# Revised European Society of Endocrinology Clinical Practice Guideline for the Management of Aggressive Pituitary Tumours and Pituitary Carcinomas

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**Abstract**

Pituitary tumours are quite common and in most cases well-controlled by surgery or medical treatment. However, a small subset of pituitary tumours presents with multiple local recurrences or tumour progression despite combined surgical, medical or radiotherapeutic treatment (aggressive pituitary tumours) and in rare occasions with metastases (pituitary carcinomas). Early identification of aggressive pituitary tumours is challenging but is of major clinical importance as they are associated with an increased morbidity and mortality even in the absence of metastases. Here, we provide a revision of the first international, interdisciplinary European Society of Endocrinology (ESE) clinical practice guideline on aggressive pituitary tumours and pituitary carcinomas (2018). This revised guideline provides up-to-date clinical guidance on diagnosis, treatment and follow-up in aggressive pituitary tumours and pituitary carcinomas.

**Summary of the recommendations**

The recommendations (R) are worded as recommend (strong recommendation) and suggested (weak recommendation). The quality of evidence behind the recommendations is classified as very low (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○) or strong (⊕⊕⊕⊕). See further **section 2.3**.

## 1 General remarks

**R 1.1** *We recommend that patients with an APT or PC should be discussed in an expert multidisciplinary pituitary team meeting (endocrinologist, neurosurgeon, pathologist, neuroradiologist, radiation oncologist, oncologist).*

## 2 Assessment of aggressiveness

### 2.1 Diagnosis of an APT

**R 2.1.1** *We recommend the diagnosis of an APT be considered in patients with an invasive tumour, and either 1. unusually rapid tumour progression or 2. clinically relevant tumour progression despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments).*

**R 2.1.2** *We recommend that imaging (MRI in most instances) be used for quantification of tumour dimensions, defining invasion, and establishing progression. We suggest that following a new treatment, tumour progression should additionally be reported according to RECIST.*

**R 2.1.3** *We suggest radiological re-evaluation within 3-6 months in patients with suspicion of having an aggressive pituitary tumour based on clinical, radiological, and pathological features.*

**R 2.1.4** *We recommend full pituitary hormonal evaluation in patients with aggressive pituitary tumours.*

**R 2.1.5** *We recommend screening for metastatic disease in patients with aggressive pituitary tumours, and either 1. site-specific symptoms or 2. discordant biochemical and radiological findings or 3. before commencing chemotherapy.*

### 2.2 Potential predictors of aggressiveness in pituitary tumours

**R 2.2.1** *We recommend all pituitary tumours should undergo histopathological study, which should include immunodetection of pituitary hormones and markers of proliferation (Ki-67 index, mitotic count) and p53 immunodetection.*

**R 2.2.2** *We suggest classifying pituitary tumours according to their proliferative status and radiological signs of invasion.* (⊕○○○)

**R 2.2.3** *We suggest interpretation of the pathological diagnosis in the clinical context of the individual patient.* (⊕○○○)

**R 2.2.4** *We suggest molecular analysis, specifically, testing for somatic variants in genes that have been associated with aggressive behaviour: TP53 and SF3B1 in lactotroph tumours refractory to treatment with dopamine agonists, and TP53 and ATRX in corticotroph macroadenomas.*

**R 2.2.5** *In patients with aggressive pituitary tumours, we suggest germline genetic testing based on young age at presentation or family history of pituitary tumours, endocrine neoplasia, or other syndromes as recommended for patients with non-aggressive pituitary tumours.* (⊕○○○)

## 3 Therapeutic options

### 3.1 Role of surgery

**R 3.1.1** *We recommend surgery should be performed by a neurosurgeon with extensive experience in pituitary surgery.* (⊕⊕○○)

**R 3.1.2** *We recommend discussion with an expert neurosurgeon regarding repeat surgery prior to consideration of other treatment options.*

### 3.2 Role of radiotherapy

**R 3.2.1** *We recommend radiotherapy to improve tumour control in patients with clinically relevant tumour progression despite surgery and standard medical treatment.* (⊕⊕○○)

**R 3.2.2** *We suggest early radiotherapy be considered in the setting of a clinically relevant invasive tumour remnant with proliferation markers and/or genetic alterations, strongly indicating aggressive behaviour.* (⊕○○○)

**R 3.2.3** *In case of rapid progression despite previous RT, we suggest considering a second course of RT after careful assessment of dose accumulation to the brain, chiasm and cranial nerves in close proximity to the target tumour.*

### 3.3 Standard medical therapies

**R. 3.3.1** *We recommend standard medical treatment in functioning pituitary tumours with maximally tolerated doses in order to control tumour growth, as per current guidelines.* (⊕⊕○○)

**3.4. Chemotherapies**

**R 3.4.1** *We recommend use of temozolomide monotherapy as first line chemotherapy for aggressive pituitary tumours and pituitary carcinomas, following documented tumour progression.* (⊕⊕○○)

**R 3.4.2** *We recommend use of temozolomide standard dosing regimen: 150-200 mg/m$^2$ for 5 consecutive days every 28 days.* (⊕○○○)

**R 3.4.3** *We recommend first evaluation of temozolomide treatment response after 3 cycles. If radiological progression is demonstrated, temozolomide treatment should be ceased.* (⊕⊕○○)

**R 3.4.4** *We recommend monitoring of haematological parameters, liver function tests and careful clinical observation for potential adverse effects during treatment.* (⊕⊕⊕○)

**R 3.4.5** *In patients responding to a first course of temozolomide, defined either as partial tumour regression, or tumour stabilization after documented rapid progression during the 6- month period preceding start of TMZ, we recommend that treatment is continued for 12 months and thereafter guided by the efficacy and tolerability, with consideration for longer duration in patients where response has not plateaued. Treatment duration exceeding 24 months must be weighed against a potential risk for cumulative severe toxicity*. (⊕○○○)

**R 3.4.6** *In patients who develop a recurrence following prior response to temozolomide treatment we suggest a second trial of 3 cycles of temozolomide.* (⊕○○○)

**R 3.4.7** *We suggest molecular testing in patients with tumour progression on TMZ in order to guide potential treatment choices.*

**R 3.4.8** *We suggest considering a trial with ICI in patients with PC and rapid tumour progression after treatment with temozolomide. Tumor agnostic data supports the use of ICI in tumors that are either mismatch repair deficient (MMRd) or exhibit high tumor mutational burden high, supporting the use in pituitary tumors with these molecular features.*

*Otherwise, we recommend participation in clinical studies as the data supporting the use of cytotoxic chemotherapy, besides temozolomide, and targeted agents in this tumor type remains limited.* (⊕○○○)

**3.5 Local treatment of metastatic disease**

**R 3.5.1** *In patients with oligo-metastatic disease we suggest consideration of loco-regional therapies, either as stand-alone treatment or in combination with systemic treatment.* (⊕○○○)

**4 Follow-up of an aggressive pituitary tumour**

**R 4.1** *We recommend that imaging (MRI in most instances) be performed every 2-12 months as guided by prior tumour progression rate, the presence of residual tumour post-surgery, and/or location of the tumour (proximity to vital structures).* (⊕○○○)

**R 4.2** *We recommend pituitary hormonal evaluation be performed every 3-12 months as guided by the clinical context.* (⊕○○○)

## 1. Introduction

The prevalence of clinically relevant pituitary tumours is 80–100 cases per 100,000 with an annual incidence of 4 new cases per 100,000 [1-3], depending on age and sex [3]. The clinical behaviour of pituitary tumours is highly variable: some remain stable for long periods; many grow slowly, in rare cases rapid tumour growth is observed. Post-operatively, about 30% of patients show tumour regrowth up to even 30 years after surgery, with an increased risk of tumour regrowth in the presence of visible residual tumour [4]. A small subset of pituitary tumours, characterized by multiple recurrences/tumour progression despite combined surgical, medical and radiotherapy treatment approaches, are classified as aggressive pituitary tumours (APT). The prevalence of aggressive tumours is not known, but is estimated to 1% or less of clinically apparent pituitary tumours [5]. Aggressive tumours often, but not always, exhibit one or more of the proliferation markers (Ki-67 ≥3%, increased mitoses, p53 expression). Tumours exhibiting 2 or 3 proliferative markers account for 2.5 % to 10% in surgical series [6-9]. Pituitary carcinomas (PC) or metastatic PitNETs (Ref :WHO Classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2024 June 1]. (WHO classification of tumours series, 5th ed.; vol. 10). Available from: https://tumourclassification.iarc.who.int/chapters/53), defined by the presence of craniospinal and/or distant metastasis, are very rare; about 0.2% of pituitary tumours [10]. Early identification of APTs is challenging but is of major clinical importance as they are associated with an increased morbidity and mortality even in the absence of metastases [11-13].

This guideline is an update of the 2018 ESE guideline and provides recommendations for management of APT/PC based on the current evidence.

## 2. Methods

### 2.1 Guideline working group

This guideline revision was initiated by The European Society of Endocrinology (ESE). The chair (G.R.) was appointed by the ESE Clinical Committee. O.D. served as the methodology lead, L.v.H. joined the guideline working group for methodology support. Members of the working group (authors) were appointed by the chair and approved by the ESE Clinical Committee: endocrinologists (A.P.A. [Endocrine Society Representative], V.P, P.B., A.P.H., A.M.C., S.P.), a neuro-oncologist (A.L.), a radiation oncologist (G.M.), a pathologist (J.T.), a molecular biologist (M.T.) and a neurosurgeon (H.M.). The

working group had in-person meetings in June 2023 and February 2024. All participants completed conflict of interest forms (see **Supplementary Table 1**).

Prior to publication a draft of the guideline was reviewed by two patient representatives and XX experts in the field (see **Acknowledgments**). Revision of the guideline was based on feedback from ESE members and following presentation at the European Congress of Endocrinology 2024 (Stockholm). All comments and suggestions were discussed and implemented as deemed appropriate by the working group (see **Supplementary Table XX**).

**Target group**

This document was developed for healthcare providers of patients with APT and PC, and served as a source document for preparation of educational material published on the ESE website, to empower patients with APT and PC and their clinicians.

### 2.2 Aims

The overall purpose of this guideline is to provide clinicians with practical guidance for identification and management of patients with APT and PC. In clinical practice, both the recommendations and the clinical judgment of treating physicians should be taken into account. Recommendations are not meant to replace clinical acumen and may need adaptation to local circumstances.

### 2.3 Summary of methods used for guideline development

The methods used have been described in more detail previously [14, 15]. In short, the guideline used GRADE (Grading of Recommendations Assessment, Development and Evaluation) as a methodological base. The first step was to define the clinical questions (see **section 2.4**), the second being a systematic literature search (see **section 2.5**). After including relevant articles, we 1) estimated an average effect for specific outcomes (if possible), and 2) rated the quality of the evidence. The quality of evidence behind the recommendations is classified as very low (⨁◯◯◯), low (⨁⨁◯◯), moderate (⨁⨁⨁◯) or strong (⨁⨁⨁⨁).

For the recommendations we considered: 1) quality of the evidence, 2) balance of desirable and undesirable outcomes, 3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc) [14] [15]. The recommendations are worded as *recommend* (strong recommendation) or *suggest* (weak recommendation). Formal evidence syntheses were performed and graded only for recommendations addressing our initial clinical questions. It is important to emphasize that there is no direct translation from the (quality of) evidence to the strength of a recommendation and there might be situations when a recommendation

is strong even if the quality of evidence is low [16]. Recommendations based on good practice were not graded. Recommendations were derived from a majority consensus of the guideline development committee, but substantive disagreements could be acknowledged in the manuscript. All recommendations provided are accompanied by an explanation.

### 2.4 Clinical questions and eligibility criteria

In the 2018 guideline, a systematic review was performed regarding efficacy of different treatment regimens in APT and PC [17]. Mostly studies on temozolomide treatment were included, reporting a positive treatment effect in 47% [95%CI 36-58%] of patients [17]. Since then, more data have become available regarding the use of temozolomide in APT and PC [13, 18, 19]. For the guideline revision, it was decided to update the literature review of therapy efficacy of temozolomide, as well as other treatment options for APT/PC. In addition, possible predictors of treatment response were reviewed.
It was also acknowledged that predicting clinical behaviour in pituitary tumours remains challenging. It was decided to systematically review literature to try to estimate average growth rate in pituitary tumours, to identify those with aggressive growth, and possible predictors of clinically aggressive behaviour.
The clinical questions for the systematic reviews are summarized in **Table 1**. Eligible study designs were observational/single arm cohort studies. Eligible articles were required to present data on adult patients (≥18 years), with a minimum of 3 patients for studies on treatment, and a minimum of 10 patients in studies assessing predictive factors (to reduce the risk of selection bias). Definition of APT/PC had to comply with the definition used in this guideline. In studies concerning growth velocity and treatment response, tumour volume had to be evaluated by magnetic resonance imaging (MRI). Studies reporting patients which were already included in the 2nd ESE Survey (describing clinical and pathological characteristics and treatment outcomes in a large cohort of APT/PC patients) [13], were excluded. Eligible studies were restricted to languages familiar to the authors (English, French, German, Dutch). Authors were contacted for clarification when reported data were not sufficient for data extraction.

### 2.5 Description of search and selection of literature

PubMed, MEDLINE, Embase, Web of Science, and Cochrane Library were searched with the help of a specialized librarian to identify potentially relevant studies. The literature searches for questions I, II, III-IIIa and IV were performed in August 2023, March 2024, July 2023 and January 2024, respectively. Searches can be found in **Appendix 1** (see section on supplementary materials at the end of this guideline).

All studies obtained from the searches were entered into reference manager software (EndNote X20, Clarivate Analytics, Philadelphia, PA) and title and abstract were screened. Potentially relevant studies were retrieved for detailed assessment. References of included studies were assessed for additional relevant articles.

The literature search for clinical question I (growth velocity in pituitary tumours), resulted in 485 papers. After assessment, eleven studies were included (see **Table 1**). For clinical question II (predictors of aggressive behaviour), 428 papers were identified, of which four were included.

For clinical question III and clinical sub question IIIa ((predictors of) therapy efficacy), 557 articles were identified; seventeen articles were included for clinical question III, of which six for clinical sub question IIIa. For clinical question IV (optimal treatment of isolated metastases of pituitary carcinomas), none of the 675 identified papers could be included.

