European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas

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The *European Society of Endocrinology* has initiated this guideline on the Management of Aggressive Pituitary

Abstract

Background: Pituitary tumours are common and easily treated by surgery or medical treatment in most cases. However, a small subset of pituitary tumours does not respond to standard medical treatment and presents with multiple local recurrences (aggressive pituitary tumours) and in rare occasion with metastases (pituitary carcinoma). The present European Society of Endocrinology (ESE) guideline aims to provide clinical guidance on diagnosis, treatment and follow-up in aggressive pituitary tumours and carcinomas.

Methods: We decided upfront, while acknowledging that literature on aggressive pituitary tumours and carcinomas is scarce, to systematically review the literature according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. The review focused primarily on first- and second-line treatment in aggressive pituitary tumours and carcinomas. We included 14 single-arm cohort studies (total number of patients = 116) most on temozolomide treatment ($n = 11$ studies, total number of patients = 106). A positive treatment effect was seen in 47% (95% CI: 36–58%) of temozolomide treated. Data from the recently performed ESE survey on aggressive pituitary tumours and carcinomas (165 patients) were also used as backbone for the guideline.

Selected recommendation: (i) Patients with aggressive pituitary tumours should be managed by a multidisciplinary expert team. (ii) Histopathological analyses including pituitary hormones and proliferative markers are needed for correct tumour classification. (iii) Temozolomide monotherapy is the first-line chemotherapy for aggressive pituitary tumours and pituitary carcinomas after failure of standard therapies; treatment evaluation after 3 cycles allows identification of responder and non-responder patients. (iv) In patients responding to first-line temozolomide, we suggest continuing treatment for at least 6 months in total. Furthermore, the guideline offers recommendations for patients who recurred after temozolomide treatment, for those who did not respond to temozolomide and for patients with systemic metastasis.

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Summary of the recommendations

The recommendations (R) are worded as recommend (strong recommendation) and suggested (weak recommendation). We formally graded only the evidence underlying recommendations for therapeutic choices. The quality of evidence behind the recommendations is classified as very low (+ooo), low (++oo), moderate (+++o) and strong (++++). See section 'Summary of methods used for guideline development'.

1. General remarks

R 1.1.1 We recommend that these patients should be discussed in a multidisciplinary expert team meeting (endocrinologist, neurosurgeon, pituitary pathologist, neuroradiologist, radiation oncologist, medical oncologist).

2. Assessment of aggressiveness

2.1 Diagnosis of an aggressive pituitary tumour

R 2.1.1 We recommend the diagnosis of an aggressive pituitary tumour be considered in patients with a radiologically invasive tumour and unusually rapid tumour growth rate, or clinically relevant tumour growth despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments).

R 2.1.2 We recommend that imaging (MRI in most instances) should be used for quantification of tumour dimensions, invasion and growth.

R 2.1.3 We recommend full endocrine laboratory evaluation in patients with aggressive pituitary tumours.

R 2.1.4 In patients with aggressive pituitary tumours, and either site-specific symptoms or discordant biochemical and radiological findings, we recommend screening for metastatic disease.

2.2 Potential predictors of aggressiveness in pituitary tumours

R 2.2.1 We recommend that all pituitary tumours should undergo histopathological analysis, which should include a minimum immunodetection of pituitary hormones and Ki-67 proliferative index evaluation. The p53 immunodetection and the mitotic count should be evaluated at least, when the Ki-67 index is ≥3% (+000).

R 2.2.2 We suggest interpretation of histopathological results in the clinical context of the individual patient (+000).

R 2.2.3 In patients with aggressive pituitary tumours, we suggest germline genetic testing based on young age at presentation or family history of pituitary or endocrine neoplasia, as recommended for patients with non-aggressive pituitary tumours (+000).

3. Therapeutic options

3.1 Role of surgery

R 3.1.1 We recommend that surgery should be performed by a neurosurgeon with extensive experience in pituitary surgery (++00).

R 3.1.2 We recommend discussion with an expert neurosurgeon regarding repeat surgery prior to consideration of other treatment options (++00).

3.2 Role of radiotherapy

R 3.2.1 We recommend radiotherapy in patients with clinically relevant tumour growth despite surgery in non-functioning tumours or surgery and standard medical treatment in functioning tumours (++00).

R 3.2.2 We suggest that adjuvant radiotherapy should be considered in the setting of a clinically relevant invasive tumour remnant with pathological markers (Ki-67 index, mitotic count, p53 immunodetection) strongly indicating aggressive behaviour (+000).

R 3.2.3 We suggest discussion with an expert radiation oncologist regarding the different radiotherapeutic options taking into consideration tumour size and location, as well as pathology, prior RT and dose.

3.3 Standard medical therapies

R 3.3.1 We recommend standard medical treatment with maximally tolerated doses in order to control tumour growth, as per current guidelines.

3.4 Medical therapies in aggressive pituitary tumours

R 3.4.1 We recommend use of temozolomide monotherapy as first-line chemotherapy for aggressive pituitary tumours and pituitary carcinomas, following documented tumour growth (++00).

R 3.4.2 We recommend first evaluation of treatment response after 3 cycles. If radiological progression is demonstrated, temozolomide treatment should be ceased (++00).

R 3.4.3 We recommend use of the standard dosing regimen: 150–200 mg/m^2 for 5 consecutive days every 28 days (+000).

R 3.4.4 We recommend monitoring of haematological parameters, liver function tests and careful clinical observation for potential adverse effects during treatment (+++0).

R 3.4.5 We suggest, in patients with rapid tumour growth in whom maximal doses of radiotherapy have not been reached, combining temozolomide with radiotherapy (Stupp protocol) (+000).

R 3.4.6 We suggest that evaluation of MGMT status by immunohistochemistry by an expert neuropathologist should be performed. High MGMT expression is suggestive of a lack of response; however, there may be exceptions (++00).

R 3.4.7 In patients responding to first-line temozolomide, as assessed after 3 cycles, we suggest treatment to be continued for at least 6 months in total, with consideration for longer duration if continued therapeutic benefit is observed (+000).

R 3.4.8 In patients with rapid tumour progression on temozolomide treatment, we suggest a trial with other systemic cytotoxic therapy. Given the variety of chemotherapeutic agents that have been reported, we cannot suggest a particular regimen (+000).

R 3.4.9 In patients who develop a recurrence following response to temozolomide treatment, we suggest a second trial of 3 cycles of temozolomide (+000).

3.5 Local treatment of metastatic disease

R 3.5.1 In patients with isolated metastases, we suggest consideration of loco-regional therapies, independent of decisions regarding the need for systemic treatment (+000).

4. Follow-up of an aggressive pituitary tumour

R 4.1 We recommend that imaging (MRI in most instances) is performed every 3–12 months as guided by prior tumour growth rate and/or location of tumour (proximity to vital structures) (+000).

R 4.2 We recommend that full endocrine evaluation should be performed every 3–12 months as guided by the clinical context (+000).

R 4.3 We recommend lifelong follow-up of patients with aggressive pituitary tumours (++00).

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, 2, 3). Incidence rates depend on age and sex (3). The clinical behaviour of pituitary tumours is highly variable: some remain quiescent for long periods of time; many grow slowly, while in rare cases rapid tumour growth is observed. Post-operatively, about 30% of the patients show tumour regrowth 0.4–37 years after surgery, with an increased risk of tumour progression in the presence of residual tumour (4). A small subset of pituitary tumours has been classified as aggressive pituitary tumours, based on resistance to medical treatment and multiple recurrences despite standard therapies combining surgical, medical and radiotherapy treatment approaches. The prevalence of aggressive tumours is not known. Such tumours often, but not always, exhibit one of the 3 markers (Ki-67 ≥3%, and/or increased mitoses, and/or p53 expression). Tumours exhibiting 2 or 3 markers were found to account from 2.5% to 10% in surgical series (5, 6, 7, 8). Pituitary carcinomas, defined by the presence of craniospinal and/or systemic metastasis, are rare, and reported to account for 0.2% of pituitary tumours (9, 10).

