Thieme

First German Guideline on Diagnostics and Therapy of Clinically Non-Functioning Pituitary Tumors

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ABSTRACT

Although non-functioning pituitary tumors are frequent, diagnostic and therapeutic concepts are not well standardized. We here present the first German multidisciplinary guideline on this topic. The single most important message is to manage the patients by a multidisciplinary team (consisting at least of an endocrinologist, a neurosurgeon, and a (neuro-) radiologist). The initial diagnostic work-up comprises a detailed characterization of both biochemical (focusing on hormonal excess or deficiency states) and morphological aspects (with magnetic resonance imaging of the sellar region). An ophthalmological examination is only needed in presence of symptoms or large tumors affecting the visual system. Asymptomatic, hormonally inactive tumors allow for a 'wait and scan' strategy. In contrast, surgical treatment by an experienced pituitary surgeon is standard of care in case of (impending) visual impairment. Therapeutic options for incompletely resected or recurrent tumors include re-operation, radiotherapy, and observation; the individual treatment plan should be developed multidisciplinary. Irrespective of the therapeutic approach applied, patients require long-term follow-up. Patient with larger pituitary tumors or former surgery/radiotherapy should be regularly counseled regarding potential symptoms of hormonal deficiency states.

Introduction

Pituitary tumors are frequent. According to data from autopsy studies, they occur in adults with a prevalence of about 10 %. More than 85 % of pituitary tumors are pituitary adenomas, and about 25–30 % of these are hormonally inactive. The latter thus represent the second most frequent tumor type after prolactinomas. They are the focus of this guideline. Hormonally active pituitary adenomas or tumors that do not primarily originate in the pituitary gland are, in this guideline, primarily considered as differential diagnoses. With respect to the therapy of these other tumors, reference is made to other relevant guidelines and recommendations.

Despite the relative frequency of pituitary tumors, the current study situation is limited, at least regarding some clinical questions. The guideline committee agrees that a structured, multidisciplinary approach is essential for optimal patient care. The guideline presented here by 12 medical societies and a patient self-help group aims to provide practical recommendations for the management of patients with hormonally inactive pituitary tumors based on international guidelines and current publications.

The original guideline in German language consists of the following documents:

- Long version with recommendation texts, background information and a detailed report on the methodology (guideline report).
- Short version with the most important recommendations and tables in short form.
- Summary of the guideline as targeted information for patients.

All three documents are freely available at http://awmf-leitlinien.de. Here, we present a short version of this guideline in English. An English translation of the entire guideline report is available in the Appendix. After a short review of the methodology, all recommendations will be presented in boxes along with a short explanatory text. For more details and references, we refer to the full version.

Methodology

At the first meeting of the guideline committee on June 19th 2018, the main clinical questions to be addressed by the guideline were defined. Based on the existing international guidelines [1–13] and extensive primary literature, recommendations and background texts were subsequently developed by seven working groups. According to the guidelines of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF), the recommendations were graded using the wording "shall" (strong recommendation), "should" (recommendation), and "can" (open recommendation).

All recommendations as well as some of the contents of the explanatory text were discussed at the second meeting of the guideline committee on February 19th 2019, and at the consensus conference on June 25th 2019, before being finally approved. The course of the consensus conference was structured in the sense of a nominal group process. All recommendations were approved by consensus or strong consensus. The strength of consensus was defined as follows (respective approval rate given in brackets): strong consensus (> 95 %), consensus (> 75–95 %), majority consensus (50–75 %), no consensus (< 50 %).

Following the consensus conference, the comments were first modified by the various working group leaders, taking into account the decisions made, before a final editorial revision of the entire guideline by the secretary and the two coordinators was performed. The guideline was then submitted to all participating professional societies for comments on November 6th 2019, and finally approved by them by December 20th 2019. The AWMF then carried out an external formal assessment. The last revision of the content of this guideline took place in December 2019. The guideline was published in January 2020 and will be valid for 5 years (i. e., until December 2024).

Definition and General Recommendation

Pituitary tumors are common in adults and, with rare exceptions, benign (see details in ▶ **Table 1**). More than 85 % of all tumors in the sellar region are pituitary adenomas. A fraction of the latter is hormonally active, and these tumors are not addressed in detail in this guideline. It is common clinical practice to designate pituitary tumors with a size of < 1 cm as microtumors (or microadenomas) and, accordingly, tumors with a size of ≥ 1 cm as macrotumors (or macroadenomas); although this cutoff is, of course, arbitrary.