**Table 1: Clinical questions**

| **Clinical question** | **Search criteria** | | | | **Papers included (*n*)** |
|---|---|---|---|---|---|
| | **Population** | **Intervention** | **Comparison** | **Outcome** | |
| *Question I:*<br><br>What is the normal growth velocity in pituitary tumours?<br><br>I.e.: is there a cut-off value above which to define a tumour as aggressive? | Individuals with pituitary tumours | - | - | Growth velocity in %/year, $mm^3$/year or mm/year | 11 [20-30] |
| *Question II:*<br><br>Are there predictors for clinically aggressive behavior? | Individuals with aggressive pituitary tumours/pituitary carcinomas | **Predictor(s)**<br>Clinical, biochemical, pathological or molecular parameters | | Clinically aggressive behavior | 4 [31-34] |
| *Question III:*<br><br>What is the efficacy of different treatment regimens in aggressive pituitary tumours/pituitary carcinomas?<br><br>Sub-question IIIa: Are there predictors for treatment response (i.e. radiological or biochemical)? | Individuals with aggressive pituitary tumours/pituitary carcinomas | **Intervention**<br>Temozolomide, immune checkpoint inhibitors, bevacizumab, radiotherapy<br>**Predictor(s)**<br>Clinical, biochemical, pathological or molecular parameters | **Comparison**<br>Comparative, placebo or no treatment | 1. Radiological response (e.g. complete response/partial response/stable disease/progressive disease as defined by tumour volume/tumour diameter or development of metastases), biochemical response (control of hormonal overproduction)<br>2. Progression free/overall survival<br>3. Adverse effects/toxicity | 17 [12, 13, 18, 19, 35-47]<br><br>6 [19, 36, 39, 42, 43, 46] |
| *Question IV:* | Individuals with isolated metastases of pituitary carcinomas | **Intervention**<br>Treatment A | **Comparison**<br>None/ treatment B (or C etc) | Treatment response (e.g. radiological response of metastases), biochemical | 0 |

| | | | | |
|---|---|---|---|---|
| What is the optimal treatment of metastases of pituitary carcinomas? | | | response (control of hormonal overproduction), (progression free/overall) survival, adverse effects/toxicity) | |

## 2.6 Summary and interpretation of evidence from the systematic reviews

**Clinical question I:** ***What is the normal growth velocity in pituitary tumours?***

Eleven studies assessing growth velocity of pituitary tumours in a total of 759 patients (387 tumours were nonfunctioning) were included [20-30]. Mean duration of follow-up ranged from 1.3 to 8.3 years. Outcome measures were reported in mm/year, $mm^3$/year or tumour volume doubling time (TVDT). Importantly, these outcome measures may not accurately capture the variable growth pattern of pituitary tumours; there may be extended periods of clinical quiescence followed by a period of rapid tumour growth. Details of included studies and GRADE assessment can be found in **Supplementary Tables 2 and 3**. Overall, the quality of evidence was very low.

Patients were divided into a treatment-naive group (209 patients) and a surgically treated group (550 patients, 153 with preoperative tumour measurements). One of the studies in the treatment-naive group did not report exact proportions of micro- and macroadenomas at baseline [23]; 87% of the remaining 150 pituitary tumours were macroadenomas. After a mean follow-up ranging from 2.9 to 7.1 years, 44% of pituitary tumours in the treatment naïve group increased in size, while 37% remained stable and 19% decreased (**Figure 1**). Studies (*n* = 3) in this group assessing growth velocity in two dimensions reported growth velocities of mean 0.46 and 0.6, and median 0.8 mm/year, respectively [20, 21, 29]. Studies (*n* = 3) assessing growth velocity in a volumetric fashion, reported mean growth velocities of 236, 340 and 1861 $mm^3$/year, respectively [21, 23, 27]; one study reported TVDT prior to surgery, with a mean of 38.2 months [24]. Except for the latter study reporting on preoperative growth velocity, growth velocity in treatment naïve tumours is likely not a good reflection of growth velocity in treated tumors, as they might present with a different clinical course.

In the surgically treated group after a mean follow-up ranging from 1.3 to 8.3 years, 58% of pituitary tumour remnants increased in size; 42% remained stable or decreased (**Figure 1**). Except for two studies who did not report exact proportions of micro- and macroadenomas at baseline [22, 28], all pituitary tumours in this group were macroadenomas. Median reported postoperative TVDTs were 27.6 and 34.6 months [22, 25], and mean were 38.8 and 61.2 months [24, 30]. Three other studies reported growth velocities of tumour remnants of median 446 $mm^3$/year [26] and mean 311 $mm^3$/year (23 $mm^3$/year for patients requiring secondary therapy) [28] and 3713 $mm^3$/year [27]. Of note, in the

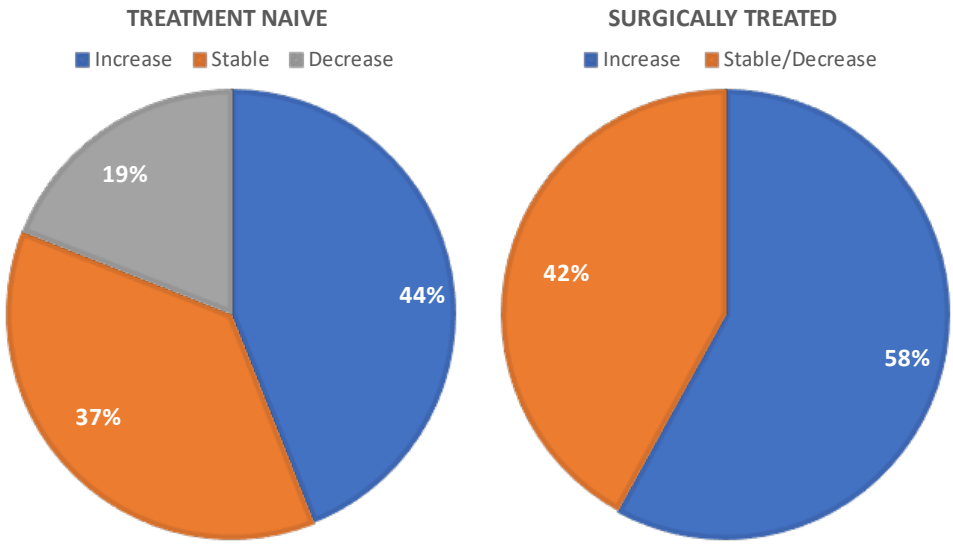
latter study, patients with large tumours remnants (mean 8.68 $cm^3$) were included which might explain the large growth velocity.

Two studies stratified TVDT for remnants of functioning tumours and non-functioning tumours; one study did not find a difference (median 33.7 vs. 35.4 months, respectively) [22], while another study reported a shorter TVDT for functioning than for nonfunctioning tumours (mean 28.6 vs. 42.4 months, respectively) [24].

**Supplementary Figure 1** illustrates volumetric growth velocity of surgically treated non-functioning tumours only (section on **Supplementary Material**).

Based on the results of this literature review, with studies displaying a large variability in growth rate, it was not possible to estimate a growth velocity cut-off value above which a tumour could be considered aggressive.

**Figure 1: Growth pattern of pituitary tumours**




**Clinical question II:** ***Are there predictors for clinically aggressive behaviour?***

Four studies were selected, assessing several factors of possible clinically aggressive behaviour [31-34]. Details of included studies and GRADE assessment can be found in **Supplementary Tables 4 and 5**. Overall, quality of evidence was very low.

Although some studies found a positive association between clinically aggressive behaviour and presence of abundant mitoses, positive p53 immunostaining or tumour invasiveness [31-33], others failed to confirm these associations [31, 33]. Tumour size was larger [31, 32] and Ki-67 index higher [31-33] in APT compared to pituitary tumours not exhibiting aggressive behaviour. None of the factors mentioned above have been prospectively shown to precisely predict or exclude aggressive behaviour.

Grade 2b pituitary tumours (combining invasion and at least 2 proliferation markers above the cut-offs: Ki-67 ≥ 3%, p53 positive, number of mitosis n>2) [7] were reported to have a sensitivity of 68% [34], and an odds ratio of 3.4 [95%CI 1.35-8.57] [31] for becoming clinically aggressive. Validation in larger cohorts of APTs is needed and the positive predictive value of 2b, i.e. the proportion of 2b tumours that will evolve into APT/ PC, remains to be established in detail.

**Clinical question III:** ***What is the efficacy of different treatment regimens in APT and PC?***

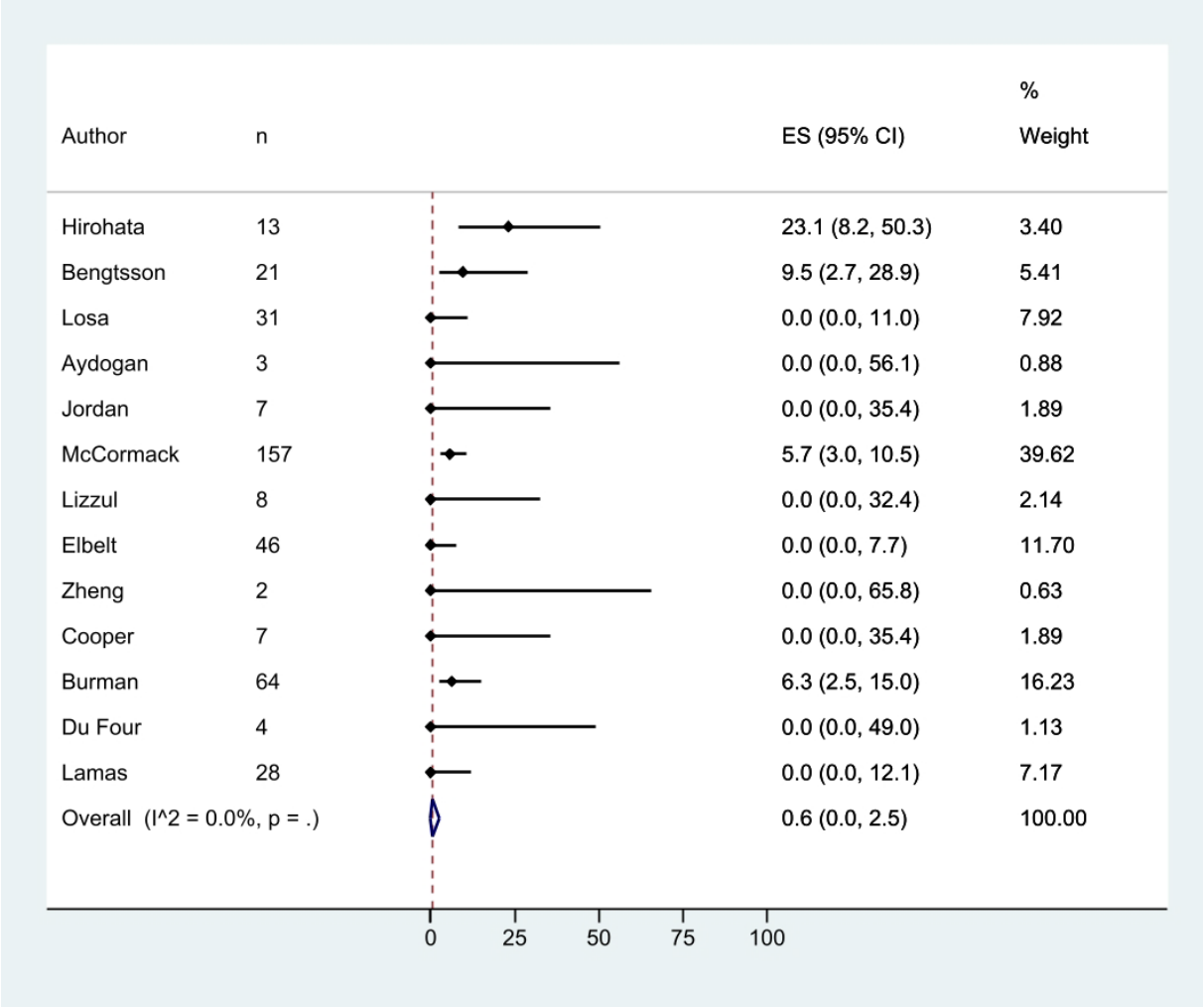
Temozolomide, immune checkpoint inhibitors, bevacizumab and radiotherapy were treatments of interest. Details and grading of included studies can be found in **Supplementary Tables 6-10**. Overall, quality of evidence (i.e., certainty in estimates) was very low. There were no comparative studies identified. Different studies had varying lengths of follow-up, posing challenges when interpreting absolute risks.

Temozolomide

A total of 439 patients were included from 11 single-arm cohort studies and 4 surveys [12, 13, 18, 19, 35-45]. One study combined temozolomide treatment with a second course of irradiation [43]; one study with capecitabine [44]. All patients had received multiple lines of treatment before receiving temozolomide. Complete radiological response, partial response, stable disease, and progressive disease were reported 0.6% [95%CI 0.0-2.5%], 32.0% [95%CI 26.9-37.4%], 32.2% [95%CI 27.6-37.1%] and 28.9% [95%CI 24.5-33.7%] of patients, respectively (**Figure 2**). It has to be acknowledged that response was measured at different time points between studies, since a standardized follow-up protocol is lacking.

Eleven studies assessed biochemical treatment response; decrease or normalisation of hormone levels was seen in 19 to 100% of hyperfunctioning tumours [12, 13, 18, 19, 37, 38, 40-42, 44, 45]. Two-year progression free survival was reported in two studies only and ranged from 47.7 to 64% [12, 19]; two-year overall survival from 79 to 83.9% [12, 19, 43]. Hematological toxicity was the most reported adverse effect (**Supplementary Table 6**).

341 **Figure 2: Meta-analysis: complete radiological response (2A) and partial radiological response (2B)**
342 **after temozolomide treatment**
343 **2A**