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 (11, 12). Despite numerous studies and advances in prognostic classification, no pathological marker has been shown as yet to reliably predict pituitary tumour behaviour (6, 13, 14, 15). This guideline proposes a definition of an aggressive pituitary tumour and provides recommendations for current management.

2. Methods

2.1 Guideline working group

This guideline was initiated by The European Society of Endocrinology (ESE). The chair (G R) and members of the working group (authors) were appointed by the chair and approved by the ESE Clinical Committee: endocrinologists (P B, A P H, A M C, S P, V P), pathologist (J T) and a methodologist (O D). The working group had three in-person meetings between May 2016 and April 2017. Additional communication occurred by teleconference and email and prior to the process, all participants completed conflict of interest forms.

Prior to publication, a draft of the guideline was reviewed by 8 experts in the field (see 'Acknowledgement' section). Revision of the guidelines was based on feedback from ESE Members, the ESE Council of Affiliated Societies (ECAS) and following presentation at the ECE 2017. All comments and suggestions were discussed and implemented as appropriate by the working/writing group.

2.2 Target group

In line with previous ESE guidelines, this document was developed for healthcare providers of patients with aggressive pituitary tumours but can also provide guidance as patient information material.

2.3 Aims

The overall purpose of this guideline is to provide clinicians with practical guidance for identification and management of patients with aggressive pituitary tumours. It was prompted by the increasing use of temozolomide (TMZ) in aggressive pituitary tumours.

2.4 Summary of methods used for guideline development

The methods used have been described in more detail previously (16, 17). 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 'Clinical questions and eligibility criteria' section), the second being a systematic literature search (see 'Description of search and selection of literature' section). 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 (+000), low (++00), moderate (+++0) and strong (++++).

For the recommendations, we took into account: (1) quality of the evidence, (2) balance of desirable and undesirable outcomes and (3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc.) (16, 17). The recommendations are worded as *recommend* (strong recommendation) and *suggest* (weak recommendation). Formal evidence syntheses were performed and graded only for recommendations addressing our initial questions. It is important to emphasise that there is no direct translation from the (quality) of evidence to the strength of a recommendation. Furthermore, there might be situations when a recommendation is strong even if the quality of evidence is low (18). Moreover, a guideline panel should carefully consider whether to abstain from recommendations in the absence of good quality evidence, as the main disadvantage of abstaining is that it suggests that all alternatives then seem equally (un)reasonable (17). This will often not be the case. 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. For transparency, all recommendations provided are accompanied by text explaining why specific recommendations were made.

2.5 Clinical questions and eligibility criteria

Prior to formulating recommendations, the working group decided to perform a systematic review regarding efficacy of different treatment regimens in aggressive pituitary tumours. As we did not expect to find many large comparative studies, we decided that single-arm cohort studies were eligible. A minimum of 3 patients were required for eligibility to avoid selection bias.

In addition, an extensive search was performed to provide an overview of publications including case reports on even less well-documented subject areas such as surgery and/or radiotherapy.

2.6 Description of search and selection of literature

A literature search in electronic medical databases was performed with the help of a trained librarian. The search revealed 811 titles. Ultimately, we included 14 studies reporting therapy in aggressive pituitary tumours with ≥3 patients: 11 examined the effect of TMZ therapy alone (Supplementary Table 1, see section on supplementary data given at the end of this article), 1 examined the combined effect of chemotherapy and TMZ (Supplementary Table 2), and two studies on peptide radio-receptor therapy (PRRT) (Supplementary Table 3).

2.7 Summary and conclusions from the systematic review

In the 11 studies on TMZ therapy in aggressive pituitary tumours, patient numbers ranged from 3 to 31, with only four studies having >10 patients. There were substantial differences between studies with respect to follow-up

duration and TMZ schedule; many studies did not provide a definition of response. Overall, the quality of the evidence was considered very low (+000). (Supplementary Tables 1, 2 and 3). In published literature, the pooled proportion of patients with a tumour response after TMZ was estimated to be 47% (95% CI 36–58%) (Supplementary Table 4) (Fig. 1).

3. Recommendations, rationale for the recommendations

1. General remarks

The diagnosis, management and treatment of aggressive pituitary tumours and pituitary carcinomas remain a challenge.

R 1.1.1 We recommend that these patients should be discussed in a multidisciplinary expert team meeting (endocrinologist, neurosurgeon, pituitary pathologist, neuroradiologist, radiation oncologist, medical oncologist).

2. Assessment of aggressiveness

2.1 Diagnosis of an aggressive pituitary tumour

R 2.1.1 We recommend that the diagnosis of an aggressive pituitary tumour should be considered in patients with a radiologically invasive tumour and unusually rapid tumour growth rate, or clinically relevant tumour growth despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments).

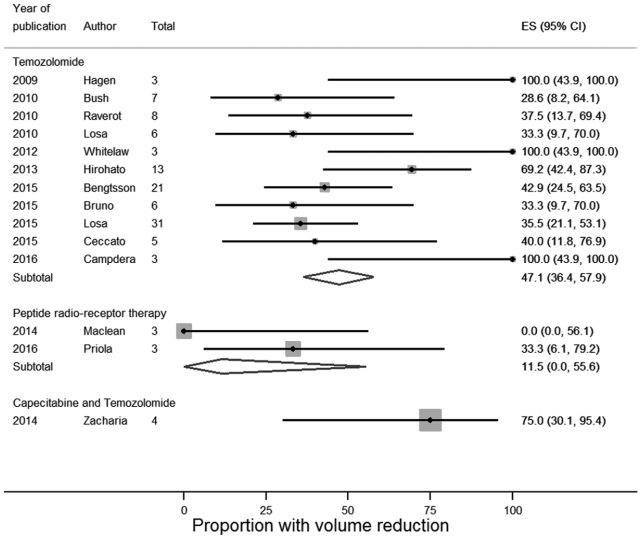

Figure 1
Meta-analysis of treatment effect in aggressive pituitary tumours and carcinomas.

Reasoning

The hallmark of aggressiveness is clinically relevant tumour growth despite the use of optimal standard therapies, which entails a combination of medical therapies, surgery and radiotherapy as proposed in clinical management guidelines (Supplementary Table 5). Standard medical therapies and resistance to such treatment are discussed in more detail in Section 3.3. With regard to surgical management, it is important to distinguish between recurrence following non-optimal surgery and recurrence after surgery performed by an expert. The growth rate of pituitary tumours is influenced by patient- and tumour-specific characteristics; this intrinsic tumour heterogeneity determines the risk of recurrence and resistance to treatment (6, 19, 20).

Invasiveness alone is not synonymous with pituitary tumour aggressiveness (21); however, invasion is a major determinant of incomplete tumour resection. Aggressive pituitary tumours are almost always macroadenomas at clinical presentation. However, pituitary tumour size at presentation does not equate to potential for aggressive behaviour, as illustrated by giant lactotroph tumours that may be very sensitive to dopamine agonist treatment (22, 23).

The time interval between the primary diagnosis and the aggressive tumour behaviour varies from months to >10 years. There may be extended periods of clinical quiescence for several years followed by a period of rapid tumour growth, invasion or metastasis (24, 25, 26, 27).

R 2.1.2 We recommend that imaging (MRI in most instances) should be used for quantification of tumour dimensions, invasion and growth.