▶ **Table 1** Differential diagnoses of tumors in the sellar region.

Tumor entity	Relative frequency
Formally benign tumors	**91.4%**
Pituitary adenomas – Hormonally inactive adenomas – Prolactin-producing adenomas (prolactinomas) – GH-producing adenomas (acromegaly) – ACTH-producing adenomas (Cushing's disease) – TSH-producing adenomas (TSH-omas) – Gonadotropin-producing adenomas (gonadotropinomas)	86.6%
Craniopharyngiomas	3.1%
Meningiomas	1.3%
Posterior pituitary tumors (e. g. spindle cell oncocytoma, pituicytoma, granular cell tumor)	0.4%
Cysts	**4.5%**
Rathke's cleft cysts	3.6%
Colloid cysts	0.6%
Arachnoid cysts	0.2%
Dermoid cysts	0.2%
Pituitary hyperplasia	**0.2%**
Lactotroph hyperplasia (during pregnancy)	0.1%
Thyrotroph and gonadotroph hyperplasia	< 0.1%
Other entities (selection)	**2.3%**
Pituitary abscess	0.3%
Lymphocytic hypophysitis	0.3%
Malignant tumors	**1.6%**
Metastases of other malignomas (e. g., lung or breast carcinomas)	0.7%
Chordomas	0.4%
Pituitary carcinomas	0.2%
Germ cell tumors (germinomas)	0.2%
Chondrosarcomas	0.1%

The data on relative frequencies were taken from the German Pituitary Registry containing more than 11,000 operated tumors. By definition, only operated cases are included in this registry. Therefore, prolactinomas, (small) benign hormonally inactive masses (which are often not operated on), and tumors that are frequently transcranially resected are obviously underrepresented in this registry. Abbreviations: ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone.

No.	Recommendation	Consensus
3.1	Every patient with a newly detected or known pituitary tumor **shall** be diagnosed and treated by a multidisciplinary team of physicians * experienced in the treatment of pituitary tumors. * Mandatory disciplines in this team are endocrinology, neurosurgery, and (neuro-) radiology, as well as, depending on the tumor size or the planned intervention, (neuro-) pathology, ophthalmology, and radiotherapy. In case of special issues, other disciplines (e. g., gynecology, neurology, and psychology), may also be required.	Strong

Short explanation

To ensure adequate diagnostics, therapy, and follow-up, patients with pituitary tumors require special expertise that usually will only be provided through multidisciplinary care.

Diagnostics

No.	Recommendations	Consensus
4.1	In patients with a pituitary tumor, a detailed medical history and clinical examination **shall** be performed in order to evaluate possible symptoms of pituitary insufficiency or hormone excess as well as local symptoms caused by the tumor mass.	Strong
4.2	In patients with clinically non-functioning pituitary tumors, biochemical confirmation of endocrine inactivity **shall** be performed. Possible hormone activity **shall** be clarified through basal morning measurement of prolactin, thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (in men) or estradiol (in premenopausal women), insulin-like growth factor 1 (IGF-1), and a 1 mg dexamethasone suppression test.	Strong
4.3	In macroadenomas, pituitary insufficiency **shall** be ruled out. This includes basal morning measurement of TSH, fT4, fT3, LH, FSH, total testosterone (in men) or estradiol (in premenopausal women), cortisol, and IGF-1. In case of abnormalities further dynamic testing procedures **shall** be carried out. Larger microadenomas (with a size of 6–9mm) may also lead to pituitary insufficiency and **should**, therefore, be biochemically evaluated accordingly.	Strong

Short explanation

A detailed diagnostic work-up (including medical history, clinical examination, and endocrine analysis) is the mainstay of an adequate patient management. In 85% of hormonally inactive macroadenomas, clinical evidence of pituitary insufficiency is already present at initial diagnosis [5, 14]. For anamnestic clues, specific symptoms, and detailed explanation for the selection of the recommended hormones, we refer to the Appendix. ▶ **Table 2** summarizes the hormone parameters that are regarded as mandatory for the initial evaluation of patients with pituitary tumors.