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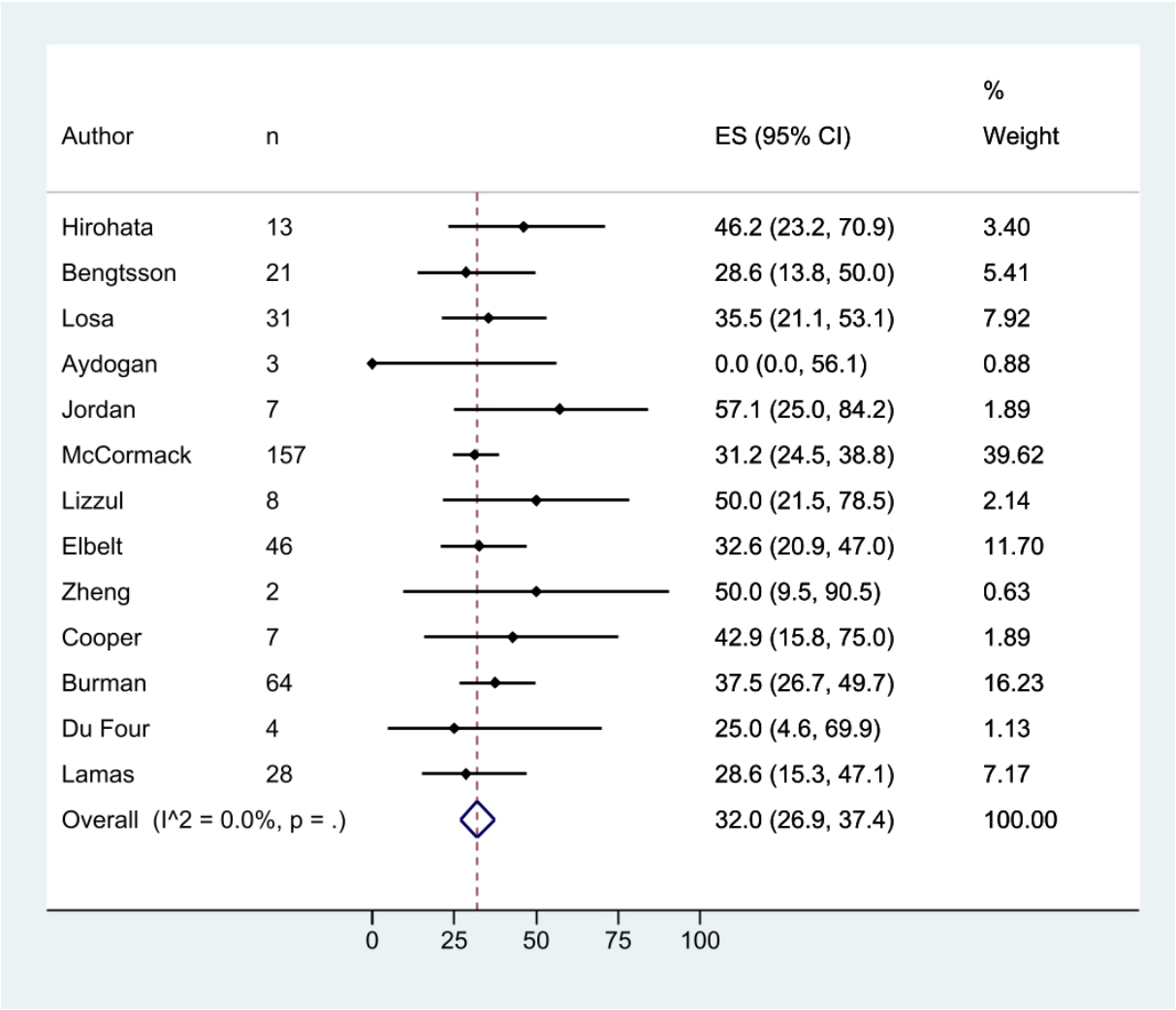
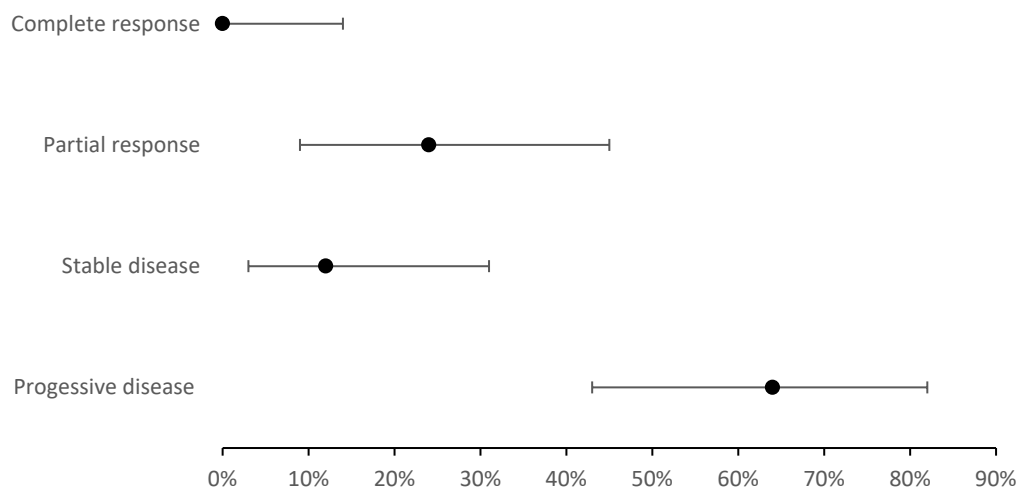
**2B**




Immune checkpoint inhibitors

Three studies were included with a total of 25 patients who had tumour progression despite previous treatment with surgery, radiotherapy and temozolomide [13, 46, 47]. They received immune checkpoint inhibitor therapy (11 patients single, 14 patients dual therapy) for mean 2.5 to 13.3 months. Partial radiological response, stable disease, and progressive disease was reported in 24% (95%CI 9-45%), 12% (95%CI 3-31%), and 64% (95%CI 43-82%) of patients, respectively (**Figure 3**). There were no patients with a complete response. Two studies assessed biochemical response; a favourable biochemical treatment effect (complete or partial response) was seen in 35% of seventeen patients with functioning tumours.

**Figure 3: Radiological response of immune checkpoint inhibitors**




Bevacizumab

There was only one study fulfilling our inclusion criteria: eleven patients in the second ESE survey on management of 171 patients with APT/PC were treated with bevacizumab after multiple treatment modalities [13]. All but one received prior temozolomide. Complete radiological response was not achieved. Partial response with a durability of effect of 16 months was achieved in one patient. Three patients achieved stable disease with a duration of 7, 7.5 and 16 months, respectively. Biochemical response or adverse effects were not reported.

Radiotherapy

In the second ESE survey results of 55 patients who received a second course of radiotherapy median 5.4 years (IQR: 3.5–8.9 years) after the first one were reported (results of first course not considered here since recurrence or progression after a first course of radiotherapy is part of the definition of APT/PC) [13]. Various radiotherapy techniques were used (**Supplementary Table 9**). Complete radiological response, partial response, stable disease, and progressive disease were reported in 3.2% (95%CI 0.4-12.5%), 42.1% (95%CI 28.7-55.9%), 47.4% (95%CI 33.7-61.2%), and 7.3% (95%CI 0.2-17.6%) of patients, respectively, which was a similar therapeutic effect as to the first course. Biochemical response or adverse effects were not reported.

**Clinical sub-question IIIa:** ***Are there predictors for treatment response?***

Of the seventeen included studies for Clinical question III, six assessed predictors of treatment response [19, 36, 39, 42, 43, 46]. Details and grading of included studies can be found in **Supplementary Tables 11 and 12**. Overall, quality of evidence was very low. Also, as patient numbers were small, statistical power to detect effect modification was very low.

Temozolomide

Five studies assessing predictors of temozolomide therapy efficacy found no relation between treatment response and Ki-67 indices or p53 expression [19, 36, 39, 42, 43]. Four studies assessed predictive value of MGMT status. Bengtsson *et al*. reported lower median MGMT staining in responders *vs*. non-responders (9% (range 5-20) *vs*. 93% (range 50-100), p <0.001) [36]. McCormack *et al*. reported a higher rate of no response among patients with high MGMT expression while complete response was only seen among tumour with low MGMT expression [42]. Minniti *et al*. reported that median local control was 15 months for patients with MGMT unmethylated tumours and not reached for patients with methylated tumours ($p$ = 0.01) [43]. However, Hirohata *et al*. found no association between MGMT immunoexpression and temozolomide treatment response [39, 42].

Immune checkpoint inhibitors

Ilie *et al*. reported results of ipilimumab monotherapy or combined with nivolumab, in 9 APT and 6 PC (9 corticotroph, 6 lactotroph tumours) [46]. PCs appeared to respond better than APTs; 4/6 showed partial tumour response vs. none of the APTs. No pathological marker (PD-L1 immunohistochemistry and CD8+ T cell infiltration) was associated with tumour response, however numbers are too small to draw firm conclusions from these observations.

In conclusion, no validated predictors of therapy efficacy of temozolomide or immune checkpoint inhibitors in APT/PC patients were identified.

**Clinical question IV:** ***What is the optimal treatment of isolated metastases of PCs?***

There were no studies identified that systematically assessed treatment of isolated and/or widespread metastases of PCs.

**Recommendations**

**1 General remarks**

**R 1.1** *We recommend that patients with an APT or PC should be discussed in an expert multidisciplinary pituitary team meeting (endocrinologist, neurosurgeon, pathologist, neuroradiologist, radiation oncologist, oncologist).*

**Reasoning**

Diagnosis, management and treatment of APT and PC remain a challenge. Management of these rare tumours should be individualized, taking into account clinical, biochemical, histological and molecular characteristics, as well as the therapeutic sequences performed. Discussion of these cases should take place at a meeting where expertise across all disciplines in managing pituitary tumours is represented

as in pituitary tumour centers of excellence [48]. This enables each of these characteristics to be taken into account, and the best therapeutic option (adapted to the patient's clinical situation) can be decided.

## 2 Assessment of aggressiveness

### 2.1 Diagnosis of an APT

**R 2.1.1** *We recommend the diagnosis of an APT be considered in patients with an invasive tumour, and either 1. unusually rapid tumour progression or 2. clinically relevant tumour progression despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments).*

**Reasoning**

Tumours of the endocrine cells of the adenohypophysis are identified in up to 10% of individuals in imaging and autopsy studies [49] however the prevalence of clinically relevant pituitary tumours is about 70–100 out of every 100,000 persons [1, 2]. The vast majority of these lesions have a good prognosis and are considered as benign pituitary tumours. They are also referred to as pituitary neuroendocrine tumours (PitNET) in the 2022 WHO Classification [50]. In a systematic review of patients with pituitary tumours, naïve to surgery, radiation or medical treatment and who were monitored with MRI for > 12 months, 44% demonstrate growth during follow-up (see **Clinical Question I**). Acknowledging considerable variation, median tumour volume doubling time exceeded two years [24]. Among the subset of pituitary tumours that require treatment, most tumours are well controlled with standard therapy—surgery and/or medical therapy as first-line, and rarely radiation therapy to manage uncontrolled growth. These standard therapies are known to be highly effective for the majority of pituitary tumours—the local control rate of radiotherapy alone is 90-100% [51].

Only a small subset of invasive pituitary tumours follows a more complicated clinical course and can be considered aggressive as defined by rapid growth or progression despite standard treatments. By majority consensus, rapid progression is when tumour progression is observed within a 6-month time frame. While a pituitary tumour can be considered aggressive based on rapid growth, rapid growth at initial presentation is not a feature of many APTs and the time interval between primary diagnosis and aggressive behaviour varies from months to >10 years [13]. There may be extended periods of clinical quiescence for several years followed by a period of rapid tumour growth, invasion, or metastasis [13].

While these tumours are not always invasive at time of diagnosis, APTs become invasive by definition. It has been established that invasion as defined by the Knosp score is a major determinant of (in)complete tumour resection by an expert neurosurgeon [33, 52-54]. However, neither invasiveness

alone, nor large tumour size, should be considered synonymous with aggressiveness [52, 55-57]. For example, giant invasive lactotroph tumours are often sensitive to dopamine agonist treatment [58-60]. Progression despite optimal treatment is an important component of aggressiveness, therefore a tumour that progresses following a suboptimal surgery may not be aggressive, nor can a pituitary tumour that has progressed outside the radiation field necessarily be considered refractory [4].

**R 2.1.2** *We recommend that imaging (MRI in most instances) be used for quantification of tumour dimensions, defining invasion, and establishing progression. We suggest that following a new treatment, tumour progression should additionally be reported according to RECIST.*

**Reasoning**

An imaging study (preferably MRI) that enables accurate measurement of tumour dimensions and invasion is recommended. The imaging protocol should include a coronal T2, pre- and post-gadolinium thin (2-3 mm) sagittal T1, coronal T1, and axial T1-weighted sequences. Comparison to prior imaging studies is essential to identify tumour progression, including older series for evaluation of long-term growth. For this patient population in particular, tumour growth should be evaluated by an expert neuroradiologist, measuring and reporting the size of the pituitary tumour in all three dimensions. The clinical team should consider assessing treatment response according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (see **Table 2**) [61].

Tumour volume can be calculated by contouring tumours slice-by-slice. This is valuable when available, as it may be more accurate for identifying tumour growth. Because volumetric assessment is labour intensive and unavailable at most centres, we suggest RECIST as a reasonable option that would enable the use of this response criteria in future studies of this uncommon tumour type [62, 63].

**Table 2: RECIST 1.1 criteria**

| | |
|---|---|
| **CR** (complete response) | Disappearance of all lesions and pathologic lymph nodes |
| **PR** (partial response) | ≥ 30% decrease SLD<br>No new lesions<br>No progression of non-target lesions |
| **SD** (stable disease) | No PR – no PD |
| **PD** (progressive disease) | ≥ 20% increase SLD compared to smallest SLD in study<br>Or progression of non-target lesions<br>Or new lesions |
| SLD = sum of length diameters | |

**R 2.1.3** *We suggest radiological re-evaluation within 3-6 months in patients with suspicion of having an aggressive pituitary tumour based on clinical, radiological, and pathological features.*

**Reasoning**

A literature search on usual growth velocity in patients with pituitary tumour remnants after surgery revealed median tumour volume doubling times (TVDT) of 27.6 months [25] and 34.6 months [22] (see **Clinical Question I**). Assuming tumour sphericity, a doubling of tumour volume roughly translates to an increase in diameter by 25% [63]. By RECIST criteria, progression of disease is a 20% increase in the longest diameter [61]. For non-aggressive tumours, we set 18 months as the reasonable lower limit of TVDT, as this is the earliest point at which progression can typically be observed by RECIST criteria. However, based on available data and clinical experience, we estimate that for the most aggressive cases (i.e., the top 5%), significant tumour growth would occur more rapidly, likely within 12 months, and for the top 1%, even within 6 months. Therefore, the consensus group suggests that MRI imaging for APTs should be performed at least every 6 months to ensure timely detection of progression.

The prior rate of growth and anatomical considerations such as compression of the optic nerve/chiasm, may necessitate more frequent imaging. All APT or PC patients should undergo MRI scanning within 3 months after surgery. In some circumstances, a shorter period may be considered.

**R 2.1.4** *We recommend full pituitary hormonal evaluation in patients with aggressive pituitary tumours.*

**Reasoning**

Assessment of pituitary endocrine function is essential to identify functioning tumours that may enable specific therapies. Screening for autonomous hormone secretion should follow current guidelines [59, 64-66]. Evaluation should be repeated at appropriate intervals (3-6 months on an individualised basis) as the hormone level may be used in conjunction with imaging as a tumour specific marker that tracks with disease progression and treatment response. As hormone secretion pattern may change during follow-up, re-evaluation should include a complete hormone evaluation at longer intervals. These intervals should consider whether the patient has undergone radiotherapy, the rate of tumour progression, and any present clinical symptoms or signs. The evaluation must screen for potential endocrine deficiencies, which, if left untreated, could increase patient morbidity [67].

In the 2$^{nd}$ ESE survey on aggressive pituitary tumour and carcinomas, 7/45 non-functioning tumours became clinically functioning (5/13 silent corticotroph and 2/6 silent somatotroph) at a median of 11 (range 3-14) years after diagnosis, potentially requiring a change in therapy [13].

**R 2.1.5** *We recommend screening for metastatic disease in patients with aggressive pituitary tumours, and either 1. site-specific symptoms or 2. discordant biochemical and radiological findings or 3. before commencing chemotherapy.*

**Reasoning**

APTs may be locally aggressive and remain confined to the sella or they can metastasize either hematogenously outside the central nervous system or via the cerebrospinal fluid resulting in leptomeningeal "drop metastases." When pituitary tumours spread leptomeningeally, the leptomeningeal deposit(s) may be on the surface of the brain, cranial nerves, or brainstem but may also deposit outside the MRI pituitary field of view (below C1 level of the spinal cord) resulting in symptoms of cord compression or cauda equina syndrome.

In the 2022 ESE survey [13], the central nervous system was the first location of metastases in about half of the patients. Corticotroph tumours were prone to disseminate to the liver and bone. Metastases occurred after a median of 6.3 (maximum 36) years from initial diagnosis, and 3.8 years after development of clinically aggressive behaviour.

We recommend routine tumour staging and screening for metastases prior to initiating chemotherapy (temozolomide per these guidelines) to allow a better evaluation of tumour response. The optimal imaging modality has not been defined. FDG-PET has a high sensitivity for identifying most neoplastic processes [69]. Unfortunately, false-negative and false-positives may occur. False positives are often due to FDG uptake by infectious or inflammatory processes. A cause of false negatives is the high background uptake of FDG by the brain and spinal cord limiting the identification of disease involving the central nervous system [70, 71]. To identify leptomeningeal deposits, the standard imaging modality is an MRI of brain and spine.