Reasoning

An imaging study (preferably MRI or CT where bone invasion assessment is indicated) that enables accurate and consistent measurement of tumour sites, dimensions and invasion is recommended. The imaging protocol should comprise thin (2–3 mm) sagittal T1, coronal T1 before and after gadolinium injection, coronal T2 or axial T1-weighted slices. Comparison with penultimate and prior remote imaging studies is essential to identify tumour progression and to guide appropriate treatment (28).

R 2.1.3 We recommend full endocrine evaluation in patients with aggressive pituitary tumours.

Reasoning

Assessment of pituitary endocrine function is essential at presentation to identify secretory tumours that may indicate specific therapies or endocrine deficiencies, which if left untreated would contribute to patient morbidity. Assessment of pituitary endocrine function should be performed, at appropriate intervals (3–6 months on an individualised basis), both to characterise potential biomarkers of disease progression to monitor in parallel with imaging studies, and to manage endocrine deficiencies.

R 2.1.4 In patients with aggressive pituitary tumours, and either site-specific symptoms or discordant biochemical and radiological findings, we recommend screening for metastatic disease.

Reasoning

Given that aggressive pituitary tumours often progress and occasionally metastasize insidiously over several years, attention should be paid and appropriate structural (MRI and CT) and/or functional (FDG- and/or SSTR-PET) imaging studies should be considered, in the setting of site-specific symptoms (neck/back pain or neurological complaints), and/or where laboratory measures are discordant with known visible extent of disease (increase in hormone levels without corresponding increase in tumour size). Common sites for metastatic disease include craniospinal deposits, neck lymphatic chains and less commonly liver, bone and lung.

2.2 Potential predictors of aggressiveness in pituitary tumours

R 2.2.1 We recommend that all pituitary tumours should undergo histopathological analysis, which should include a minimum immunodetection of pituitary hormones and Ki-67 proliferative index evaluation. The p53 immunodetection and the mitotic count should be evaluated at least, when the Ki-67 index is ≥3% (+000).

Reasoning

Based on immunohistochemistry (IHC), pituitary tumours are classified into somatotroph (GH, Pit 1 positive), lactotroph (PRL, Pit1 and ER positive), corticotroph (ACTH, Tpit positive), thyrotroph (TSH, Pit1 positive), gonadotroph (FSH/LH, SF1 positive), null cell (negative for hormones and transcription factors) tumours and plurihormonal and double tumours (29). Transcription factors staining could be helpful for immunonegative tumours but not for the assessment of aggressiveness.

The use of proliferative markers as prognostic tools in the assessment of a pituitary tumour is controversial. Nevertheless, some criteria (Ki-67 >3%, extensive p53 immunoreactivity and increased mitotic activity) were incorporated into the 2004 WHO Classification (30). However, there are difficulties with the interpretation of this classification, and it has never been validated in a clinical context. There remains no clear consensus on the Ki-67 index that may identify tumours at a high risk of recurrence, with widely different cut-offs proposed, ranging from 1.3% (5) to 10% (31), sometimes adapted to the tumour subtype (32). However, a cut-off ≥3% is mostly used. Most studies are based on a limited number of cases, short follow-up or expert opinion only. Some authors consider that a Ki-67 >10% is a sign of malignancy (31), again without prospective validation.

Mitotic count has been recently re-evaluated and mitotic count >2 is suggestive of risk of recurrence (13). The prognostic value of p53 is also debated because a reliable method of quantification has not been validated (33). However, a common definition of positive staining (>10 strongly positive nuclei per 10 HPFs) has been agreed upon (6, 13, 34, 35).

The combination of invasion (determined radiologically) and use of proliferative markers (Ki-67 index ≥3% and mitotic count >2) and p53 (assessed by IHC pathologically) has been proposed to be superior in identifying pituitary tumours with a higher risk of progression/recurrence (6, 36).

We acknowledge that no marker alone is sufficient to predict tumour behaviour. However, in the recent ESE survey at least one pathology marker was available for 97 aggressive pituitary tumours and 34 carcinomas (unpublished ESE survey). Ki-67 ≥3% was the most frequent positive marker in aggressive pituitary tumours (79/97, 81%) and carcinomas (29/34, 85%); also p53 positivity (35/48; 73% and 18/23; 78%, respectively) and a mitotic count >2 mitoses/10HPFs were also frequently observed (26/41, 63% and 18/20, 90%, respectively, $P=0.03$). The frequency of these markers was not different between aggressive pituitary tumours and carcinomas, but higher than observed in surgical series (6, 36).

Based on these results, and the last WHO classification on pituitary tumour (29), we recommend the evaluation

of Ki-67 index at minimum, the p53 immunodetection and the mitotic count when the Ki-67 index is ≥3%.

R 2.2.2 We suggest interpretation of histopathological results in the clinical context of the individual patient (+000).

Reasoning

In a study by Trouillas *et al.*, invasive and proliferative (Ki-67 >3% and p53 positive or number of mitosis >2) tumours (grade 2b) demonstrated a poorer prognosis with an increased probability (12 fold) of tumour progression/recurrence compared to non-invasive and non-proliferative tumours (grade 1a) (6).

It is also recognised that lactotroph tumours in men (37, 38) and silent corticotroph (ACTH positive) tumours demonstrate a more aggressive course, and may recur earlier than silent gonadotroph tumours (39, 40, 41). Rarely, initially silent corticotroph tumours may evolve to secrete ACTH after many years of follow-up, and this transformation may also herald more aggressive tumour behaviour (42, 43, 44, 45). Silent subtype III or plurihormonal silent tumours (40) also may exhibit a more aggressive clinical course compared with silent gonadotroph tumours (46).

R 2.2.3 In patients with aggressive pituitary tumours, we suggest germline genetic testing based on young age at presentation or family history of pituitary or endocrine neoplasia, as recommended for patients with non-aggressive pituitary tumours (+000).

Reasoning

Current suggestions on genetic testing in patients with pituitary tumours do not elaborate specifically on aggressive tumours (15, 47, 48). In the absence of sufficient data in this regard, we suggest that indications for genetic testing should be applied as for non-aggressive pituitary tumours.

Some studies have suggested that more aggressive pituitary tumours may be found in association with MEN1 and AIP patients. Comparison of MEN1-positive pituitary tumours with an unselected group of non-MEN1 sporadic pituitary adenomas revealed that MEN1 tumours were larger and more often histologically invasive (49). In another study, young patients with pituitary tumours (mostly somatotroph tumours) were found to be more likely to carry AIP mutations among apparently sporadic populations (48). Other genes implicated in pituitary tumour predisposition include GPR101 (XLAG), p27Kip1 (multiple endocrine neoplasia type 4 (MEN4)), PRKAR1A (Carney complex), GNAS (McCune–Albright syndrome), neurofibromatosis type 1, SDHx mutations and DICER1 syndrome (50). However, currently little is known about the potential for more aggressive pituitary tumour behaviour under these conditions.

3. Therapeutic options

3.1 Role of surgery

R 3.1.1 We recommend that surgery should be performed by a neurosurgeon with extensive experience in pituitary surgery (++00).

Reasoning

Surgical approaches to either obtain complete near-total resection or clinically relevant debulking should be balanced with safety considerations. Multiple studies have demonstrated that lower morbidity and mortality correlate with surgeon experience (51). Some studies suggest that the wider exposure and the enhanced direct visualisation 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. In other instances, 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

Even in the setting of a patient with multiple prior surgeries and where significant tumour debulking is not attainable, surgery may still have a role to ameliorate local mass effects such as acute chiasmal compression, acute loss of vision or severe intractable headache or to offer control of hormone hypersecretion. Therefore, we recommend that at intervals, as directed by individual patient needs, further surgical intervention should be discussed within a multidisciplinary framework by the endocrinologist, neurosurgeon, neuroradiologist, radiation oncologist and medical oncologist to formulate the best patient care plan (52).

