in APTs. Some cases also show a biochemical response, with reduction of hormone secretion in functional APTs. According to the majority of research, assessing the patient after three to six cycles can help ascertain whether they are responding to TMZ^[2]. Following 3 cycles of TMZ, patients who respond to TMZ can continue the drug for a minimum of 6 months^[2]. However, if there is continued clinical benefit, therapy is frequently continued^[2]. A second trial of three cycles of temozolomide is recommended for patients who experience a recurrence after responding to therapy^[2].

In non-responders it is recommended to add another cytotoxic drug^[2]. The longest course of treatment in the ESE survey was 36 months, with a median duration of 9 months^[60].

TMZ can be used in prolactinomas which are resistant to dopamine agonists, surgery and RT, Crooke cell tumours, not responding to surgery and RT and non-functional adenomas not responding to surgery and RT^[64].

Re-operation also has higher surgical complications in large multilobulated tumours. Hence TMZ may be considered prior to redo-surgery and radiotherapy^[64]. It can cause fatigue in 60% of patients, but it is usually well tolerated. Dose reduction or stopping the drug is needed if patients develop pancytopenia, as myelosuppression was reported in 31% of patients. Full blood counts should be monitored on 22nd day of each 28 days cycle.

There is limited direct comparison evidence between TMZ and radiation therapy, particularly for large APTs, despite the fact that TMZ has demonstrated effectiveness in treating APTs. According to this study, 80.6% of patients had disease control while using TMZ. Notably, all patients had received radiotherapy and surgery before starting TMZ, indicating that it may be useful in situations that are refractory. A 3 months trial of TMZ may be warranted in this situation.

According to a study TMZ reported a 5-year progression free survival rate of 21.9% for patients with APTs^[65]. The 5-year over all survival rate was 57.4% for APTs^[66]. Patients responding to TMZ had a median survival of 44 months, whereas non-responders had a median survival of 16 months^[67]. These findings suggest that TMZ can improve overall survival in patients with APTs.

According to the ESE survey, complete response was no visible tumour on imaging; partial response was greater than 30% decrease in tumour size; stable disease was less than 10% increase and less than 30% decrease in tumour size; and progressive disease was new metastases or greater than 10% increase in tumour size^[50]. The overall clinical and radiological response rate when using TMZ in pituitary carcinomas is 69% and in APT is 60%^[63]. The response rate to TMZ, as shown in ESE survey; out of 156 patients, 6% had radiological complete response, 31% had partial response, while 33% of them had stable disease and 30% had tumours that advanced with first dose of TMZ^[64]. Three circumstances were found to have improved responsiveness to TMZ therapy: low MGMT immunohistochemistry expression, concurrent radiation therapy, and functional tumours^[27].

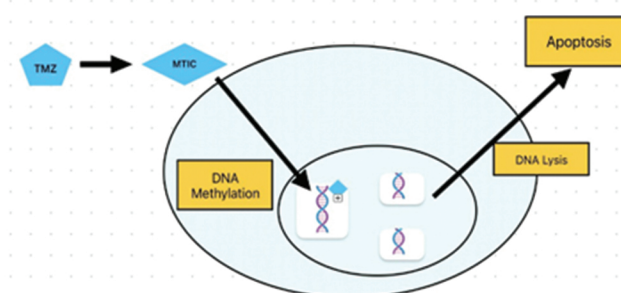


Figure 2: Temozolomide (TMZ) mechanism of action. Temozolomide converts into MTIC (3-methyl-(triazene-1-yl)imidazole-4-carboxamide-active metabolite) and causes irreversible DNA damage during DNA replication by methylating DNA active metabolite.

15. What are the other treatment options available for APT?

Other systemic chemotherapy has been utilized in a limited number of patients who did not respond to TMZ. Given the limited and variable efficacy of these alternative chemotherapy regimens, further research and clinical trials are necessary to establish more effective treatments for patients with TMZ-resistant APTs. Lomustine, an alkylating agent is used frequently as a part of chemotherapeutic regimens, with/without other cytotoxic agents such as fluorouracil (5-FU), adriamycin, cisplatin, carboplatin, procarbazine, mitotane, etoposide, vincristine and doxorubicin in various combinations [2]. Few patients appeared to have achieved disease control or even partial remission [67,68]. Even though complete tumour regression has not been documented, transient tumour regression and/or stabilization have been accomplished in some tumours [68].