Given the presence of somatostatin receptors (SSTR) in some pituitary tumours, there is data supporting the use of PET using one of several radiolabeled octreotide analogs, such as gallium-68 DOTATATE or gallium-68 DOTATOC, for the identification of metastases [72, 73]. The sensitivity of radiolabeled octreotide analogs for identifying metastases is uncertain, although in some patients the metastases had higher uptake of gallium-68 DOTATATE than FDG [72, 74], whereas in single patients FDG was the most informative [75].

An unexplained rise in hormone secretion and site-specific symptoms would be additional indications for imaging. The best imaging study would depend on the clinical context. For hormonal progression in the presence of stable imaging of the primary site, FDG-PET-CT is preferred in most cases. For new

neurologic symptoms, MRI of the brain and/or spine would be the preferred imaging modality to look for leptomeningeal drop metastases.

## 2.2 Potential predictors of aggressiveness in pituitary tumours

**R 2.2.1** *We recommend all pituitary tumours should undergo histopathological study, which should include immunodetection of pituitary hormones and markers of proliferation (Ki-67 index, mitotic count) and p53 immunodetection.*

**Reasoning**

Tumour types and subtypes should be defined by the pattern of pituitary hormones and expressed as approximate percentages of positive cells. In hormone-negative tumours, or in tumours with only scarce immunoreactive cells, the three transcription factors (T-PIT, PIT-1, SF1) should be studied to characterize the lineage and diagnose a subset of silent gonadotroph, corticotroph and plurihormonal PIT1-positive pituitary tumour [50, 76][WHO Classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2024 June 1]. (WHO classification of tumours series, 5th ed.; vol. 10). Available from: https://tumourclassification.iarc.who.int/chapters/53]. When these pituitary-specific transcription factors are negative, additional IHC staining should be performed to exclude a metastasis from other tumours [77] or other tumours from the sellar region.

The European pituitary pathologist's group (EPPG) developed a standardised histological report, which states that "mitotic count and Ki-67 index must be carefully assessed and that a cut-off of ≥ 3% for the Ki-67 index and a mitotic count > n=2 for 10 high power fields are currently considered to bear prognostic relevance" [76]. It should be noted that none of the above-mentioned factors can reliably predict or exclude aggressive behaviour on its own however (see **Clinical Question II**). The prognostic value of p53 is debatable and a reliable method of quantification has not been validated. However, a common definition of positive staining is >10 strongly positive nuclei per 10 HPFs [6] and in case of strong immunostaining, p53 may be expressed in percentage without cut-off [76]. While *TP53* mutations may be seen in association with increased p53 expression [78], lack of p53 staining does not rule out a loss-of-function mutation [79].

The two ESE surveys on APT/PC demonstrated the clinical relevance of these three markers (ki67 index, mitotic count and p53) [13, 42]. A mitotic count n>2 was frequently observed in APT and PC (31% and 55% respectively). Ki-67 ≥ 3% was the most frequent positive marker in APT (77.5%) and PC (82.3%) with 41% of the tumours tested having a Ki-67 ≥ 10%. These figures were much higher than observed in a surgical series of unselected pituitary tumours, in which only 3% of cases presented a Ki-67 ≥ 10%

582 and 5% demonstrated a mitotic count >2 [80]. Moreover, an initial Ki-67 ≥10% may be associated with
583 worse outcome [10, 13].
584
585 **R 2.2.2** *We suggest classifying pituitary tumours according to their proliferative status and radiological*
586 *signs of invasion.* (⨁○○○)
587
588 **Reasoning**
589 To date, no marker alone is sufficient to predict tumour behaviour (see **Clinical question II**). A five-
590 tiered classification system combining markers of proliferation (Ki-67 index, mitotic count) and p53
591 immunodetection with signs of radiological invasion has mainly been studied in unselected cohorts of
592 surgically treated pituitary tumours to determine tumours with a higher risk of progression/recurrence
593 [7]. Fewer studies have assessed the predictive role of the five-tired classification to identify aggressive
594 or malignant behaviour. Grade 2b tumours also have a higher risk of developing clinically aggressive
595 behaviour and requiring ≥ 3 adjuvant therapeutic lines as compared to non-proliferative tumours [31,
596 81]. In the ESE survey 68% of 43 APT and PC investigated, were classified as grade 2b at initial pathology
597 [34]. Grade 2b pituitary tumours [7] were reported to have a sensitivity of 68% [34], and an odds ratio
598 of 3.4 [95%CI 1.35-8.57], p 0.0096 [31] for becoming clinically aggressive (see **Clinical question II;**
599 **Supplementary Table 4**). In the ESE survey 68% of 43 APT and PC investigated, were classified as grade
600 2b at initial pathology [PMID: 36952293], underlying that also non-2b tumours can become aggressive.
601 However, the prospective predictive value, e.g. the proportion of 2b tumours that are/will become
602 aggressive or malignant, remains to be established.
603
604 **R 2.2.3** *We suggest interpretation of the pathological diagnosis in the clinical context of the individual*
605 *patient.* (⨁○○○)
606
607 **Reasoning**
608 In addition to pathology results some clinical characteristics are found more frequently among APT
609 and PC and should be taken into consideration. Most APT/PC are corticotroph and lactotroph tumours
610 [13, 42]. The high incidence of corticotroph tumours, of which about 45% had Cushing's disease,
611 contrasts with an incidence of 5-10% of pituitary tumours in national studies [82], and indicates that
612 corticotroph tumours have a special propensity to become aggressive [80]. Lactotroph tumours are
613 the most frequent pituitary tumour, mostly treated medically, and represented only 11% in a surgical
614 cohort compared to 24% of APT/PCs [80].
615 Similarly, compared to the general population, the percentage of males is high in APT/PC
616 corresponding to 63% of the 2$^{nd}$ survey ESE cohort of 171 patients [13]. This is particularly true for

lactotroph and corticotroph tumours [10, 13], while the benign forms of these tumours usually have a female predisposition. The WHO classification now identifies lactotroph tumours in men as “high risk tumours” but does not mention the corticotroph tumours in men [50, 83].

Although rare, the secretory capability changes from initially silent corticotroph tumours to functioning corticotroph tumour with Cushing’s disease after many years of follow-up may herald more aggressive tumour behaviour [10, 13].

**R 2.2.4** *We suggest molecular analysis, specifically, testing for somatic variants in genes that have been associated with aggressive behaviour: TP53 and SF3B1 in lactotroph tumours refractory to treatment with dopamine agonists, and TP53 and ATRX in corticotroph macroadenomas.*

**Reasoning**

We suggest screening lactotroph tumours refractory to treatment with dopamine agonists, corticotroph macroadenomas (largest tumour diameter ≥ 10 mm) and/or grade 2b lactotroph or corticotroph tumours, with targeted sequencing or oncology gene panels.

Pathogenic somatic *TP53* variants have been increasingly reported in corticotroph APT/PC cases and after genetic screening of corticotroph macroadenoma and treatment-refractory corticotroph tumour cohorts [77, 84-86]. An international multicentre study on unselected functional corticotroph tumours identified *TP53* variants in 9/86 cases and demonstrated significant association with higher Ki-67, invasion, incomplete tumour resection, multiple therapeutic interventions and disease specific death [87]. In addition, *TP53* variants were identified in 3/7 treatment refractory aggressive lactotroph tumours and in 2 cases of highly proliferative and metastatic lactotroph tumours [86, 88, 89].

Loss-of-function *ATRX* variants have been detected most frequently in corticotroph macroadenomas [86, 90] but have been reported in isolated cases of aggressive lactotroph and somatotroph tumours [90]. *ATRX* variants were reported in 9/48 APT/PC (4/30 APT, 5/18 PC) and were more common in the corticotroph tumours 7/22 (32%) compared with tumours of the Pit-1 lineage 2/24 (8%) [90]. Loss of nuclear ATRX staining has been demonstrated in APT and PC, but not in non-aggressive pituitary tumours; ATRX immunonegative pituitary tumours were reported to carry loss-of-function *ATRX* variants [90, 91]. Therefore, immunohistochemistry for ATRX may be a cost-effective way to identify the cases to sequence for *ATRX* variants.

Pathogenic and likely pathogenic *SF3B1* variants are infrequent in the general lactotroph tumour population (2.5%), but they were found in 3/6 metastatic lactotroph tumours [92, 93]. An international multicentre study on surgical series of 282 lactotroph tumours significantly correlated *SF3B1* variants with higher Ki-67, high Trouillas grade (grade 2b and grade 3), multiple therapeutic interventions including chemotherapy, likelihood to develop metastases and shorter postoperative survival.

It is noteworthy that *ATRX*, *TP53* and *SF3B1* variants were found in earlier tumour specimens, prior to radiation and development of metastasis, which allows for early detection. Detection of somatic variants in *TP53*, *ATRX* in corticotroph and *SF3B1* in lactotroph tumours may alert to worse disease outcome and therefore guide the timely implementation of more intense treatment schemes and vigilant patient follow-up. Furthermore, molecular testing, including for these genes, in patients with APT that do not respond to several lines of treatment may identify potentially targetable genetic defects (e.g., in [94]).

**R 2.2.5** *In patients with aggressive pituitary tumours, we suggest germline genetic testing based on young age at presentation or family history of pituitary tumours, endocrine neoplasia, or other syndromes as recommended for patients with non-aggressive pituitary tumours.* (⨁○○○)

**Reasoning**

The majority of pituitary tumours are sporadic, but ~5% are found in syndromic setting or as isolated familiar pituitary adenomas (FIPA) [95]. It is not well established if aggressive behaviour is more common in patients harbouring germline mutations. According to the latest consensus, genetic testing might be considered for children and young patients with pituitary tumours irrespective of APT/PC [96].

## 3 Therapeutic options

### 3.1 Role of surgery

**R 3.1.1** *We recommend surgery should be performed by a neurosurgeon with extensive experience in pituitary surgery.* (⨁⨁○○)

**Reasoning**

The goals of surgical intervention, whether complete resection, near-complete resection, or debulking, must judiciously weigh the merits of reduced tumour burden against safety imperatives. Multiple studies have demonstrated that increased surgeon experience is associated with improved surgical outcomes and reduced complication rates [97, 98]. The transnasal approach remains the gold standard in most cases. Some studies suggest that the wider exposure and the enhanced direct visualization attainable with endoscopic approaches may facilitate a more extensive surgical resection of these aggressive tumours that often extend beyond the sella into the cavernous sinuses and other parasellar structures. Surgical adjuncts including the use of neuronavigation and intra-operative imaging may further enhance maximal safe surgical resection [99]. In selected cases, a transcranial approach may offer advantages in resection of tumours that extend significantly into the suprasellar region.

**R 3.1.2** *We recommend discussion with an expert neurosurgeon regarding repeat surgery prior to consideration of other treatment options.*

**Reasoning**

In instances where a patient has previously undergone surgery and achieving complete or near-complete tumour resection is unlikely — particularly if the initial surgery was deemed inadequate — revisiting surgical intervention with an experienced neurosurgeon may still be crucial. This includes mitigating the local effects of pituitary tumour mass, such as urgent relief from optic chiasm compression, immediate regulation of hormone overproduction, or acquiring additional tissue samples to enable genetic testing for targeted treatment approaches. Consequently, it is our recommendation that the potential for further surgical measures be evaluated on a case-by-case basis. This should occur within a multidisciplinary team context according to **R1.1**.

### 3.2 Role of radiotherapy

**R 3.2.1** *We recommend radiotherapy to improve tumour control in patients with clinically relevant tumour progression despite surgery and standard medical treatment.* (⊕⊕○○)

**Reasoning**

Radiation therapy may offer the possibility of long-term control of tumour growth and should be discussed in all patients with an APT. Both fractionated external beam radiation therapy (EBRT) and stereotactic radiosurgery (SRS) are highly effective in pituitary tumours, although little data are available in more aggressive phenotypes.

**Radiotherapy techniques**

EBRT is usually delivered in 25-30 fractions with a total dose of 45-54 Gy in 1.8 Gy fractions. SRS delivered in a single or few fractions is typically performed using Gamma Knife (GK), Cyberknife, and LINAC-based SRS technologies. Traditionally, patients treated with GK are placed in a fixed frame with a target accuracy <0.5 mm, while in LINAC-based SRS patients are immobilized in a high precision frameless stereotactic mask fixation system; a submillimetric positioning accuracy is achieved using advanced image guided radiation therapy (IGRT) technologies, such as orthogonal x-rays (ExacTrac®Xray system) and cone beam computed tomography (CBCT). For patients receiving conventionally fractionated stereotactic radiation therapy (SRT), dose conformity is improved using intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) techniques [100]. In patients with pituitary tumours, limited data suggest that proton therapy using

722 either 50.4 - 54 GyRBE in conventional fractions or proton SRS with a median dose of 20 GyRBE offer
723 excellent local control rate with an incidence of hypopituitarism similar to those seen after photon
724 SRT/SRS [101-104].
725
726 **Type of radiotherapy**: Both SRS and EBRT offer similarly high, long-term local control around 90% at 5
727 years in patients with residual or progressive pituitary tumours [105-107]. To date, there are no
728 controlled trials comparing fractionated EBRT and SRS. Fractionated approaches, given with a total
729 dose of 45 to 54 Gy in 1.8 Gy fractions, are often delivered in larger tumours involving the optic
730 pathway, whereas SRS is usually used in well-delimited tumours measuring less than 3 cm not abutting
731 optic structures [100]. Though SRS with doses of 13-16 Gy is typically given as single fraction for most
732 tumours, hypo fractionated SRS (2-5 fractions) has been employed in patients with tumours in close
733 proximity or involving the optic apparatus who are considered not suitable for single-fraction SRS.
734 Using doses of 18-25 Gy in 3-5 sessions, a few studies report a local control around 95% at 3 years
735 [108-111].
736
737 **Target delineation**: An accurate imaging and delineation of the tumour is fundamental. The gross
738 tumour volume (GTV) is defined as the visible lesion on MRI, typically, this is the contrast-enhancing
739 lesion. Margin expansion from GTV to generate the clinical target volume (CTV) is not usually applied
740 when delineating a pituitary tumour; however, for aggressive tumours a margin of 2-3 mm may be
741 added to encompass potential tumour infiltration and paths of tumour spread, e.g. rapidly growing
742 pituitary tumour invading the cavernous sinus, sphenoid sinus, bone and brain parenchyma [100].
743
744 **Efficacy in the context of APT and side effects**
745 Scarce data are available regarding the efficacy of radiotherapy in aggressive pituitary tumours. Minniti
746 *et al.* reported 5-year and 10-year local control rates of 97% and 91%, respectively, in 68 patients with
747 large (> 3 cm) residual or recurrent nonfunctioning pituitary adenomas treated with fractionated SRT
748 (median dose 45 Gy in 1.8 Gy fraction) [112]. Local control of 70-80% at 5-10 years after fractionated
749 radiotherapy has been reported in other series [113, 114], however, these tumours did not fulfill
750 criteria of aggressiveness based on this guideline and pathological characteristics (p53, mitotic count,
751 Ki-67 index) were not reported. Burman *et al*. reported the radiological response of 152 patients with
752 APT/PC receiving radiotherapy; complete response, partial response, stable disease, and progressive
753 disease occurred in 3.2%, 41.9%, 47.6%, and 7.3% of patients, respectively (see **Clinical question III**)
754 [13].