3.2 Role of radiotherapy

R 3.2.1 We recommend radiotherapy in patients with clinically relevant tumour growth despite surgery in non-functioning tumours or surgery and standard medical treatment in functioning tumours (++00).

Reasoning

Radiation therapy may offer the possibility of long-term control of tumour growth and should therefore be discussed in all patients with an aggressive pituitary tumour. 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. EBRT is usually delivered in 25–30 fractions with a total dose of 45–54 Gy. SRS can be delivered as a single-dose (typical dose: 12–14 Gy, max. 16 Gy). Fractionated SRS (usually 25 Gy in 5 fractions) is usually suggested in cases where a single-dose SRS endangers the optic pathway (53).

Comparison of the reported success rates is hindered by varying techniques and doses used for radiation therapy, as well as by different imaging protocols to assess tumour volume (54). Favourable outcome with SRS is more frequent in patients >50 years in age, in tumours <5 cc in volume, and in patients without prior radiation (55, 56). In pituitary tumour growth despite prior radiotherapy, both the target region and the doses applied during the first radiotherapy course should be discussed with an expert radiation oncologist to investigate whether additional doses to the region of current growth may be indicated.

The indication for radiotherapy must be balanced against potential side effects. In regular tumours, it is advisable to be very restrictive with RT, but in aggressive tumours, the balance between benefit and risks is very different although the side effects are similar. The most frequent long-term side effect of radiotherapy is hypopituitarism, affecting single or multiple pituitary axes. This probably occurs in almost all patients, when followed for a sufficiently long time, indicating the need for patient education and lifelong evaluation for pituitary insufficiency at regular intervals. Hypopituitarism itself may be a risk factor for premature mortality, other potential radiotherapy-related causes being vascular injury and haemodynamic changes (57). Furthermore, radiotherapy is associated with an increased risk of malignant brain tumours (RR = 3.3) or meningioma (RR = 4.1), and higher (RR = 14.1 and 7.6, respectively), in patients treated with RT before the age 30 years (58). In previous smaller studies, the absolute risk was estimated to be 1–3% over 15–20 years, increasing to approximately 5% after 30 years (59, 60). The risk of optic pathway injury is low with EBRT, with an estimate of 1% at 10 years and 1.5% at 20 years (61). For SRS, most series report neurological deficit rates of <5%, most commonly optic neuropathy (54). 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.

R 3.2.2 We suggest that adjuvant radiotherapy should be considered in the setting of a clinically relevant invasive tumour remnant with pathological markers (Ki-67 index, mitotic count, p53 immunodetection) strongly indicating aggressive behaviour (+000).

Reasoning

While radiation therapy is widely considered to reduce the risk of recurrence, the true effect is difficult to quantify due to the lack of randomised studies. Results need to be compared to the natural history of tumour progression after incomplete resection, which is estimated to be ≤5% at 5 years and 10–25% at 10 years for gross totally resected tumours (61). One study compared post-operative results for patients with NFA from two centres, one of them routinely performing radiation therapy, the other rarely adopting this approach. Progression-free survival rates for patients with RT were 93% at 5, 10 and 15 years, compared to 68, 47 and 33%, respectively, in patients without RT (62). The indication of radiotherapy should be discussed in patients with a tumour of high risk of recurrence and/or progression, as has been described in 'Potential predictors of aggressiveness in pituitary tumours' section.

R 3.2.3 We suggest discussion with an expert radiation oncologist regarding the different radiotherapeutic options taking into consideration tumour size, location, prior RT and dose as well as pathology.

Reasoning

For final evaluation and confirmation of doses to be delivered, thereby determining potential side effects, an experienced radiation oncologist is required (61). For SRS, the tumour target should be at least 3–5 mm distant from the optic chiasm and less than 3 cm in diameter. Otherwise, fractionated EBRT may be the only option. Furthermore, EBRT should be preferred for tumours with irregular anatomy, including diffuse local infiltration and suprasellar or brainstem extension, to avoid high dose radiation of healthy tissue (54). SRS may

be more convenient for the patient with single session therapy compared to daily application of EBRT over several weeks. Importantly, there are no controlled trials comparing fractionated EBRT and SRS. Of note, SRS has been used as salvage therapy with some success in a small series of patients with persistent active tumour despite prior fractionated EBRT (63). Stereotactic guidance by high-resolution imaging allows very precise delivery of radiation to the tumour and is also increasingly used with EBRT. There are different modalities available to deliver radiation therapy, including linear accelerators (e.g. LINAC and more recently Cyber-knife, a frameless system using robotic mounting and real-time image guidance), multisource Cobalt 60 units (e.g. Gamma Knife) and particle beam accelerators (with limited availability due to the high costs). While there may be some theoretical advantages in using one modality over the other, the decision often lies with the availability of a system at the treating centre.

3.3 Standard medical therapies

R 3.3.1 We recommend standard medical treatment with maximally tolerated doses in order to control tumour growth, as per current guidelines (++00).

Reasoning

Prolactinoma

Cabergoline is the most effective and best tolerated drug for treating prolactinomas (64) (Supplementary Table 5). In most prolactinomas, normoprolactinemia and a reduction of tumour volume can be achieved with a dose ≤2 mg/week (65). Male gender, invasive growth and giant tumours (i.e. diameter >4 cm) are associated with a lower response (66, 67). These tumours can often be controlled by increasing the weekly dose of cabergoline, by 0.5 mg every 1–3 months, up to 3.5 mg (66). However, some large tumours may be exquisitely sensitive to dopamine agonists. Some prolactinomas respond slowly and can eventually be managed using the same dose of cabergoline. 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 (65).

Acromegaly

Somatotroph tumours express somatostatin receptors (sst), predominantly sst2 and sst5 and less abundantly sst1 and sst3 (68). First (lanreotide, octreotide) and second generations (pasireotide) of somatostatin analogues are available (Supplementary Table 5) for treating acromegaly. In a recent study in treatment of naive patients, the PRIMARYS study (Lanreotide Autogel), normalisation of IGF-I combined with GH levels <2.5 µg/L was achieved in 27/63 (43.5%) of the patients (69). In a larger study of 358 medically naive patients, octreotide LAR was compared to pasireotide LAR, a multi-sst ligand acting on sst1–3 and particularly sst5. Normal IGF-I combined with GH levels <2.5 µg/L was achieved in 19% of the patients given octreotide LAR vs 31% given pasireotide LAR (70). Treatment with somatostatin analogues leads to tumour volume reduction by >25% in 20% of the patients (71, 72). A higher proportion, 63% of 89 patients with macroadenomas (95% CI 52.0–72.9), achieved ≥20% tumour volume reduction in the PRIMARYS study, the maximal decrease occurring within the first six months (69). Similar responses have been reported using octreotide (70, 73). An increase in tumour volume while on treatment with somatostatin analogues has been observed in 1–2% patients (71, 72), and is related to more aggressive tumour behaviour (74).

Pegvisomant, a GH receptor antagonist, is reported to normalise IGF-I in 63% (75) and 93% of the patients (76) depending on the clinical setting, whereas the effect on tumour size appears neutral. In the setting of a pituitary tumour partially controlled by somatostatin analogues, combination with pegvisomant could lead to IGF-I normalisation in most patients (77). Despite a potential benefit of dopamine agonist therapy alone or in addition to somatostatin analogue or pegvisomant (78), there are no prospective studies demonstrating its action on tumour growth in unselected or naive patients.

Cushing's disease

Corticotroph tumours express sst5 receptors, and less frequently sstr2 and dopamine receptors (Supplementary Table 5). Pasireotide is presently the only drug targeting the pituitary that is approved for treatment of Cushing's disease. In a study on 162 patients, pasireotide led to normalisation of UFC in 26% of the patients. There are limited data regarding the effect on tumour size (79). Dopamine agonists have not been confirmed to have any effect on corticotroph tumour growth (80).