PRRT (Peptide receptor radionuclide therapy) radiolabelled somatostatin receptor ligands deliver radiation to tumours expressing somatostatin receptors [69]. Pituitary tumours express somatostatin receptors which uptake these radiolabelled ligands [70]. PRRT can be used instead of temozolomide (TMZ) in tumours that express somatostatin receptors. Somatostatin receptor expression in tumours can be assessed using somatostatin receptor (SSTR)-PET scan such as 68Ga-DOTATATE/ DOTANOC scans, to choose candidates for PRRT. Of 27 published cases with available information regarding the response to PRRT, 5 (18%) showed a partial response, 8 (30%) demonstrated stable disease, and 14 patients (52%) had progressive disease [71]. According to available data, PRRT does not appear to substantially increase the possibility of hypopituitarism [69].

Tyrosine kinase inhibitors - erlotinib, gefitinib (TKIs), everolimus (an mTOR inhibitor), and bevacizumab (an anti-VEGF antibody) have also been used as molecular targeted therapy for APT. A pilot study was done in 4 patients with aggressive lactotroph tumours and 3 patients showed stabilization of the disease and one patient with pituitary carcinoma showed disease progression with tyrosine kinase inhibitors (TKI) [72]. Erlotinib, had no effect on patients with corticotroph APT, however gefitinib resulted in partial resolution of lactosomatotroph APT [73]. In TMZ failure, bevacizumab can be used. It prevents vascular endothelial growth factor (VEGF) from attaching to cells and prevents the growth of the tumour vessels. Two patients experienced partial remission; 6 patients had stable disease out of 19 patients who were treated with bevacizumab for APT/PC [73,13].

Immune checkpoint inhibitors (ICIs) are the newest treatment option being researched for APTs. Their use in pituitary tumours is justified by the fact that these tumours contain infiltrating immunological cells; lymphocytes [11]. ICIs target regulatory processes known as immunological checkpoints such as CTLA-4, PDL1 and prevent over-activation of T cells. Selectively inhibiting such checkpoints of T cells in the tumor microenvironment promotes activation / proliferation of those T cells and therefore killing of tumor cells [75].

Anti-PD-1/PD-L1 antibodies; nivolumab and anti CTLA-4 antibodies; ipilimumab are immune check point inhibitors which activate the immune system [76]. One study showed that a patient with an APT had complete remission, 7 patients with pituitary carcinoma

Table 4: Summary of adverse effects of each treatment modality.

Treatment modality	Adverse effects
Redo-surgery	Damage to vital structures
Radiotherapy	Hypopituitarism, radiation induced optic neuropathy, temporal lobe necrosis, decrease cognitive abilities especially in children
Temozolomide	Fatigue, pancytopenia, Stevens-Johnson syndrome, haematological malignancies, liver function abnormalities and pneumonitis
PRRT	Nephrotoxicity, transient pancytopenia Bevacizumab- hypertension, gastrointestinal hemorrhage, venous thromboembolism
Molecular targeted therapy	Tyrosine kinase inhibitors, everolimus-hepatotoxicity, pancytopenia
Immune check point inhibitors	Colitis, hepatitis, hypophysitis, pneumonitis

had partial remission, 3 patients had normal hormones levels after being treated with immune check point inhibitors [13,76].

16. What follow-up strategy is recommended for APT?

Compared to non aggressive PitNETs, APTs require a more stringent postoperative imaging regimen, including early and frequent MRIs to efficiently monitor for recurrence and direct prompt therapies. Within 48 hours following surgery, early postoperative MRI is advised for APTs in order to determine the degree of resection and create a baseline for comparisons in the future. Three months after surgery, a follow-up MRI is usually conducted to monitor for early signs of recurrence or progression. More frequent imaging may be necessary due to the aggressive nature of APTs. For the first two years, it is recommended to do MRI once in every three to six months and afterwards, every 6–12 months, depending on tumour behaviour and clinical judgment [32]. Tumour subtype, invasiveness, proliferative markers, and patient-specific characteristics should all be taken into consideration when determining the appropriate imaging frequency.

Regular assessments of pituitary hormone levels are recommended post RT to detect hypopituitarism and the need for commencement of hormone replacement therapy. There is insufficient evidence to establish a standardized imaging schedule, hormone assessment following RT; thus, clinical judgment plays a crucial role. It is advised to have an ophthalmologic follow-up after surgery to evaluate any changes in visual function [32]. Monitoring radiation related side effects such as secondary tumours, as well as the late development of pituitary carcinoma, which can take place decades after the initial diagnosis, should be considered for long-term follow-up.

A comprehensive follow-up during and after giving TMZ for APTs involves regular clinical evaluations to assess for adverse effects, including hematologic toxicities (e.g. neutropenia, thrombocytopenia) kidney and liver function tests. Baseline MRI should be done

before starting TMZ, repeat imaging after three cycles, or approximately after three months and consider earlier imaging if there is a clinical suspicion of progression^[77].