The indication for radiotherapy must be balanced against potential side effects. In non-aggressive pituitary tumours it is advisable to be restrictive with RT, but in aggressive tumours the balance between benefit and risks may be different, although the side effects are similar. The most frequent long-term side effect of radiotherapy is hypopituitarism [115]. This increases over time, indicating the need for patient education and lifelong evaluation for pituitary insufficiency. Hypopituitarism itself may be a risk factor for premature mortality, other potential radiotherapy related causes being vascular injury and haemodynamic changes [116]. Furthermore, radiotherapy is associated with an increased risk of malignant brain tumours (RR = 3.3) or meningioma (RR = 4.1), this risk was higher (RR = 14.1 and 7.6, respectively) in patients treated with RT before the age 30 years [116, 117]. The absolute risk of second brain tumour was estimated to be 1-3% over 15-20 years, increasing to approximately 5% after 30 years [118, 119]. In a large study comparing 996 patients exposed to different radiotherapy modalities, radiotherapy exposure was associated with increased risk of a second brain tumour [120], rate ratio 2.18 (95% CI 1.31–3.62) with a cumulative 20-year incidence of 4% for the irradiated compared to 2.1% for the controls.

The risk of optic pathway injury is low with EBRT, with an estimate of 1% at 10 years and 1.5% at 20 years [121]. For SRS, most series report neurological deficit rates of <5%, most commonly optic neuropathy [122]. The maximum dose to the optic nerve system should be kept below the threshold of 8–12 Gy to avoid injury to the visual system.

For radiotherapy in combination with temozolomide, see **R 3.4.2**.

**R 3.2.2** *We suggest early radiotherapy be considered in the setting of a clinically relevant invasive tumour remnant with proliferation markers and/or genetic alterations, strongly indicating aggressive behaviour.* (⊕○○○)

**Reasoning**

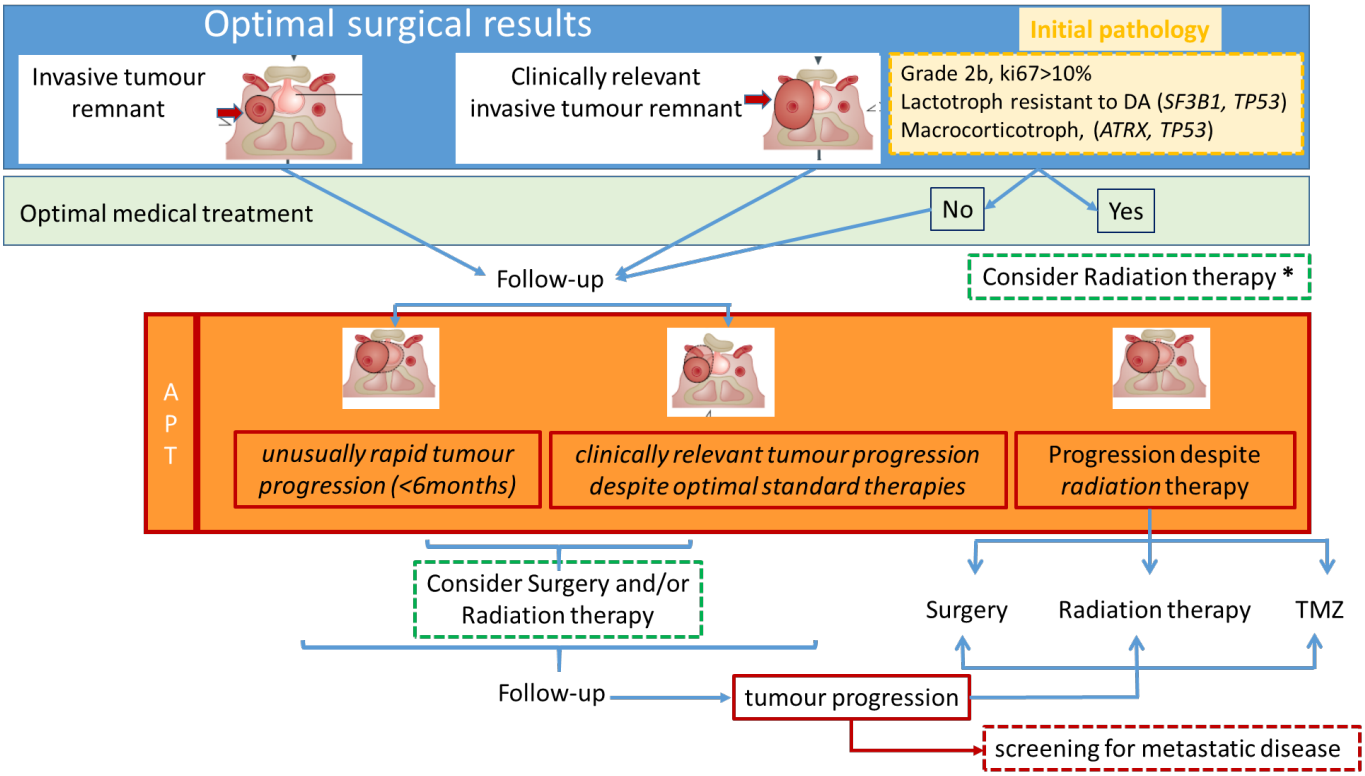
Despite a significant proportion of postoperative residual nonfunctioning pituitary tumours demonstrating regrowth [123] the timing of radiotherapy for residual pituitary tumours remains controversial [124, 125]. Some studies have suggested that early postoperative SRS (within 1 year after surgery) may decrease the probability of tumour progression of subtotally resected nonfunctioning pituitary tumours as compared with late SRS [125, 126]; however, a recent large study involving 375 patients with residual nonfunctioning pituitary tumours managed with SRS showed a similar probability of tumour control of about 95% at 5 years and hormonal/visual deficits following early (within 6 months of resection) and late treatment (for residual tumour progression) [124]. Similar

outcomes have been reported after conventionally fractionated stereotactic radiotherapy given early after surgery or at tumour progression [100, 112, 127-129].

For patients with residual tumour, we suggest early RT should be considered in the presence of pathological or molecular markers suggesting the potential of aggressive behaviour and where there is no short-term benefit from additional surgery (see **Figure 4**).

Radiation treatment should be evaluated on the basis of a postoperative MRI performed within 3 months from surgery. For tumours following an aggressive course, characterized by rapid growth prior to radiotherapy, combined treatment with temozolomide should be explored in this setting in clinical trials.

**Figure 4: APT treatment algorithm**




***** For tumours following an aggressive course, characterized by rapid growth prior to radiotherapy, combined treatment with temozolomide should be explored in this setting in clinical trials.

**R 3.2.3** *In case of rapid progression despite previous RT, we suggest considering a second course of RT after careful assessment of dose accumulation to the brain, chiasm and cranial nerves in close proximity to the target tumour.*

**Reasoning**

A second course of RT has emerged as a feasible treatment option in patients with recurrent brain tumours [130]. Evidence from animal studies and clinical series shows that brain and spinal cord have marked repair potential suggesting that reirradiation may represent a feasible option in selected patients [131-135].

For final evaluation and confirmation of doses to be delivered, thereby determining potential side effects, an experienced radiation oncologist is required for the optimal choice of the radiation treatment [121]. Advanced radiation techniques are usually recommended including either stereotactic radiosurgery or stereotactic radiotherapy. The decision often lies with the availability of a system at the treating center.

There has been no trial that has tested the role of re-irradiation on overall survival or progression free survival in patients with APT. Few published series suggest that a second course of RT, both SRS and SRT using either photons or protons, may be a feasible salvage treatment option for selected patients with skull base recurrent tumours, including APTs [136, 137] and meningiomas [138-140], and is associated with a risk of symptomatic radionecrosis, cranial deficits, and radiation-induced optic neuropathy of < 15%. While consistent recovery has only been described for CNS tissue and thus should be considered when assessing cumulative doses to these organs [135], recovery for optic nerves and chiasm remains unclear and thus no recommendation for the use of a discount factor for these organs is possible. We recommend that prescription for reirradiation should follow similar principles as for a primary course of radiotherapy with the primary goal of respecting safe or acceptable dose limits for optic chiasm and cranial nerves when deciding dose and fractionation.

### 3.3 Standard medical therapies

**R. 3.3.1** *We recommend standard medical treatment in functioning pituitary tumours with maximally tolerated doses in order to control tumour growth, as per current guidelines.* (⊕⊕○○)

**Reasoning**

**Prolactinoma**

Cabergoline is the preferred dopamine agonist owing to its long half-life, high efficacy and good tolerability (see **Table 3**) [59]. In most prolactinomas normoprolactinemia and a reduction of tumour volume can be achieved with a dose ≤2 mg/week [141]. However, variable degrees of therapy resistance are encountered. These tumours can often be controlled by increasing the weekly dose of cabergoline up to 3.5 mg [142]. High dopamine agonist efficacy is maintained in giant prolactinomas,

with reduced tumour volume reported in approximately three quarter of patients [143]. Of note, some large tumours may be exquisitely sensitive to dopamine agonists.

If a prolactinoma does not exhibit a favorable response in the first 3–6 months of treatment, it probably will not respond adequately to cabergoline. However, some prolactinomas respond slowly. Male gender is associated with a lower response [142] and worse prognosis. In a subset of patients, prolactin levels may be normalised without a decrease in tumour size, the mechanism for this phenomenon remains to be clarified [141].

**Table 3: Doses for conventional pituitary-directed treatment of functioning pituitary tumours, as suggested by current guidelines.**

Lactotroph tumours [59]

- cabergoline: 0.25 to 3.5 mg/wk; occasionally up to 11 mg/wk (or up to maximal tolerable doses).

Somatotroph tumours [144]

- lanreotide autogel/depot: 60-120mg monthly deep sc.
- octreotide long-acting release (LAR): 10-40mg monthly im.
- pasireotide long-acting release (LAR): 20-60mg monthly im

Corticotroph tumours [66]

- pasireotide 600-900 mg sc. twice daily
- pasireotide LAR10–30 mg monthly IM

Thyrotroph tumours [145]

- lanreotide autogel/depot: tailored individually
- octreotide long-acting release (LAR): tailored individually

**Acromegaly**

According to the latest consensus on criteria for acromegaly, biochemical remission is considered the primary assessment treatment outcome but should be interpreted in the clinical context (signs and symptoms) of acromegaly [65]. Biochemical remission is defined if active disease cannot be detected. Somatostatin Receptor Ligands (SRL) are the first medical treatment option [144, 146]. Octreotide is now available in both injectable and oral formulations [147, 148]. Octreotide and lanreotide, as first line medical treatments, are effective in achieving biochemical control in 25-45% of patients [144]. Control rate with monotherapy octreotide or lanreotide is higher in patients treated with high dose SRLs [149].

The dopamine agonist cabergoline, can be used as monotherapy in patients with mild acromegaly [150]. It may also be used in combination with conventional SRLs or in patients with GH/PRL co-secreting tumours. Multireceptor targeted SRL, pasireotide and the growth hormone receptor

antagonist (GHRA), pegvisomant (PEGV) are second line options [151], achieving higher rates of biochemical control in comparison with first generation SRLs [152, 153].

In selected complex patients, as third line therapy, PEGV could be used in combination therapies either with conventional SRLs or pasireotide [154, 155]. Combination therapy is suggested to be used in patients with inadequate biochemical control with monotherapy. PEGV in combination with pasireotide has been used in patients who are resistant to conventional SRLs [155, 156].

**Cushing's disease**

Corticotroph tumours express SSTR5, and less frequently SSTR2 and dopamine receptors [157]. Pasireotide is presently the only drug targeting the pituitary approved for treatment of Cushing's disease. In a study on 162 patients, pasireotide led to normalisation of UFC in 26% of patients [158]. Pasireotide treatment also decreased median tumour volume by 17.8% on 10 mg and 16.3% on 30 mg with 43% and 47% of patients showing a >20% reduction in the subgroup of 73 patients evaluated by pre- and posttreatment MRI [159]. Effects of dopamine agonists on biochemical and tumour control in Cushing's disease are inconsistent [160-162].

**Thyrotroph tumours**

Related to the high expression of SSTR2 in these tumours [163], more than 90% of thyrotroph tumours respond to somatostatin analogues, with restoration of a euthyroid state in 73-100% of cases, and a reduction in tumour size in 20-70% (**Table 3**) [164, 165]. The response to dopamine agonists with regard to TSH secretion and tumour shrinkage has been variable, with best results in mixed thyrotroph/lactotroph tumours [164, 166].

**Resistance to standard medical treatment**

**Dopamine agonists**

The International Pituitary Society defined 'resistance' as lack of normalization of prolactin serum levels or lack of relevant mass shrinkage (≥ 30% reduction in maximum diameter) when treated with standard dopamine agonist doses (up to 2.0 mg per week of cabergoline) for at least 6 months [59]. In contrast, prolactin levels in 'refractory' prolactinoma are not controlled even by dose escalation to maximally tolerated doses of dopamine agonists. Furthermore, refractoriness is distinguished from 'aggressiveness', which should be reserved for patients with ongoing tumour progression despite treatment with maximally tolerated doses of dopamine agonists.

Complete resistance to dopamine agonists represents less than 10% of macroprolactinomas [141]. Dopamine resistant lactotroph tumours often are invasive macroadenomas, and according to some studies are more angiogenic and proliferative [167].

Furthermore, high doses, up to 11 mg/week have been shown to result in prolactin normalisation in some patients [168] (**Table 3**). It is proposed that the highest tolerated dose of dopamine agonist be used in patients with aggressive prolactinomas.

**Somatostatin analogues**

In acromegaly, resistance to treatment may be partial or complete. Complete treatment resistance occurs in less than 10% of patients [169]. To date, several mechanisms for resistance have been proposed [170-173]. Sparsely granulated somatotroph tumour with low SSTR expression may be a marker of low response to first generation somatostatin analogues [172, 174], however the association is quite heterogeneous [175]. Somatotroph tumours from *AIP* mutation carriers are less responsive to first generation somatostatin analogues, and data suggest that the response to second generation somatostatin analogue-pasireotide is similar in *AIP* sufficient and *AIP* deficient tumours [176]. Good quality T2-weighted MRI signal predicts hormone and tumour responses to somatostatin analogs in acromegaly at a group level, with higher MR T2 signal intensity (hyperintense adenomas) implicating inferior responsiveness to somatostatin therapy [177], although many tumours cannot be categorized as being clearly hypo- or hyperintense [171].

**Standard therapies in Aggressive Pituitary Tumours**

Aggressive pituitary tumours usually respond poorly to the endocrine medical treatments used for non-aggressive tumours. However, in single patients with metastatic disease, non-cytotoxic drugs have been reported to, at least temporarily, reduce tumour burden; bromocriptine in two lactotroph tumours [178] and a high dose of octreotide in a malignant thyrotroph tumour [179].

Morbidity and mortality in patients with aggressive corticotroph tumours are often related to cortisol excess and drugs reducing glucocorticoid excess should be given aiming at achieving eucortisolism [180]. There is little experience with pasireotide in aggressive corticotroph tumours. In eight patients with Nelson's syndrome pasireotide had minimal effects on tumour volume, in spite of reductions in ACTH levels in most patients [181]. In three patients with aggressive corticotroph macroadenomas (1 PC) pasireotide was not clinically useful [182], and in three patients with recurrent corticotroph tumour after discontinuation of TMZ, pasireotide had no effect [12]. There are several reports of corticotroph tumour growth after bilateral adrenalectomy, and after achieving eucortisolism following treatment with steroidogenic inhibitors [183]. This risk seems higher in patients with macroadenomas and aggressive corticotroph tumours [184, 185]. However, in the 2022 ESE study many clinicians judged

that accelerated tumour growth had already occurred before bilateral adrenalectomy [13]. Whether bilateral adrenalectomy might trigger aggressive behaviour remains unknown. The biology of the corticotroph tumour *per se* might be the major determinant of continued progressive growth. There is not sufficient evidence to recommend or recommend against bilateral adrenalectomy in patients with aggressive corticotroph tumours in whom cortisol excess cannot be controlled by pharmacotherapy, surgery and radiotherapy.