Assessment of corticotropic function includes determination of basal morning serum cortisol as the first step:

- Basal serum cortisol ≤ 4.0 µg/dL (110 nmol/L): high probability of secondary adrenal cortical insufficiency.
- Basal serum cortisol ≥ 15.0 µg/dL (414 nmol/L): high probability of corticotropic axis sufficiency.
- If a basal serum cortisol in the diagnostic gray range is detected (i. e., 4.1–14.9 µg/dL (111–413 nmol/L)), a dynamic functional test needs to be performed (gold standard: insulin hypoglycemia test; alternatively: metopyrone test, adrenocorticotropic hormone (ACTH) test (using 250 µg Synacthen®), or corticotropin-releasing hormone (CRH) test).

No.	Recommendations	Consensus
4.4	Magnetic resonance imaging of the sellar region **shall** be performed for the radiological detection and characterization of pituitary tumors.	Strong
4.5	For pituitary tumors that are in contact with the visual path according to magnetic resonance imaging, ophthalmologic evaluation **shall** be performed.	Strong

Short explanation

Due to superior space resolution in the sellar and supresellar region, magnetic resonance imaging (MRI) is - in comparison to computed tomography (CT) - clearly the gold standard in the diagnosis of pituitary adenomas. A possible protocol for MRI imaging of the sellar region (including information on dynamic contrast agent sequences) is presented in ▶ **Table 3**.

▶ **Table 2** Mandatory hormone parameters at initial diagnosis of a pituitary tumor.

Laboratory parameters
– Prolactin
– TSH, fT4, fT3
– LH, FSH, sex hormones • Estrogen in premenopausal women • Total testosterone in men
– IGF-1
– Basal morning cortisol[A]
– 1 mg dexamethasone suppression test
[A] Cortisol is usually only to be determined for macroadenomas and large microadenomas (≥ 6mm); borderline findings require dynamic function tests (see text below). Abbreviations: FSH, follicle-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

▶ **Table 3** Recommendation for a MRI imaging protocol of the sellar region.

	Description
MRI characteristics	A field strength of at least 1.5 and ideally 3 Tesla, a slice thickness of 1.5–2 mm, a small field of view, a high matrix and, ideally, an in-plane resolution of 0.5 mm x 0.5 mm
	T2 weighting (T2w) in the coronal plane, aligned with the infundibulum (sagittal T2w localizer); in addition, at least one slice in the axial or sagittal plane
	T1 weighting (T1w) coronal and sagittal native
	T1w coronal and sagittal after intravenous administration of contrast medium (e. g., 0.05 mmol/kg body weight (for microadenomas) or 0.1 mmol/kg body weight (for macroadenomas) of a gadolinium-containing contrast medium)
	3D T1 MPRAGE volume data set with an isotropic voxel size of 1mm after intravenous administration of contrast medium
Administration of contrast medium	Contrast medium flow rate: 2 ml/s
	Time of injection: start of 2nd dynamic measurement
	Duration of the dynamic measurement: 30 s max.
	Number of measurements: 6–8
	MRI sequence: coronal T1 turbo spin echo
	Voxel size: 0.5 x 0.5 x 2 mm
	Flushing: 20 ml NaCl flush with a flow rate of 2 ml/s
Abbreviations: MPRAGE, magnetization prepared rapid gradient echo; MRI, magnetic resonance imaging; NaCl, saline solution; T1w, T1 weighting; T2w, T2 weighting.	

Visual disturbances including visual field defects and blindness may be observed in more than half of pituitary macroadenomas. As the defects develop slowly and are partly compensated by the unaffected eye, they are not necessarily noticed by the patients. The ophthalmologic evaluation includes the measurement of visual acuity and visual field as well as an examination of the fundus. As a rule, static perimetry of the central 30 degrees of the visual field is sufficient.