Thyrotroph tumours

Related to the high expression of SSTR2 in these tumours (81), 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% (82, 83) (Supplementary Table 5). The response to dopamine agonists with regard to TSH secretion and tumour shrinkage has been variable, with best results in mixed thyrotroph/lactotroph tumours (82, 83).

Resistance to standard medical treatment

Dopamine agonists

Complete resistance to dopamine agonists, defined as failure to normalise prolactin and a less than 50% decrease in size on doses of cabergoline up to 3.5 mg/week, represents less than 10% of macroprolactinomas (66). Dopamine-resistant lactotroph tumours often are invasive macroadenomas, and according to some studies are more angiogenic and more proliferative (84). The resistant tumours often express a lower number of dopamine D_2 receptors and ER receptors (38); other mechanisms have been proposed (85).

Furthermore, high doses, up to 11 mg/week, have been shown to result in prolactin normalisation in most patients (86) (Supplementary Table 5). It is proposed that the highest tolerated dose of dopamine agonist should be used in patients with aggressive prolactinomas.

Somatostatin analogues

In acromegaly, treatment resistance, defined as a complete lack of biochemical and tumour response, occurs in less than 10% of the patients. The molecular basis is poorly understood. Several mechanisms have been proposed, such as defective expression or genetic alterations of somatostatin receptors (sst) and impaired signal transduction (87). A correlation has been demonstrated among sst2 mRNA, protein expression and the GH-lowering response to octreotide (88, 89). However, marked case-to-case variations among individual tumours have been found, and some tumours with high sst2 may show a poor response to SSA (90). Pituitary somatotroph adenomas from *AIP* mutation carriers are less responsive to sst2 analogues and recent data suggest that membranous sst2a are downregulated, whereas the expression of sst5 and the response to pasireotide are similar in AIP-sufficient and AIP-deficient tumours (91).

3.4 Medical therapies in aggressive pituitary tumours

Aggressive pituitary tumours usually respond poorly to the standard 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 (92) and a high dose of octreotide in a malignant thyrotroph tumour (93). Standard medical treatments do not arrest growth of aggressive gonadotroph/NFPA tumours.

Morbidity and mortality in patients with aggressive corticotroph tumours are mostly related to cortisol excess. Drugs reducing adrenal glucocorticoid synthesis should be given in doses aiming at achieving eucortisolism. There is little experience with pasireotide in aggressive corticotroph tumours. A single patient with a large corticotroph tumour following bilateral adrenalectomy had a lowering of ACTH and sustained reduction of the suprasellar tumour (94). In another eight patients with Nelson's syndrome, pasireotide had minimal effects on tumour volume, in spite of reductions in ACTH levels in most patients (Daniel *et al.*, abstract Endo 2016, OR 18-5). In a recent report on three patients with aggressive atypical corticotroph macroadenomas, of which one was a carcinoma, pasireotide was not clinically useful (95), 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, as well after achieving eucortisolism after treatment with steroidogenic inhibitors (96). This risk seems higher in patients with macroadenomas and aggressive corticotroph tumours (97, 98). To what extent 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.

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 growth (++00).

Reasoning

The first use of temozolomide (TMZ) in the treatment of aggressive pituitary tumours was described in four cases in 2006 (99, 100, 101). These reports were rapidly

followed by a number of case reports in which most patients responded with a regression of tumour burden. This marked effect, however, could reflect publication bias. Eleven studies with at least 3 patients each have been published during 2010–2016 (Supplementary Table 1). These studies included a total of 106 patients, of whom 34 had carcinomas, treatment schedules mostly being TMZ 150–200 mg/m^2/day 5 days every 4 weeks. Two studies used a slightly different schedule (102, 103). The duration of treatment was often not specified. Despite a heterogeneous mix of patients, and differences in treatment schedules and imaging procedures, the response rate (defined as percentage of patients with a partial or complete tumour regression) has been broadly similar across the studies, with a reported volume reduction in 47% (95% CI 36–58). A comparable efficacy, 37%, was observed in 156 evaluable patients reported to the large ESE survey on aggressive pituitary tumours (unpublished ESE survey). Clinically functional tumours responded better than non-functioning. Published data indicate that the response to TMZ in patients with primary aggressive corticotroph tumours and patients with Nelson's syndrome is comparable. Overall, complete tumour regression has been seen in 13 patients, 5 carcinomas and 8 aggressive tumours, representing about 5% of all patients treated (25, 103, 104, 105, 106, unpublished ESE survey: personal communication).

It should be noted that there are no head-to-head studies comparing temozolomide to other treatment options. However, given the course of the condition (spontaneous regression is not likely to occur), the panel felt reasonably comfortable to recommend the use of temozolomide given that the literature suggests a positive effect in a significant percentage of patients treated. This has not been shown for other treatment options.

Combination of TMZ with other drugs

A study using treatment with capecitabine before TMZ (CAPTEM) found a partial response of long duration in 4 out of 4 corticotroph tumours, of which one was a carcinoma (105). In studies with NET cell lines, the authors had observed a synergistic apoptosis when TMZ had been given after pretreatment with capecitabine compared with TMZ alone. Methylguanine methyltransferase (MGMT) levels were measured in 3 of the 4 patients, and were low in these three patients, which possibly contributed to the outcome (see 'Predictors of response to temozolomide' section). Others have added capecitabine to TMZ after TMZ failure, or at progression after an initial response to TMZ alone, but had not observed an enhanced effect (11, 12, 25, 107).

In the ESE survey, combination chemotherapy with TMZ as first-line treatment was reported in 6 cases: capecitabine (in 3), bevacizumab (1), thalidomide (1) and BCNU (1) (unpublished ESE survey). Two of the 6 cases (one with bevacizumab and one with capecitabine) achieved a partial response, two demonstrated stable disease (capecitabine, thalidomide), and other two had progressive disease (capecitabine, BCNU). At this stage, improved efficacy with TMZ in combination with other chemotherapy has not been demonstrated.

Pasireotide and octreotide have been used in combination with TMZ in a few patients with aggressive tumours (102, 108, 109). The contribution of the somatostatin analogues to the treatment effects could not be determined, given the small numbers examined.

R 3.4.2 We recommend first evaluation of treatment response after 3 cycles. If radiological progression is demonstrated, temozolomide treatment should be ceased (++00).

Reasoning

In general, an effect of TMZ is observed within 3–6 months, with parallel decreases in circulating hormone concentrations and tumour volumes (25, 107).

R 3.4.3 We recommend use of standard dosing regimen: 150–200 mg/m^2 for 5 consecutive days every 28 days (+000).

Reasoning

In most reports on aggressive pituitary tumours/carcinomas, TMZ has been administered in cycles, 150–200 mg/m^2 for 5 consecutive days every 28 days, here referred to as 'standard therapy regimen'. In the first cycle, 150 mg/m^2/day is used, with an increase to 200 mg/m^2/day in subsequent cycles if there is no toxicity. In patients with glioblastomas, TMZ is first given at a daily dose of 75 mg/m^2 for 6 weeks in combination with radiotherapy, followed by 6–12 months of 'standard therapy', referred to as 'the Stupp protocol'. 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 aggressive pituitary tumours and other malignancies with the hypothesis that larger doses over longer time would eventually deplete MGMT stores, and thereby increase the efficacy of TMZ therapy. However, in naive glioblastomas, dose-dense schedules had similar efficacy as the standard regimen,

but with more side effects, particularly severe neutropenia (110). There are no studies comparing different dosing schedules in patients with aggressive pituitary tumours. In the ESE survey, 93% of the patients received standard dosing, with 6 cases employing the 'Stupp' protocol, continuous dosing was given in two case and a dose-dense regimen in one case (unpublished ESE survey). It should be noted that no studies exist comparing the effect of different dosing schedules. The recommendation for this specific dose is pragmatic, as there is too little experience with different dosing schedules to recommend any variation on standard dosing.