### 3.4. Chemotherapies

**R 3.4.1** *We recommend use of temozolomide monotherapy as first line chemotherapy for aggressive pituitary tumours and pituitary carcinomas, following documented tumour progression.* (⊕⊕○○)

**Reasoning**

The first use of temozolomide (TMZ) in the treatment of aggressive pituitary tumours was described in 2006 [186-188]. Early case reports were subject to publication bias in favour of treatment response. The original ESE Guideline on APT/PC reported an objective response (i.e. complete or partial radiological response) in 47% [95%CI 36-58%] of patients [17]. An updated literature review for this guideline, found an objective response, i.e. CR or PR, in 37.3% of patients [95% CI 31.3-43.4%] (**Clinical question III**). Decrease or normalisation of hormone levels was seen in 28.6 to 100% of hyperfunctioning tumours [12, 13, 18, 19, 37, 38, 40, 41, 44, 45]. A hormonal response, even in the presence of stable disease, may be clinically significant and reduce morbidity.

A higher response rate, up to 69%, has been reported in a study where TMZ treatment was instituted earlier in the treatment algorithm, before endocrine medical therapy, for instance in patients with acromegaly who could not afford treatment with somatostatin analogues. Most of the patients did not fulfil the guideline definition of an APT [189]. The guideline panel underlines that without evidence of aggressive growth, use of TMZ should be considered investigational, and cannot be recommended outside of a trial.

There are no head-to-head studies comparing temozolomide to other treatment regimens. Given the course of the condition (spontaneous regression is not likely to occur), the guideline panel recommends the use of temozolomide since a positive effect in a considerable percentage of patients has not been shown with other treatments.

**Biomarkers of response to temozolomide**

*O6-methyl guanine DNA methyl transferase (MGMT)*

MGMT, a DNA repair enzyme, counteracts the action of TMZ and ascertainment of its expression in APT/PC, via immunohistochemistry (IHC), may provide a biomarker of response to TMZ. In particular,

high MGMT expression is associated with lack of response – in the earlier ESE survey 76% of non-responders exhibited high MGMT expression [42]. Low MGMT expression does not guarantee a response although 46% of those with low expression in the ESE survey showed tumour regression and among those with complete response low MGMT is universal (see **Clinical Question IIIa**) and associated with higher overall survival following TMZ [190]. In the first ESE guideline, it was suggested that evaluation of MGMT status by IHC by an expert neuropathologist should be performed [17]. There remain concerns about technical aspects of MGMT IHC analysis, analysis of MGMT in historical tumour samples (noting MGMT status may change over time) and access to a neuropathologist with experience in MGMT IHC. The results of the systematic review for **Clinical sub-question IIIa** show that some studies have demonstrated an association between MGMT expression and response to TMZ, however a patient cannot be denied a trial of TMZ regardless of MGMT status in the absence of another treatment option. For these reasons, the panel no longer suggests routine performance of MGMT IHC prior to a trial of TMZ. Some groups continue to report MGMT promoter methylation status and while this is standard in the glioma field, has not been useful in predicting outcome of TMZ in APT/PC [191].

*DNA Mismatch repair (MMR) proteins*

In addition to MGMT, the expression of mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) may be important for the cytotoxic effect of TMZ. In a study of 13 patients with aggressive pituitary tumours (10 carcinomas), intact MSH6, but not low MGMT, was found to be a prognostic indicator of good response to TMZ (see **Clinical sub-question IIIa**) [39]. Among 4 patients with absent MSH6, there was failure to respond to TMZ although 2 also had positive MGMT expression [39]. In other studies [36, 44] MSH6 and MLH1, MSH2, PMS2 did not predict the effect of TMZ.

Loss of MSH6 during tumour progression, despite low MGMT, has been linked with development of TMZ resistance in 2 cases [89, 192]. However, in one patient with a pituitary corticotroph carcinoma with a germline MMR gene deficiency (Lynch syndrome) there was initially a marked response to TMZ followed by rapid tumour progression [193].

None of these results support the study of mismatch repair proteins expression to predict response to temozolomide.

**Combination of TMZ with other drugs**

At present there is insufficient evidence to recommend use of TMZ in combination with other oncological therapies, particularly given the potential for increased toxicity.

*TMZ plus capecitabine*

Sequential treatment with capecitabine followed by temozolomide (CAPTEM) is commonly used for management of advanced neuroendocrine tumours (NETs), although superiority to TMZ alone in NETs is not consistently found across all studies [194, 195]. Among 20 patients treated with CAPTEM, 9 had a radiological response. In 7 of the 9 responders in whom MGMT immunoexpression was analyzed, 6 had low levels [77]. Thus, no conclusion regarding a superior effect of CAPTEM to TMZ monotherapy can be drawn since a low MGMT level is associated with an effect of TMZ. Further complicating assessment of efficacy of this combination is that regimes have been variable between cases.

*TMZ plus other oncological therapies*

In limited cases anti-angiogenesis drugs have been combined with TMZ, most commonly bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor. In 4 cases upfront combination therapy was employed with prolonged progression free survival of 18, 60 and 96 months in 3; although the 2 cases with longest progression free survival (PFS) also had concurrent radiotherapy [196-198]. The 4$^{th}$ case demonstrated discordant results with partial radiological response, but progressive biochemical disease [199]. An additional 2 cases utilized bevacizumab as add-on therapy to TMZ – in one case demonstrating a partial response after stable disease on TMZ and the other continued progressive disease [42]. In a couple of reported cases, combination therapy with other anti-neoplastic drugs (thalidomide, BCNU) have no demonstrated efficacy [199].

**R 3.4.2** *We recommend use of temozolomide standard dosing regimen: 150-200 mg/m$^2$ for 5 consecutive days every 28 days.* (⊕○○○)

**Reasoning**

In the vast majority of reports on APT/PC, TMZ has been administered in cycles, 150-200 mg/m$^2$ for 5 consecutive days every 28 days, here referred to as the “standard dosing regimen”. In the first cycle 150mg/m$^2$/day is used, with an increase to 200mg/m$^2$/day in subsequent cycles if there is no toxicity. Continuous dosing, 50 mg/m$^2$, or dose-dense regimens, with 50 mg/m$^2$ 7/ 14 days, or 21/ 28 days, have been tried both in APT and other malignancies with the hypothesis that larger doses over a longer time would eventually deplete MGMT stores, thereby increase the efficacy of TMZ therapy. However, in glioblastomas dose dense schedules had similar efficacy as the standard regimen, but with more side effects, particularly severe neutropenia [200]. There are no studies comparing different dosing schedules in patients with APT, so we cannot recommend an alternative to standard dosing.

There is increasing use of combination radiotherapy with temozolomide. Alkylating agents, such as TMZ or lomustine, are considered radiosensitizers based on synergistic effects with RT in experimental

studies [201, 202]. Combined fractionated RT and alkylating agents, termed the "STUPP protocol", is the standard of care for adult-type gliomas (glioblastoma). Under this protocol, TMZ is typically given at 75mg/m2/day concomitant to fractionated EBRT followed by TMZ monotherapy using 150-200mg/m2 for 5/28 day cycles for a total of 6 cycles. In pituitary tumours, currently no data are available on toxicity of concomitant treatment and data on the efficacy are very limited. When data of the two ESE surveys were combined [77], the radiological response rate was higher in 20 patients receiving the STUPP protocol compared to patients receiving temozolomide monotherapy (75% vs. 40%).

In a recent retrospective study 37 patients treated with combination TMZ/radiotherapy (but limited to 3 months of TMZ in total) were compared with 30 patients receiving radiotherapy alone [203]. Combination therapy was superior to radiotherapy alone (92% vs 70%) with regards to a composite measure of clinical efficacy (tumour volume, biochemistry, clinical). Importantly, this study included "low grade" pituitary tumours (not defined by authors), and outcomes may not be directly applicable to APT/PC. In another cohort of 21 patients receiving TMZ along with re-irradiation , there was a 73% and 65% progression-free survival at 2 and 4 years respectively [43]. Notably in this cohort it is uncertain whether stabilization of disease was achieved by the second course of radiation alone as most patients had either shown lack of response on TMZ monotherapy or progressed following a previous course of TMZ. Radiation-related toxicity was seen with 3 patients developing worsening of cranial nerve palsies

The lack of comparative studies or long-term data and the potential for confounding should be underlined. The working group therefore recommends that such a combined approach cannot be currently recommended and should be evaluated in controlled studies. Concurrent TMZ and a course of radiotherapy could be considered in cases of rapid tumour progression of a large residual, inaccessible to additional surgery, particularly in cases of high proliferative markers and/or somatic mutations suggestive of a poor prognosis (see **R 2.2.4**), or when a rapid tumour response is required. In the latter context, the possibility of starting treatment with temozolomide alone, supplemented by radiotherapy, has also been discussed. The combinations should thus only be given after discussion with a multidisciplinary team balancing risks and benefits and treatment alternatives.

**R 3.4.3** *We recommend first evaluation of temozolomide treatment response after 3 cycles. If radiological progression is demonstrated, temozolomide treatment should be ceased.* (⊕⊕○○)

**Reasoning**

In general, an effect of TMZ is observed within 3-6 months, with parallel decreases in circulating hormone concentrations and tumour volumes [36, 204]. A treatment response should be ascertained both biochemically (in functioning tumours) and radiologically.

**R 3.4.4** *We recommend monitoring of haematological parameters, liver function tests and careful clinical observation for potential adverse effects during treatment.* (⊕⊕⊕○)

**Reasoning**

TMZ is as an oral outpatient-based chemotherapy and is generally well-tolerated. Adverse effects reported with ≥ 10% incidence are listed in **Table 4**, information mainly based on the use of TMZ in malignant gliomas. Dose-dense regimes are associated with increased myelotoxicity [200].

**Table 4: Common adverse effects** (adapted from Temodar® (temozolomide) Product Information, version 9/2023)

| | |
|---|---|
| Alopecia | Asthenia |
| Fatigue | Fever |
| Nausea | Dizziness |
| Vomiting | Incoordination |
| Headache | Viral infection |
| Constipation | Amnesia |
| Anorexia | Insomnia |
| Convulsions | Lymphopenia |
| Rash | Thrombocytopaenia |
| Hemiparesis | Neutropaenia |
| Diarrhea | Leukopaenia |

In patients with APT/PC, adverse effects, mostly mild, are reported in around a half of patients (see **Clinical Question III**), fatigue most commonly, followed by nausea/vomiting [36, 205, 206]. Prophylactic use of anti-emetic therapy (e.g. ondansetron) is recommended during days 1 to 5 of the standard therapy regimen. Across 3 large cohorts and the ESE survey, a total of 190 patients, 29 (15%) patients discontinued TMZ as a result of side effects (15 with pervasive fatigue, nausea in 6, cytopaenias in 3, 1 each due to headache/oedema/hypotension, adrenal crisis, fungal septicaemia, abnormal liver function tests, and hearing loss) [11, 12, 207, 208]. The rate of discontinuation of TMZ due to side effects was lower at 6% in the 2022 ESE survey [13]. Myelosuppression occurs in a third of

patients [36] and frequently a dose reduction (**Table 5**) or delay in treatment cycles can allow the patient to continue treatment [12, 36]. TMZ-induced aplastic anaemia (absolute neutrophil count <500 cells/$mm^3$ and platelet count <20 x $10^9$/L for at least 4 weeks) occurred in <1% of patients treated with TMZ, in a recent study of 3821 patients with CNS malignancies [209]. Onset is very rapid, occurring in most patients before completing 2 cycles of TMZ. In one-third of patients who fail to achieve haematological recovery there is substantial morbidity and reduced survival. Given the occasional reports of abnormal liver function, hepatitis and hepatostatic disease, it has been recommended to monitor liver function tests (LFT) regularly, particularly if concurrent hepatotoxic drugs are given [210]. The temozolomide product information suggests monitoring LFTs at baseline, midway through first cycle, prior to each subsequent cycle and 2-4 weeks after treatment is ceased. **Table 5** outlines dose reduction and discontinuation thresholds for non-haematological adverse effects as recommended by the manufacturer.

Reported rare side effects are hearing loss [211], hypersensitivity pneumonitis [212], Stevens-Johnson syndrome [213] and cholestatic hepatitis [214].

**Table 5. Guideline for temozolomide dose reduction and discontinuation**
(adapted from Temodar® (temozolomide) Product Information, version 9/2023)

| Toxicity | Interruption and Dose Reduction | Discontinue TMZ |
|---|---|---|
| Neutropenia | Withhold if < 1.0 x $10^9$ /L<br>When > 1.5x$10^9$/L resume at reduced dose for next cycle* | If dose < 100mg/$m^2$ required |
| Thrombopenia | Withhold if < 50 x $10^9$/L<br>When > 100 x $10^9$/L resume at reduced dose for next cycle* | If dose < 100mg/$m^2$ required |
| Nonhaematological Toxicity (except for alopecia, nausea, vomiting) | Withhold if Grade 3 (CTCAE**)<br>When ≤ Grade 1 resume at reduced dose for next cycle* | Recurrent Grade 3 (CTCAE**)<br>Grade 4<br>If dose < 100mg/$m^2$ required |

* Dose levels: 100mg/m2 (minimum dose), 150mg/m2 and 200mg/m2

** Common Terminology Criteria for Adverse Events (CTCAE version 4.0)(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm): Grade 3 (severe, not immediately life threatening), Grade 4 (life-threatening).

Haematological malignancy, particularly myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) has been reported following alkylating therapy including temozolomide but is rare.

[215, 216]. In a recent systematic review of 27 reported cases of secondary haematological neoplasms associated with use of TMZ for other types of malignancies, median treatment duration was 19 months and cumulative dose 18,000mg/$m^2$ [216]. Among published pituitary cases there is 1 reported case of AML in a woman with PC occurring after 18 months of TMZ therapy preceded by 3 months treatment with cisplatin/ etoposide [[19]and Lamas C personal communication], and one case of MDS in a man with an aggressive prolactinoma first given daily low dose TMZ for 18 months and 10 years later a second period of TMZ for 15 months [217].

Patients receiving concurrent radiotherapy, corticosteroids (or with Cushing syndrome), or dose-dense regimes may be at increased risk of opportunistic infection, particularly *Pneumocystis pneumonia* (PCP). In these settings, or if significant lymphopenia develops, prophylactic trimethoprim-sulfamethoxazole or pentamidine has been recommended [218].