FDG-PET and/or SSSTR-PET, may be indicated in addition to conventional imaging studies to either stage the disease or determine suitability for PRRT^[2].

Early detection of metastasis in APTs is challenging due to their rarity and the subtlety of initial metastatic signs. For the best patient care, a proactive, customized imaging strategy combined with careful clinical evaluation is necessary. If metastasis is suspected, additional imaging such as chest, abdominal, and pelvic CT scans or MRIs may be required.

Lifelong follow up is needed with imaging and hormonal profile to assess treatment response, adverse effects of drugs and evolution to pituitary carcinoma.

17. What is the prognosis of APT?

Pituitary adenomas usually behave in a benign manner, although a small number of these tumours progress into APTs and can even turn into carcinomas. Because of the clinical behaviour of APT with invasion into surrounding structures, rapid growth and relapse after conventional treatment, overall prognosis is generally poor^[2]. In the largest cohort of APTs, the median survival was 17.2 years in tumours with Ki-67 index >10%. Eighty four percent of patients had tumour related causes of death and 10% had treatment related causes of death^[75]. Patient who responded to TMZ had survival benefits^[78]. Early detection of APTs, and multimodal treatment approaches probably improve the prognosis.

18. What are the strategies suggested in managing a patient with APT in a resource-limited setting?

The diagnosis and management of a patient with an APT can be challenging in a resource-limited setting due to the lack of advanced imaging modalities, immunohistochemical markers, and novel therapeutic modalities. Paucity of advanced surgical technology leading to incomplete tumour resection, minimum theatre facilities with long waiting lists, lack of experienced high volume neurosurgical centres causing delayed interventions, lack of stereotactic radiosurgery and unavailability of novel chemotherapeutic agents are specific problems encountered during management.

However, an integrated approach can still be used to enhance patient outcomes. The diagnosis should rely on clinical and biochemical evaluation, along with conventional imaging techniques like magnetic resonance imaging (MRI). When histopathological assessment is feasible, immunohistochemical markers like Ki-67 proliferative index and p53 expression can aid in identifying aggressive tumour behaviour. A multimodal treatment strategy should be adopted, combining surgical intervention, even if limited to debulking or decompression, with adjuvant radiotherapy using available facilities. Conventional medical therapy, such as dopamine agonists for prolactinomas or somatostatin analogues for growth hormone-secreting tumours, can be used to control hormonal hypersecretion. Temozolomide, an oral chemotherapeutic agent, may be considered if available, especially in cases of documented tumour

growth despite standard therapies. Patient education regarding early identification of symptoms and properly planned follow up after surgery may lead to prompt early intervention. Improving palliative care facilities is also an important aspect due to delayed presentation and diagnosis. The patient care pathway can be reinforced by the enhancement of diagnostic capabilities, the expansion of treatment accessibility including advances in surgical and radiation techniques, and incorporating multidisciplinary teams. Collaboration with regional referral centers can facilitate access to advanced diagnostics and therapeutics when necessary.

It is important to utilize all available resources, including training of local experts in the neurosurgical field and improving of basic skills related to TSS techniques and perioperative management. Multidisciplinary teams discussions, regular case discussions with experts from regional or international centres, and establishment of local neurosurgical and endocrinology interest groups to share experiences and best practices are important approaches to optimize the patient care. Creating local and national registries for APTs to track incidence, treatment outcomes, and complications, conducting audits to find gaps and developing protocols, and creating low-cost electronic health record (EHR) systems to track long-term follow-up may ensure continuity of care.

By emphasizing on these approaches, healthcare systems with limited resources can improve APT management and guarantee that patients receive thorough and efficient care despite existing constraints.

Conclusion

Aggressive pituitary tumours are difficult to detect early. However early recognition is crucial for therapeutic decisions since they are linked with higher rates of morbidity and mortality. APTs are resistant to currently available standard treatments, leading to early recurrence. Currently, there is no specific marker or investigation to guide management decisions in APTs. When determining the aggressiveness of pituitary tumours, a combination of investigations, such as brain MRIs, histology, immunohistochemical markers, and novel molecular markers can be helpful. Even with the best application of standard therapy, these tumours may either fail to respond or exhibit recurrence.

A multimodal treatment approach is needed in the management of patients with APTs. Due to the rarity and heterogeneity of these tumours, clinical experience builds up slowly and is not necessarily derived from clinical studies. It would also be beneficial to establish global and national registries for these types of tumours. The lack of early prognostic indicators of future aggressive behaviour and specific markers of therapeutic response, are major challenges in the management of APTs.

Declaration

Conflict of interest : None

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

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