R 3.4.4 We recommend monitoring of haematological parameters, liver function tests and careful clinical observation for potential adverse effects during treatment (+++0).

Reasoning

TMZ is as an oral outpatient-based chemotherapy and is generally well-tolerated. Adverse effects reported with ≥10% incidence are listed in Supplementary Table 6; this information is mainly based on the use of TMZ in patients with malignant gliomas. Dose-dense regimes are associated with increased myelotoxicity (110).

In patients with aggressive pituitary tumours, fatigue is the commonest side effect of temozolomide therapy, occurring in 60% of the patients (25, 111). In a series of 24 patients (25), adverse effects were reported in 54% of the patients. Most were mild, similar to a report of 31 patients (12), and in a review of the 40 earliest published cases (111). Nausea/vomiting occurred in around one-third of temozolomide-treated patients consistently across studies of pituitary and other tumours (111, 112). Prophylactic use of anti-emetic therapy (e.g. ondansetron) is recommended during days 1–5 of the standard therapy regimen. Importantly, myelosuppression was reported in 31% of the patients (25). Frequently, a dose reduction (Supplementary Table 7) or delay in treatment cycles can allow the patient to continue treatment (12, 25).

A full haematological profile should be obtained at day 22 during standard 28-day TMZ dosing cycles, and repeated weekly until neutrophil count exceeds 1.5×10^9/L and platelet count exceeds 100×10^9/L before commencing a new treatment cycle. Supplementary Table 7 outlines dose reduction and discontinuation thresholds for adverse effects as recommended by the manufacturer.

Out of a total of 190 patients, across 3 large published pituitary cohorts and the ESE survey, 29 (15%) patients discontinued TMZ as a result of side effects (15 with pervasive fatigue, nausea in 6, haematological abnormalities in 3, 1 each due to headache/oedema/hypotension, adrenal crisis, fungal septicaemia, abnormal liver function tests (LFTs) and hearing loss) (11, 12, 25, 111). A further case of hearing loss has been described (102), as has been reported in patients with non-pituitary tumours (113). In other published pituitary tumour cases, haemorrhage into cerebral metastases has been reported as a complication of severe thrombocytopaenia (114). A case of liver toxicity complicating ketoconazole therapy when TMZ was introduced was reported (115). In the wider literature, rare cases of hypersensitivity pneumonitis (116), Stevens–Johnson syndrome (117) and cholestatic hepatitis (118) have been described. Given the occasional reports of abnormal liver function and hepatitis and hepatostatic diseases, it has been recommended to monitor LFTs regularly, particularly if concurrent hepatotoxic drugs are given (119). The Temodar product information suggests monitoring LFTs at baseline, midway through first cycle, prior to each subsequent cycle and 2–4 weeks after treatment is ceased.

Haematological malignancies have been reported many years after TMZ treatment; however, in post-marketing surveillance, the absolute risk is very low (<1 per 10 000 people treated) (120, 121).

Patients receiving concurrent radiotherapy, corticosteroids (or Cushing's syndrome) and dose-dense regimes may be at an increased risk of opportunistic infection, particularly *Pneumocystis pneumonia*. In these settings, or if significant lymphopenia develops, prophylactic trimethoprim-sulfamethoxazole or pentamidine have been recommended (122).

R 3.4.5 We suggest, in patients with rapid tumour growth in whom maximal doses of radiotherapy have not been reached, combining temozolomide with radiotherapy (Stupp protocol) (+000).

Reasoning

In the 'Stupp model' (2005), patients with glioblastomas are given TMZ for a month at 75 mg/m^2/day concomitant with 6 weeks of fractionated EBRT followed by TMZ monotherapy using 150–200 mg/m^2 for 5/28 day cycles for a total of 6 months. This schedule was based on experimental data indicating a radio-sensitising effect of TMZ (123, 124). The Stupp model has been used in a small number of patients with pituitary tumours; a total of 17 are reported in the literature. The response rate was 76%, i.e., higher than that reported with TMZ alone. However, some of the patients had not received prior RT (11, 125, 126, 127).

In an Italian multi-centre study, 27/31 patients (87%) had been treated with RT (12). The tumour had recurred after RT, except in 3 patients who received TMZ concomitantly with RT or one month thereafter. In a recent published case, a patient with a pituitary carcinoma treated with TMZ+bevacizumab concurrent with RT, and subsequently with TMZ alone for an additional 12 cycles, complete regression was achieved and sustained five years (128).

In summary, TMZ given concurrently with RT appears beneficial; however, a recommendation for its routine use as first-line therapy cannot be made given the low quality of the evidence.

R 3.4.6 We suggest that evaluation of MGMT status by immunohistochemistry by an expert neuropathologist should be performed. High MGMT expression is suggestive of a lack of response; however, there may be exceptions (++00).

Reasoning

Predictors of response to temozolomide

- MGMT TMZ acts by inserting a methyl group to DNA bases, mainly guanine. An endogenous DNA repair protein, O(6)-methylguanine methyltransferase (MGMT) can remove this methyl group and thereby potentially counteract the cytotoxic effect of TMZ. There is an association between the low MGMT expression, due to gene silencing by MGMT promoter methylation, and the response to TMZ treatment in glioblastomas (129). The value of MGMT status as a predictor of TMZ response in aggressive pituitary tumours is less clear. Promotor methylation of the gene occurs less frequently in pituitary tumours, and MGMT measured by PCR-based methods has not been associated with response to TMZ (11, 102, 107, 111, 130). The reasons are not understood and may involve mechanisms regulating MGMT expression independent of promotor methylation. Most studies in pituitary tumours have used MGMT IHC. The degree of staining has been arbitrarily divided into three categories, low (staining of <10% of the cell nuclei), intermediate (10–50%) and high (>50%), alternatively low <10%, intermediate 10–90% and high >90%.

The response to TMZ in relation to MGMT status (determined by IHC) has been reported in 102 unique patients with homogenous staining in 99 cases (Fig. 2) (11, 25, 102, 103, 104, 105, 107, 111, 131, 132, 133). Overall, it appears that a low MGMT content is mostly associated with a positive response to TMZ, a high MGMT

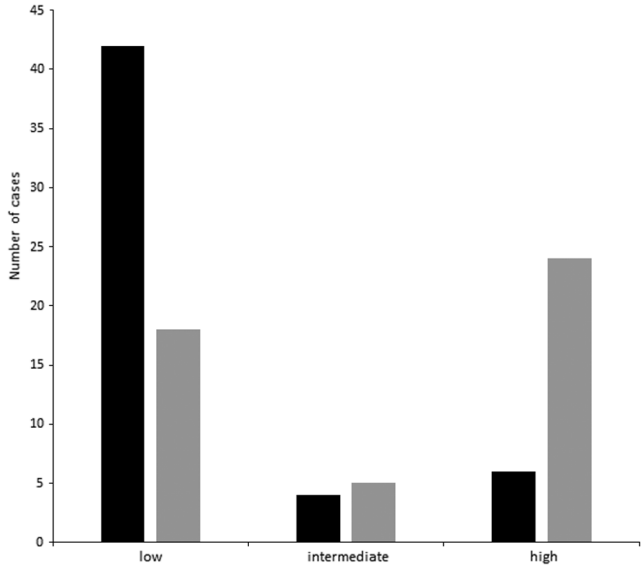

Figure 2
Response to temozolomide in 99 aggressive pituitary tumours in relation to MGMT staining (low, intermediate, high); response (solid column); no response (grey column). Response is defined as tumour regression; no response as no-tumour regression (included cases with stable tumour size).

with lack of response and notably, no response may occur also in spite of low MGMT expression. Heterogeneity within tumours, and non-standardised IHC method and expression criteria are likely to influence the relationship between MGMT expression and TMZ response.