**R 3.4.5** *In patients responding to a first course of temozolomide, defined either as partial tumour regression, or tumour stabilization after documented rapid progression during the 6- month period preceding start of TMZ, we recommend that treatment is continued for 12 months and thereafter guided by the efficacy and tolerability, with consideration for longer duration in patients where response has not plateaued. Treatment duration exceeding 24 months must be weighed against a potential risk for cumulative severe toxicity*. (⊕○○○)

**Reasoning**

In patients with glioblastomas the standard treatment period with TMZ is 6-12 months based on the pivotal 6-month protocol [219]. In some patients treatment is continued for several years based on good tolerability and effect [220]. In pituitary tumours, length of treatment duration with a first course of TMZ has varied from 2 to 66 months (median 10 in responders) [221]. The time of follow-up after discontinuation of TMZ ranged from 2-91 months.
In the first ESE survey the median treatment duration was 9 months (range 1-36 months) [42]. Often treatment duration was predetermined based on local protocols. Since it is likely that treatment was continued for a longer time in responders and shorter in those with adverse effects, conclusions on a cause-effect relation cannot be drawn. In the 2022 ESE survey, patients with complete tumour regression (CR), partial regression (PR), and tumour stabilization (SD) were treated for median 12.3 (IQR 6-13), 12 (6-18), and 7 (5-16) cycles, respectively [13]. Twenty-five percent of the responders (CR/PR) were treated for at least 1.5 years. Patients with progressive disease (PD) were given median 5.5 cycles.

Whether a longer treatment period in responding patients improves the probability of a sustained remission is unknown. Clearly, with longer observation fewer patients remain in remission. In the North-European multi-centre study (*n* = 21), the proportion of responding patients decreased from 48% at the time of TMZ discontinuation to 33% after 32 months [36]. In the German multicenter study (*n* = 47) [18], the proportion of responders decreased from an initial 33% to 20% after 32-month follow-up with a median progression free survival of 23 months. In the Spanish multicenter study (*n* = 27) [19], the 2-year progression free survival after TMZ treatment was 64%. In the first ESE survey [42], the proportion of responders decreased from 34% to 20% at median 21-month follow-up after TMZ cessation. In the 2022 ESE survey [13] the estimated duration of the TMZ effect in responding patients, determined as the time to next intervention (surgery, RT, TMZ re-challenge, or other therapies) after TMZ discontinuation was 6.4 and 3.3 years after achieving CR and PR, respectively, and 1.4 years in patients with SD. This illustrates that, although recurrence is common, responders can experience a relatively long period free from additional treatment.

Treatment tolerance, in combination with a risk, albeit very small, of cumulated severe bone marrow toxicity, e.g. myelodysplastic syndrome and leukemia (see Safety), balanced against the treatment effect and a possible additional survival benefit from longer treatment duration should be considered when deciding on treatment duration. Evaluation of treatment response and tolerability should be performed every 3 months. In patients achieving a complete response (no visible tumour and hormonal normalization) within 12 months of treatment it is recommended to discontinue the drug thereafter. In patients with PR/SD, continued treatment more than 12 months should be decided on a case-to-case basis taking into account side effects and patient preference. Where there is partial tumour regression at the 12-month evaluation it may be reasonable to extend the treatment period until there is no evidence of an additional therapeutic benefit (no further decrease in tumour volume/ hormonal levels). In patients demonstrating tumour stabilization after 12 months on TMZ it is advisable to stop treatment unless there is clear evidence of a slower growth rate compared to a 6-month observation period *prior* to TMZ start.

**Treatment options in tumours progressing on TMZ / recurring after TMZ discontinuation**

**R 3.4.6** *In patients who develop a recurrence following prior response to temozolomide treatment we suggest a second trial of 3 cycles of temozolomide.* (⊕○○○)

**Reasoning**

Thirty-eight patients who achieved tumour regression after the first course of TMZ, and in whom the tumour subsequently progressed, were given a second course with the drug ([13, 19, 35] Lamas C,

personal communication). Re-challenge was generally less effective than the 1st course; PR/SD was achieved in 22 of the 38 patients (58%). The remaining patients had tumour progression (**Table 6**). In patients with CR/PR at the first course a longer interval between the two TMZ treatment periods was associated with a better effect of the second course. The data suggest that re-challenge with TMZ could be attempted in responders to the first course since alternative treatment options are often accompanied by more side effects.

**Table 6. Re-challenge with temozolomide in 42 APT/PC patients**

| Response to 1st TMZ course | Response to 2nd TMZ |
|---|---|
| Complete response (CR) n=5 | PR n=3<br>SD n=2 |
| Partial response (PR) n=18 | PR n=4<br>SD n=6<br>PD n=8 |
| Stable disease (SD) n=15 | PR n=2<br>SD n=5<br>PD n=8 |
| Progressive disease (PD) n=4 | SD n=1<br>PD n=3 |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. The Table is updated from Burman et al JCEM 2023 [77].

**R 3.4.7** *We suggest molecular testing in patients with tumour progression on TMZ in order to guide potential treatment choices.*

**Reasoning**

As there has been a rapid growth in therapies linked with specific gene alterations, next-generation sequencing (NGS) technology platforms (either large panels or whole-exome/genome approaches) and more recently additional transcriptomic and epigenome analyses are increasingly used to guide therapy choice. NGS analysis may provide additional information, such as tumour mutational burden (TMB), mismatch repair deficiency (MMRD) and microsatellite instability (MSI) status, which are biomarkers of response to immune checkpoint inhibitor therapy in some cancers (see below) [222] but not proven yet in the context of pituitary tumours. Such large-scale molecular testing across multiple cancer types reveal up to 40% of patients with actionable genetic aberrations. However less than half

of these patients end up being treated with genotype-matched drug and around 20% respond to matched therapy [223]. Significant challenges include lack of access to appropriate clinical trials, cost of testing and targeted therapies, complexity of interpretation of genetic data and intratumoural heterogeneity in space or time. Several large institutions now offer molecular profiling programs and provide matching to active clinical trials [224-226]. A key element of these services is access to a molecular tumour board comprising oncologists, pathologists, medical geneticists and bioinformaticians who can provide genetic interpretation and suggest treatment pathways. There is a paradigm shift in oncology towards "pan-cancer" therapeutic decision-making based on molecular profiling and basket clinical trials are critical for APT/PC patients. For example, *NTRK* fusions predict response to TRK kinase inhibitors which have been approved by the United States Food and Drug Administration (FDA) to treat all solid tumours with *NTRK* fusions [223]. Similarly, in mid-2022, the FDA approved use of combination dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) for *BRAF* V600E-mutated unresectable or metastatic solid tumours with no further treatment options (https://url.au.m.mimecastprotect.com/s/8DHuCE8w24ulmQlViNMIeD?domain=fda.gov). Outside of cancer-agnostic clinical trials, patients with APT/PC may also be able to access targeted therapies by way of compassionate access schemes with pharma. The guideline panelists acknowledge there are no data in APT/PC, and accept the various challenges and limited objective responses currently seen with molecular-guided treatment plans. However, in the absence of highly effective therapies beyond TMZ support this approach particularly where patients can be enrolled in institution-led cancer screening programs with access to clinical trials. The panel felt it was important to perform genomic analysis on recent tumour tissue, hence consideration for minimal invasive surgical biopsy could be considered as it poses minimal risk. The utility of genomic testing in APT/PC was illustrated in a patient with a lactotroph APT resistant to temozolomide. Molecular profiling allowed the identification of a somatic activating *ESR1* mutation and treatment with elacestrant, a second-line ER degrader, in combination with radiotherapy [94].

**R 3.4.8** *We suggest considering a trial with ICI in patients with PC and rapid tumour progression after treatment with temozolomide. Tumor agnostic data supports the use of ICI in tumors that are either mismatch repair deficient (MMRd) or exhibit high tumor mutational burden high, supporting the use in pituitary tumors with these molecular features.*
*Otherwise, we recommend participation in clinical studies as the data supporting the use of cytotoxic chemotherapy, besides temozolomide, and targeted agents in this tumor type remains limited.* (⊕○○○)

**Reasoning**

Immune checkpoints, such as CTLA-4 and PD-1, are molecules on immune competent cells which serve to maintain immune tolerance by binding to partner molecules on target cells. Tumours may evade the immune system by upregulating checkpoint partners, such as PD-L1 and PD-L2, on their cell surfaces, or by producing factors that increase checkpoint expression on immune cells [227]. Immune checkpoint inhibition with anti-CTLA-4 antibodies (ipilimumab) and anti-PD-1/PD-L1 antibodies (e.g. nivolumab or pembrolizumab) disrupt this interaction and enable an immune attack. ICI have markedly prolonged the survival in some advanced cancers. However, immune side effects occurring in about 30% in PD1 inhibitors and 50% in combined treatment of the patients, can be severe and potentially life threatening, e.g. pneumonitis, colitis, nephritis and hepatitis [228, 229].

The current evidence for treatment with ICI in APT/PC rests on case reports and small series. We searched for publications including > 3 APT/ PC patients treated with ICI. Three studies were included with a total of 25 patients [13, 46, 47]. Partial radiological response, stable disease, and progressive disease occurred was reported in 24% (95%CI 9-45%), 12% (95%CI 3-31%), and 64% (95%CI 43-82%) of patients, respectively (see **Figure 3**). In a summary of 29 cases [13, 46, 47, 230-237] complete/partial radiological regression or tumour stabilization for at least 6 months, was achieved in 9/16 PCs and 2/13 APTs.

There are two ongoing clinical trials for ICI therapy in patients with APT/PC (NCT 04042753 ipilumab + nivolumab; NCT02834013 ipilumab + nivolumab *vs.* nivolumab, the trial includes also patients with other rare tumours).

In view of the limited chemotherapeutic effect of alternative drugs a trial with ICI seems indicated in patients with PC*s* with progression on TMZ treatment and should preferably be performed in the context of clinical trials. The similar effects of dual inhibition and PD-1 blockers alone in APTs/PCs; response in 5/19 with dual therapy *vs.* in 3/10 with PD-1 blockers [237], is an argument for initial treatment with PD-1 blockers as monotherapy since severe side effects are less common than in dual therapy [238].

Clinical trials enrolling patients with multiple tumor types have shown that treatment with the PD1 inhibitor, pembrolizumab, result in high response rate in tumors with MMRd [239-241]. Analysis performed on the basket study, KEYNOTE-158, also demonstrated a high response rate to pembrolizumab in tumors with a high tumor mutational burden; this data lead to the approval of pembrolizumab in the United States by the Food and Drug Administration for the treatment of adult patients with unresectable or metastatic tumors with a tumor mutational burden of 10 mutations/megabase or greater [242].

Observations in APTs /PCs indicate that mutations in the DNA repair mismatch (MMR) genes and high tumor mutational burden could be beneficial for the drug effect [77], whereas other biomarkers

typically associated with a response to ICI (high mutational load, heterozygosity in HLA class 1 antigens, tumour infiltrating lymphocytes and high PD-L1 expression) have not been invariably predictive [77, 238].

**Targeted therapies**

At this time, given the lack of cases demonstrating objective responses to targeted therapies, the panel felt use of these therapies remains experimental.

*VEGF inhibition*

VEGF plays an important role in angiogenesis and has been found in higher levels among APT/PC compared with non-aggressive pituitary tumours [243]. Bevacizumab, a VEGF monoclonal antibody inhibitor, when given as monotherapy in 18 patients previously treated with TMZ, resulted in partial tumour response in 1, stable disease in 9 patients and tumour progression in 9 (assessment of tumor response was available in 14 patients) (review in [237] and [77]). In other cases bevacizumab has been combined with other chemotherapeutic drugs, mostly TMZ, and where outcome reported, partial response or stable disease has been seen in 3/12 cases (review in [237] and [77]).

When combined with TMZ and RT either response or extended stable disease has been described in 3 cases [196, 197, 199]. Similarly, a marked response to combination TMZ and Apatinib, a selective inhibitor of VEGFR-2, has been reported in a somatotroph APT [198]. There is minimal data on other VEGF inhibitors in APT/PC. Sunitinib, a multi-tyrosine kinase inhibitor including against VEGF, has been tried in 3 cases with no response [13, 42, 244]. If access to ICI therapy is difficult and in the absence of a molecular-guided druggable target or clinical trial, VEGF inhibition may be considered as second line therapy although more data is needed.

*mTOR inhibition*

Raf/MEK/ERK and PI3K/Akt/mTOR pathways are up-regulated in pituitary tumours [245]. The mTOR inhibitor everolimus, has been reported in 14 APT/PC with partial tumour response in just 1 lactotroph APT and stabilization of progressive disease in another 4 (of whom 1 with PC for 12 months) [13, 42, 217, 244, 246-248].

*EGFR inhibition*

EGFR overexpression has also been seen in APT/PC providing the rationale for use of lapatinib, a tyrosine kinase inhibitor of EGFR and ErbB2 [249]. In 6 aggressive lactotroph tumours a stable disease was reported in 5 patients and progressive disease in 1. These patients were TMZ-naïve and not all fulfil the criteria of APT, with the only patient demonstrating PD having had TMZ previously [250, 251].

In addition, a sustained response has been observed in a null cell carcinoma after treatment with lapatinib following surgery and RT [37]. However, in 3 cases in the ESE survey no significant response was observed [13, 42]. In a patient from the first ESE survey with a lacto-somatotroph APT/PC and no prior TMZ exposure a partial response was seen to gefitinib, however erlotinib in another case demonstrated progressive disease [42].

**Peptide receptor radionuclide therapy (PRRT)**

Somatostatin receptors (types 1, 5 and 2) are widely expressed in different pituitary tumour subtypes [163]. Pituitary uptake of 68Ga-DOTATATE and other radiolabeled somatostatin analogues has been demonstrated on PET/CT [252, 253], suggesting that PRRT could be a treatment option for pituitary tumours, as described for some neuroendocrine tumours [254], including pituitary metastases [255]. In addition to the presence of abundant somatostatin receptors on the tumour cells, other factors such as internalization and elimination of the radiolabeled ligand, influence treatment responses.

The effect of PRRT has been reported in 19 patients with aggressive pituitary tumours (15 APTs, 4 PCs) of which 10 were of the Pit 1 lineage [13, 256-263]. Treatment was mostly given with 177LU-DOTA-TATE in 1 to 3 cycles. CR and PR was achieved in 0 and 4 patients with APTs [13, 256-258]. None of the 4 with tumour regression had received RT prior to PRRT. Five patients had SD of whom 2 with PCs attained stabilization of the spinal/leptomeningeal metastases for 40 and 48 months, respectively. PD or death within a year after treatment completion occurred in 10. The maximum standardized uptake (SUV max) assessed by 68Ga-PET was reported in 7 cases. Tumour regression was observed in 2 of 3 tumours with SUV max considered high (eg > 20) but not in 3 of 3 with SUV max below 10 [data collated in [77]]. In summary, the limited data suggests that PRRT at best results in PR in a small proportion of patients but could be considered in selected cases with high tumour uptake of the ligand.