Given the lack of other efficacious treatments for aggressive pituitary tumours and the limited experience on MGMT, a trial of TMZ therapy may be considered in patients with high MGMT expression.

- DNA mismatch repair (MMR) proteins The expression of other MMR 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 (9 carcinomas), intact MSH6 but not low MGMT was found to be a prognostic indicator of good response to TMZ (104). Other MMRs were not studied. Loss of MSH6 was reported to occur during progression of an atypical prolactinoma to carcinoma which may have caused resistance to TMZ treatment (134). In this patient, MGMT remained low. In other studies (25, 105), MSH6, MLH1, MSH2 and PMS2 did not predict the effect of TMZ.

- Markers of cell proliferation and p53 Tumour-proliferative markers (Ki-67, mitotic rate) and p53

expression have not been shown to be useful predictors of the response to TMZ (12, 25, 104, 107).

R 3.4.7 In patients responding to first-line temozolomide, as assessed after 3 cycles, we suggest treatment to be continued for at least 6 months in total, with consideration for longer duration if continued therapeutic benefit is observed (+000).

Reasoning

In patients with glioblastomas, the standard treatment duration is 6–12 months based on a 6-month treatment protocol (135). In some patients, however, treatment is continued for several years based on good tolerability and effect (136). In the literature on pituitary tumours, the length of treatment duration with a first course of TMZ has varied, and the reasons for discontinuation were often not reported. The time of follow-up after discontinuation has ranged from 2 to 33 months. In the ESE survey, the median treatment duration was 9 months with a range of 1–36 months, and the median time of follow-up after TMZ discontinuation was 21 months, interquartile range being 11–42 (unpublished ESE survey). Often, treatment duration was predetermined at the outset of treatment based on local protocols. Whether a longer treatment period in responding patients improves the chance of obtaining a sustained remission cannot be answered by the existing observational studies. It is clear that with longer observation, fewer patients remain in remission. In the North-European multi-centre study, responding patients decreased from 48% at the time of TMZ discontinuation to 33% after 32 months (25). In the French multi-centre study, the percentage with sustained response decreased from 51% at the time of TMZ discontinuation to 45% at last follow-up at 16 months (0–72) after drug discontinuation, with a median relapse-free survival post-TMZ treatment of 30 months (18–51). The median survival was 44 months (42–infinity) among responders and 16 months (9–25) among non-responders (11). In the Italian multi-centre study on 31 patients, progression-free survival at 2 years in the entire cohort was 48% (95% CI 30–66%) (12). In the ESE survey, TMZ treatment durations in responders, progressors and patients with a stable disease were 13.1 (95% CI 11.3–14.9), 5.7 (CI 4.7–6.7) and 10.6 (CI 8.5–12.3) months, respectively (unpublished ESE survey). 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.

R 3.4.8 In patients with rapid tumour progression on temozolomide treatment, we suggest a trial with other systemic cytotoxic therapy. Given the variety of chemotherapeutic agents that have been reported, we cannot suggest a particular regimen (+000).

Reasoning

- Other cytotoxic drugs as first-line medical treatment Historically, a variety of cytotoxic drugs have been used in the treatment of aggressive pituitary tumours/carcinomas, of which lomustine (CCNU) in combination with 5-FU, based on their ability to penetrate into 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 (137). In a series of seven patients with functioning tumours, (four carcinomas) treated with CCNU/5-FU (138, 139), there was a transient response in a single case, a locally aggressive prolactinoma. In two aggressive somatotroph tumours, partial remissions were reported, in one case by a combination of doxorubicin and CCNU (140), in the other by methotrexate and 5-FU following extensive surgery (141). In a giant prolactinoma invading the cerebral tissue, four courses of CCNU, procarbazine and etoposide lead to improvement of vision and halted tumour growth for 12 months (142), but a subsequent course given with the onset of tumour progression was not effective. In 2 case reports of corticotroph tumour, cisplatin (carboplatin)–etoposide combination was found to result in partial regression for a limited period of time (143, 144). In a case of a corticotroph carcinoma, four cycles of cyclophosphamide, adriamycin and 5-FU lead to a stabilisation of systemic metastases for 3 years (145). In a TSH-secreting carcinoma, a combination of cyclophosphamide, 5-FU and adriamycin lead to 50% reduction of metastatic pulmonary lesions. The effect lasted for a couple of months (93). Combinations of cisplatin, procarbazine, lomustine and vincristine given to three patients with metastatic prolactinomas were not effective (9).

In the ESE survey, cytotoxic agents were used as first-line therapy in six patients with aggressive pituitary tumours (lomustine in 2 cases, etoposide in 2, carboplatin or cisplatin and etoposide in 2) (unpublished ESE survey). Partial regression was seen in one case with combination of carboplatin and etoposide, and in another case by using lomustine monotherapy; progression was seen in the other four cases. Significant side effects were seen in

cases using etoposide including cytopaenias and nausea/vomiting.

R 3.4.9 In patients who develop a recurrence following response to temozolomide treatment, we suggest a second trial of 3 cycles of temozolomide (+000).

Reasoning

Second attempt with TMZ ± combinations

There is little experience of a second treatment course with TMZ in patients who initially had responded to the drug, but in whom the tumours relapsed/progressed after treatment discontinuation. In total, 16 patients in 6 studies have been reported (11, 12, 25, 115, 134) (unpublished ESE survey). In 15 patients, TMZ was given as monotherapy, in one patient (134) in combination with other drugs. Partial remission was achieved in 1 of 16 patients, 2 had stable disease and 13 had progression.

Potential targeted therapies

Raf/MEK/ERK and PI3K/Akt/mTOR pathways are upregulated in pituitary tumours (146). Preclinical and clinical studies suggest that new targeted therapies may be useful for controlling pituitary tumour growth (147, 148, 149, 150, 151). However, everolimus was tried in 5 patients with aggressive pituitary tumours or carcinomas without success (44, 152). There were 3 cases among the ESE cohort in whom everolimus was used; all had disease progression (unpublished ESE survey).

There is some evidence supporting the use of tyrosine kinase inhibitors targeting the VEGFR pathway in the treatment of pituitary tumours (153, 154, 155, 156). Lapatanib ($n=5$), sunitinib ($n=1$) and erlotinib ($n=1$) have been tried in first- or second-line treatment; all but one demonstrating tumour progression, the last one, a prolactinoma, demonstrated minimal tumour shrinkage (22%) with lapatanib (157) (unpublished ESE survey).

Finally, VEGF-targeted therapy (bevacizumab) has been tried with some success in a few patients. Ortiz reported a 44-year-old male with a silent corticotroph pituitary carcinoma in whom prolonged tumour stabilisation was achieved (158). As monotherapy, bevacizumab was used in 2 cases as second-line therapy after progression on TMZ (unpublished ESE survey): in one case, a partial response was seen after 3 months, while the other exhibited stable disease. There was an additional case demonstrating progressive disease with bevacizumab in the setting of third-line therapy. Bevacizumab has also been used in combination with a second course of TMZ in 3 patients, 1 associated with a partial response (unpublished ESE survey).