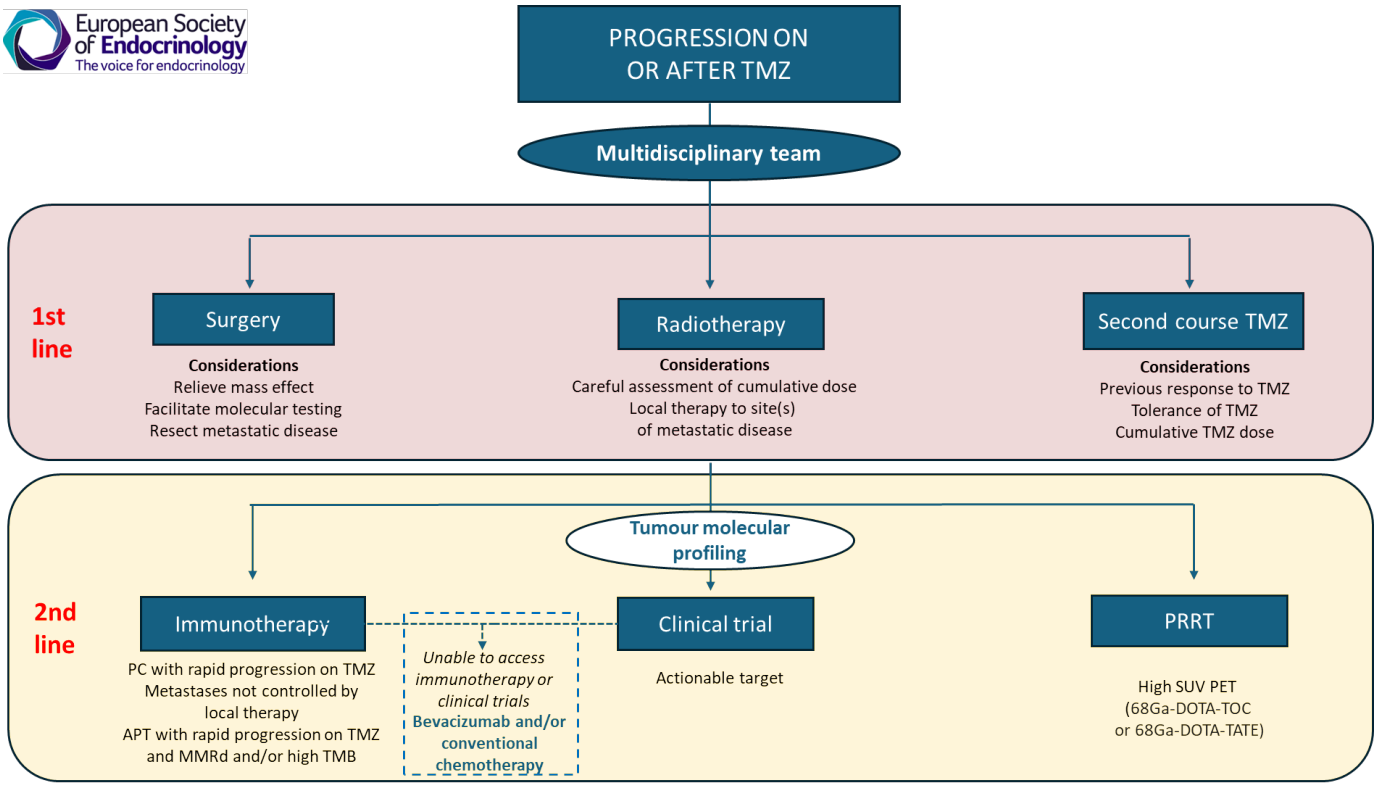
The treatment with PRRT is generally safe, with a lower risk of serious adverse effects compared to external beam radiotherapy or chemotherapy [264]. In a phase 2 study [265] including 42 patients with progressive meningiomas, including 33 previously treated with radiotherapy, the treatment with 90Y-DOTATOC at a dosage of 1.1 or 5.5 GBq or with 177Lu-DOTATATE at a dosage of 3.7 or 5.5 GBq was well tolerated. No cases of symptomatic worsening of patient conditions due to early or late toxicity were noted and only 1 patient had grade 3 platelet toxicity, which persisted at the time of subsequent treatment, causing therapy delay first and subsequent therapy cessation.

Although it is theoretically possible to combine EBRT with radiopharmaceutical therapy based on the observation in a few studies that normal tissue involved in these two irradiation modalities overlap only partially [266-268] , no studies have evaluated this combination in patients with pituitary tumours. Overall, PRRT remains an investigational treatment and should be considered if other local therapy options (surgery, radiotherapy) are exhausted.

**Other cytotoxic drugs**

Historically, a variety of cytotoxic drugs have been used in the treatment of APT/PC, of which Lomustine (CCNU) in combination with 5-FU, based on their ability to penetrate the brain, has been the most commonly employed. All evidence is based on case-reports. There are no reports on complete tumour regression, but in some tumours partial, usually transient, regression and/or stabilisation has been achieved [73, 269].

**Figure 5: Progression on or after temozolomide**




## 3.5 Local treatment of metastatic disease

**R 3.5.1** *In patients with oligo-metastatic disease we suggest consideration of loco-regional therapies, either as stand-alone treatment or in combination with systemic treatment.* (⊕○○○)

**Reasoning**

In scenarios where the disease is localised and the burden is low, particularly in ectopic sites like cervical lymph nodes, bones, or hepatic metastases, we recommend a multidisciplinary team discussion that includes consideration of loco-regional alongside systemic therapeutic options [270]. Potential interventions may encompass minimally invasive surgical removal of isolated lymph nodes or metastatic deposits, and targeted external beam radiation therapy. Specifically for liver metastases, therapies might include radiofrequency ablation or microwave ablation for a few metastatic deposits, or chemoembolization or bland embolization for a more significant number of liver metastases.

### 4 Follow-up of an aggressive pituitary tumour

**R 4.1** *We recommend that imaging (MRI in most instances) be performed every 2-12 months as guided by prior tumour progression rate, the presence of residual tumour post-surgery, and/or location of the tumour (proximity to vital structures).* (⊕○○○)

**Reasoning**

There are no evidence-based consensus recommendations for the optimal strategy for surveillance imaging of APT/PCs. Accurate localization of the site of active disease is crucial to the management of APT/PCs and, imaging remains the primary determinant of whether surgery or radiotherapy can be offered. Magnetic resonance imaging (MRI) is recommended, however, CT scan without contrast enhancement may assess skull-base lesions and can be performed if there is contra-indication for MRI [271].The use of gadolinium in MRI is not always required for the follow-up of large pituitary lesions. Imaging frequency is best determined on individualised basis, commonly every 6-12 months, considering the aspects below:

(i) Trajectory of tumour progression: tumours with rapid growth in proximity to vital anatomical structures may cause serious morbidity and require more frequent monitoring every 2-3 months.

(ii) Proliferative and molecular markers: tumours with pathology reports with markers suggestive of high cell proliferation and possible rapid growth, e.g., Ki-67 > 10%, may require more frequent monitoring.

(iii) Active treatment regimens that require closer follow-up: TMZ, ICI, or anti-VEGF.

In addition to conventional imaging studies (MRI, CT), non-standard MR sequences such as diffusion-weighted imaging (DWI), or molecular (functional) imaging studies can provide additional data to inform patient management [272, 273]. More recently, radiotracers targeting amino acid transporter LAT1 11C-methionine and F-fluoro-ethyl-tyrosine combined or not with MRI or CT have been used in some clinical settings in pituitary disease and may be helpful in the follow-up of aggressive tumours

however, they are not widely available, and there is no data on their utility in the management of APT/PCs [274, 275].

**R 4.2** *We recommend pituitary hormonal evaluation be performed every 3-12 months as guided by the clinical context.* (⨁○○○)

**Reasoning**

In secretory tumours where a biomarker of tumour response to therapy is available, such as serum prolactin or ACTH, and where response to treatment is being assessed, biomarker measurement on a 3-4 monthly basis is recommended. An increase in circulating hormone concentrations may prompt investigation for disease progression and/or metastatic disease. In addition, given treatment-related hypopituitarism, including radiation effects on pituitary endocrine function which can occur many years following therapy, we recommend a complete endocrine evaluation to monitor adrenal, thyroid, and sex steroid function at least yearly or more often if clinical symptoms suggest dysfunction [229, 276].

**R 4.3** *We recommend life-long follow-up of patients with aggressive pituitary tumours.* (⨁⨁○○)

**Reasoning**

The course of APT is variable. Evolution to a more rapid growth rate and/or transformation to a pituitary carcinoma may occur years after the initial identification of a pituitary tumour [270, 277]. Time to development of complications of treatment, such as radiation-induced hypopituitarism or secondary malignancies, is also well recognised not to emerge for many years. Therefore, we recommend life-long follow-up of aggressive pituitary tumours with endocrine and imaging assessment at intervals as outlined above.

### *3. Special circumstances*

#### *a. Paediatric*

Pituitary tumours in childhood and adolescence are relatively rare. In children 90% of pituitary tumours are functional while 10% are non-functioning. Giant pituitary tumours are very rare in the pediatric population, with the majority being prolactinomas and/or acromegaly. They are invasive and more resistant to dopamine agonist therapy and other therapeutic modalities [278, 279].

Although extremely rare, four patients with PCs are reported to have had disease commencing in childhood [280]. Five paediatric patients receiving temozolomide treatment for pituitary tumours were identified in the literature, with two more paediatric-onset patients receiving temozolomide as adults.

These tumours were null cell (*n* = 1) and Crooke cell carcinoma (*n* = 1) with multiple liver, intracranial and intraspinal metastases leading to patient death despite multiple treatments [263, 281].

Three patients with aggressive prolactinomas diagnosed at 13, 14 and 16 years of age (2 girls and one boy) and a 13 year old girl with aggressive Cushing's disease have all been successfully treated with TMZ for 6, 12, 12 and 25 cycles [11, 282, 283]. Follow-up data on these cases are limited. Despite the rarity and paucity of data these recommendations can be used to guide clinical decision making in paediatric patients.

***b. Elderly***

Pituitary tumours in the elderly (patients older than 65) [284] are mostly clinically non-functioning (NFPA) [285, 286]. Most pituitary tumours in this age group are large, slowly growing invasive tumours [287, 288]. Low growth rate of tumour remnants is reported by some (in 21% of the patients despite subtotal and partial tumour resection), while other authors report progression rates comparable in elderly and young patients [286-288]. There is no absolute contraindication to either radiotherapy or oncological drugs in the elderly. Importantly, treatment decisions in APT/PC in the elderly should consider life expectancy and comorbidities.

Pituitary carcinomas in the elderly are rare, with malignant lactotroph, corticotroph or gonadotroph FSH tumours reported as either single case reports or in small series of pituitary carcinomas [277, 289, 290]. The experience of TMZ in elderly patients with aggressive pituitary tumours is limited, but case reports indicate that they may respond just as well. Age was not predictive of tumour response [11, 12, 36, 42] with similar response in patients older than 65 compared to younger patients.

***c. Fertility***

Most patients with APT are extensively treated with surgery, radiotherapy and alkylating agents, such as temozolomide, that can affect their fertility.

Alkylating agents can impair sperm production in men [291] or deplete the pool of ovarian oocytes in women [292]. Despite these potential risks, there are few data about fertility outcomes in brain tumour patients and none reported in patients with APT. Given the risk of treatment-induced infertility, patients with APT should be counselled regarding fertility preservation [293]

Any chemotherapy may be associated with some risk of gonadal toxicity, and patients of childbearing age should be informed of the risk before starting any chemotherapy. Sperm cryopreservation should be considered before initiation of cancer therapy because the quality of the sample and sperm DNA integrity may be compromised even after a single treatment session [294]. Fertility preservation options in females depend on the patient's age, type of treatment, whether she has a partner, the time available. Consultation with a fertility specialist is advised to discuss the embryo, oocytes or ovaries cryopreservation, when future fertility is a consideration [294]. The FDA advises females of reproductive potential to use effective contraception during treatment with temozolomide and for 6

months after the last dose. Male patients with female partners of reproductive potential are advised to use condoms during treatment with temozolomide and for 3 months after the last dose

***d. Pregnancy***

The improved management of pituitary tumours as well as improvements in fertility therapies has led to an increasing number of pregnancies in patients harbouring pituitary tumours. A review and the ESE guidelines on pituitary tumour management in pregnancy in general have provided valuable recommendations for close follow-up during pregnancy, which is in most cases favourable [295, 296]. Pregnancy in most patients does not accelerate tumour growth, particularly in treated tumours (lactotroph or somatotroph) as well as corticotroph tumours in the setting of Nelson's syndrome, compared with its course before pregnancy [295, 297, 298]. However, no published data are available for pregnancy in the context of APT.

**Perspectives**

The application of clinico-pathological grading, in particular identification of Grade 2b tumours, indicates tumours at high risk of recurrence. While a significant percentage of ultimately aggressive tumours arise from Grade 2b tumours, a substantial proportion are missed. Proliferative markers do not reliably identify tumours that become aggressive in time, although Ki67 >10% found in about 35% of APT/ PC [42], is rarely present in benign pituitary tumours [80]. There is a need to identify additional prognostic markers to recognise APT and PC at an early stage. The current WHO pathological classification does indicate pituitary tumour types at risk of aggressive behaviour but these have not been integrated into well-validated prognostic models. Recent data confirmed that mutations in *ATRX*, *TP53* and *SF3B1*, are present already in analyses of initial surgical tumour tissue, and are present almost exclusively in APTs and PCs, particularly in corticotroph and lactotroph tumours, but only in about a third of the tumours. Other molecular markers have yet to be identified. Aggressive corticotroph tumours and corticotroph carcinomas with *TP53* and/or *ATRX* variants were occasionally found to concomitantly carry somatic variants in *PTEN* or *DAXX* [90, 299]. A recent study of 26 APT/PC patients suggests that *ATRX* and *DAXX* may be mutually exclusive [86]. Presently, we do not know the exact incidence of mutational alterations in APT/PC, and how they influence the clinical course (time to metastases, overall survival, etc.), and response to treatment.

Hypodiploid genome characterized by recurrent chromosomal loss of heterozygosity (LOH) (due to loss of chromosomes 1, 2, 3, 4, 6, 10, 11, 15, 17, 18, 21, and 22) were found to be associated with aggressive clinical behaviour in corticotroph tumours [86]. This hypodiploidy can be interrogated by comparative genomic hybridization, next-generation sequencing (NGS) or Fluorescence in situ hybridization (FISH).

These encouraging results need to be confirmed in other independent studies. Genome-wide methylation analysis, including copy number variation (CNV) performed in large cohort of APT/PC found that aggressive/metastatic pituitary tumours clustered separately from benign pituitary tumours [300]. Numerous CNV events affecting chromosomal arms and whole chromosomes were frequent in aggressive and metastatic, whereas benign tumours had normal chromosomal copy numbers with only few alterations. These findings may potentially serve as biomarkers for identification of pituitary tumours with a worse prognosis at the time of first surgery. More frequent use of NGS oncology panels along with collaborative efforts to bring together this data will be valuable. Multicentre, prospective studies are needed to determine new and confirm suggested molecular markers of aggressiveness.

Temozolomide given as monotherapy remains the first-line chemotherapy for APTs and PCs. The optimal treatment duration in responding patients, as well as the potential place of TMZ given concurrently with radiotherapy, deserve to be explored in clinical trials/ international standard protocols. New therapeutic options have emerged as potential second line treatment (ICIs, targeted therapies, PRRT), however the exact place of these options and potential predictor of responses remain to be identified. We encourage publication of national case series reporting the outcome of these treatments but also case report of new therapeutic options, and treatments identified from molecular testing.

Establishing national/international registries to collect clinical, pathological and molecular data from patients with aggressive pituitary tumours is desirable to improving patient care. Such registries could assess the effectiveness of proposed treatments and possibly identify prognostic markers of response to treatment, ultimately improving our understanding and management of these difficult cases.

It is essential that all practitioners in teaching hospitals and private hospitals are made aware of the importance of these initiatives in strengthening collaboration between specialists and ensuring better outcomes for patients.

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