Peptide receptor radionuclide therapy (PPRT)

Somatostatin receptors (types 1, 5 and 2) are widely expressed in different pituitary tumour subtypes (81). Moreover, pituitary uptake of 68Ga-DOTATATE or other radiolabeled somatostatin analogues has been demonstrated on PET/CT (159, 160), suggesting that PPRT could be an option for pituitary tumours, as described for neuroendocrine tumours (161, 162), including pituitary metastasis (163). Fourteen patients with aggressive pituitary tumours (lactotroph ($n=5$), gonadotroph ($n=3$), corticotroph ($n=2$) somatotroph ($n=3$) and mixed somatolactotroph ($n=1$)) treated with PPRT are reported in the literature. Tumour uptake was assessed by octreoscan or 68Ga-DOTATATE PET/CT. Four patients were treated with 111Indium-DPTA-octreotide (164, 165), 4 with 177Lutetium DOTATATE (25, 166, 167), 3 with 90Yttrium-DOTATOC (25, 168, 169) and 3 with 177Lutetium DOTATOC (11, 25). Patients received 2–4 cycles. Two patients demonstrated significant tumour shrinkage on treatment but one did not have a hormonal response (164, 168). Three patients have been reported to have stable disease with follow-up of 1 year and 3.5 years in 2 of these patients (165, 166, 167). Nine tumours progressed on treatment or shortly after treatment cessation (165, 167, 169).

3.5 Local treatment of metastatic disease

R 3.5.1 In patients with isolated metastases, we suggest consideration of loco-regional therapies, independent of decisions regarding the need for systemic treatment (+000).

Reasoning

In the case of localised low-burden disease at ectopic sites such as bone and/or hepatic metastases, we recommend consideration of loco-regional therapeutic approaches (9, 170). These may include laparoscopic surgical resection of solitary lymph node metastases, focused beam external radiotherapy and/or liver-directed approaches such as chemo or bland embolisation or radio or microwave ablation in the setting of hepatic tumour deposits.

4. Follow-up of an aggressive pituitary tumour

R 4.1 We recommend that imaging (MRI in most instances) should be performed every 3–12 months as

guided by prior tumour growth rate and/or location of tumour (proximity to vital structures) (+000).

Reasoning

MRI is recommended in preference to computed axial tomography (CAT); however, CAT scan without contrast enhancement may assess skull-base lesions or explore possible tumoural calcification in differential diagnosis (171). Imaging frequency is best determined on an individualised basis, commonly every 6–12 months, but factoring in (i) the prior growth trajectory of the tumour, (ii) proliferative markers and (iii) active treatment regimens such as TMZ. In general, imaging following 3 cycles of TMZ (i.e. 3 months) is recommended. In addition to conventional imaging studies (MRI, CAT), various functional imaging studies including fluoro-deoxy-glucose (FDG)-PET and somatostatin receptor (SSTR)-PET may be indicated to either better stage disease or to assess suitability for PRRT.

R 4.2 We recommend that full endocrine evaluation should be performed every 3–12 months as guided by the clinical context (+000).

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 month basis is recommended. In addition, given treatment-related hypopituitarism, particularly radiation effects on pituitary endocrine function, which can occur many years following therapy, we recommend a full endocrine evaluation to monitor adrenal, thyroid and sex steroid functions at least yearly, or more often if clinical symptoms suggest dysfunction (28).

R 4.3 We recommend lifelong follow-up of patients with aggressive pituitary tumours (++00).

Reasoning

Evolution of a more rapid growth rate and/or transformation to a pituitary carcinoma may occur years after initial identification of an aggressive pituitary tumour. Times for development of complications of treatment, such as radiation-induced hypopituitarism or secondary malignancies are also well recognised not to emerge for many years. Therefore, we recommend lifelong follow-up of aggressive pituitary tumours with endocrine and imaging assessments at intervals as outlined earlier.

4. 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-functional. Giant pituitary tumours are very rare in the paediatric population, with the majority being prolactinomas and/or acromegaly. They are invasive and more aggressive in nature, i.e., resistant to DA therapy and other therapeutic modalities (172, 173).

Although extremely rare, 2 paediatric pituitary carcinomas have been described in two girls aged 9 and 16. 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 (169, 174).

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, 132, 175). 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 (176) are mostly clinically non-functioning (NFPA), although in general, they stain positive for gonadotroph hormones (177, 178). Most pituitary tumours in this age group are large, slowly growing invasive tumours (179, 180). Low growth rate of tumour remnants is reported by some (in 21% of the patients despite subtotal and partial tumour resections), while other authors report progression rates comparable in elderly and young patients (178, 179, 180). There is no absolute contraindication to either radiotherapy or oncological drugs in the elderly. Importantly, treatment decisions in aggressive pituitary tumours and pituitary carcinomas in the elderly should take into account 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 (9, 181, 182). 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 in recent large series (11, 12, 25) (unpublished ESE survey) with similar response in patients older than 65 years as compared to younger patients.

c. Fertility There are no particular recommendations to guide fertility discussions for TMZ, but general recommendations are advised, as with any other chemotherapeutic agents that may be used. Most patients with aggressive pituitary tumours are extensively treated which is expected to affect their fertility capabilities. However, improvements in fertility therapies (IVF facilitation) have led to an increasing number of pregnancies in patients harbouring pituitary tumours but none was an aggressive pituitary tumour.

Contraception is needed during and after chemotherapy. The post-chemotherapy delay is 6 months for a woman and 1–2 years for a man. 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. In men, oligo-azoospermia has been described even with TMZ, sometimes permanently after the first cycle of chemotherapy. Sperm cryoconservation should be advised prior to commencement. In women, the risk of chemotherapy-induced premature ovarian failure is significantly affected by patient age. Consultation with a fertility specialist is advised to discuss the preservation of oocytes, ovaries or embryos.

d. Pregnancy The improved management of pituitary tumours (medical and surgical therapies) as well as improvements in fertility therapies has led to an increasing number of pregnancies in patients harbouring pituitary tumours. No specific studies in pregnancy are reported but recent reviews on pituitary tumour management in pregnancy in general have provided valuable recommendations for close follow-up during the course of pregnancy, which is in most cases favourable (183). Pregnancy in most patients does not accelerate tumour growth, particularly in treated macroadenomas (lactotroph or somatotroph) as well as corticotroph tumours in the setting of Nelson's syndrome, compared with its natural course before pregnancy (183, 184, 185).

Perspectives

The publication of the ESE clinical practice guidelines on aggressive pituitary tumours and carcinomas will hopefully improve identification and treatment of these rare tumours. Future efforts, similar to other European networks working on rare endocrine tumours, should combine the efforts of researchers and clinicians to establish an international register for this rare disorder. Our recent experience in compiling the European survey on aggressive pituitary tumours highlights many clinicians who are interested in developing such an international clinical register. The overall aim of such a register would be to work towards attaining consensus in diagnosis and foster improved treatment and follow-up strategies for these patients. Such registers can facilitate the establishment of clinical trials and biobanking of tumour specimens leads to improved understanding of the aetio-pathogenesis of these tumours and characterises improved prognostic and therapeutic markers. Research on these rare aggressive pituitary tumours is likely to reveal new molecular mechanisms of tumour growth that may allow the identification of new therapeutic targets.

A multidisciplinary approach to these tumours is key for both clinical management of patients and research. An international consortium supported by scientific societies is desired.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-17-0796.

Declaration of interest
Research contracts: GR (Novartis and Ipsen), PB (Novartis); Consulting: GR (Lectures for Ipsen and Novartis), PB (Advisory Boards of Pfizer and lectures for Novartis, Ipsen and Pfizer), AH (Strongbridge, Ferring, Ipsen, Lexicon, Novo Nordisk, Novartis), AMC (lectures for Ipsen and Novartis), SP (lectures for Ipsen, Novartis, and Pfizer, Advisory board member for Ipsen and Novartis), VP (lectures for Novartis and Pfizer). Other(s): AH (Endocrine Society: Associate Editor JCEM) and Pituitary Society: President Elect). The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of these guidelines.

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