Therapy

Procedures for initial diagnosis

No.	Recommendations	Consensus
5.1	In case of asymptomatic, hormonally inactive pituitary microtumors (< 1 cm), the patient **shall** primarily be monitored ("wait and scan"). In most asymptomatic, hormonally inactive pituitary macrotumors (≥ 1 cm), the patient **can** primarily be monitored ("wait and scan").	Strong
5.2	In case of symptomless, hormonally inactive pituitary tumors, as a rule, drug therapy with dopamine agonists **should** not be performed. If it is unclear whether, in a clinically hormone-inactive adenoma, functional hyperprolactinemia or rather a prolactinoma is present, temporary treatment with dopamine agonists **can** be attempted. Follow-up **should** be both via determination of serum prolactin levels and radiologically.	Strong
5.3	In case of an (impending) impairment of vision, surgical treatment of the pituitary tumor **shall** be performed. Tumors showing significant growth in size (particularly with regard to critical surrounding structures such as the visual pathway) **should** be operated on. The detection of a relevant pituitary insufficiency **can** be considered an indication for surgery. Pituitary tumors are rarely the cause of headache, therefore, an indication for surgery based on this symptom alone **should** be made with caution.	Strong
5.4	In case of severe or rapidly progressive neuro-ophthalmologic deficits, an emergency presentation to a neurosurgeon **shall** be performed.	Strong
5.5	Neurosurgical intervention **should** be performed by a neurosurgeon with sufficient experience in pituitary surgery.	Strong
5.6	Since the results of microsurgical and endoscopic transsphenoidal surgery are equivalent, the choice of the visualization mode **should** depend on the surgeon's experience with the optical technique and his preference.	Strong
5.7	When using a transsphenoidal access, the sphenoid sinus and the sella turcica **shall** be opened wide enough to remove all tumor parts that were considered resectable preoperatively.	Strong
5.8	Neuronavigation and intraoperative ultrasound imaging **can** be used to increase the safety and the resection rate in transsphenoidal surgery of pituitary tumors. Intraoperative magnetic resonance imaging **can** be used to increase the resection rate in pituitary tumor surgery.	Strong

Short explanation

As published data and our experience indicate that a relevant increase in size or new endocrine dysfunction are rare events, a "wait and scan" strategy is actually the preferred option for patients with incidentally detected asymptomatic pituitary microadenomas. The advantages and disadvantages of this procedure as compared to surgery need to be discussed with the patient in detail.

Due to the moderate number of published series and, thus, comparatively small numbers of reported cases, the evidence for a recommendation regarding the therapy of asymptomatic hormone-inactive pituitary adenomas with dopamine agonists is insufficient. However, the differentiation of hormone-inactive pituitary adenomas from prolactinomas in the presence of mild to moderate hyperprolactinemia may be difficult in individual cases. Thus, in these unclear cases, treatment with dopamine agonists seems justified.

The indications for the operation of pituitary tumors result from the different (impending) complications of these tumors, and the guideline committee deliberately formulates specific strength of recommendation for each indication. Usually, transsphenoidal surgery is the appropriate first-line therapy for symptomatic hormone-inactive pituitary adenomas. Transcranial surgery is rarely indicated as a primary intervention. The previous experience of a pituitary surgeon and the annual number of cases of transsphenoidal surgeries performed influence the resection result and the complication rate. Studies on radiotherapy as a primary treatment have not been able to demonstrate results comparable to those of surgical procedures [10].

The chiasmal syndrome is an absolute indication for surgery. If the visual impairment has not yet set in, but is imminent, the guideline committee also sees a clear indication for surgery. The members of the guideline committee are convinced, though, that the sudden onset of symptoms in the context of a pituitary apoplexy requires high attention.

During initial observation of a clinically non-functioning pituitary adenoma, surgery is indicated if in the course of time a significant progression in size is observed. Size progression is difficult to define. In the full version in the Appendix approaches to this problem are discussed.

In the presence of anterior pituitary insufficiency, the guideline committee also makes a recommendation for transsphenoidal surgery (at least if ≥ 2 pituitary axes are affected). However, this is deliberately formulated as a "can-recommendation".

Data on the causal relationship between headache and pituitary tumors are inconclusive. Nevertheless, the authors of the guideline are convinced that headache alone is a rare indication for surgery.

The complication rates in large series did not exhibit a significant difference between microsurgically and endoscopically operated patients and therefore, the method applied depends on the surgeon's preference.

At first glance, intraoperative MRI seems to have a positive influence on the surgical results. However, the method is time-consuming and cost-intensive. In addition, either the use of special non-magnetic instruments or repositioning of the anesthetized patient is required for the examination. Despite positive effects on safety (neuronavigation) and resection rate (intraoperative imaging), in the opinion of the neurosurgeons involved in the development of this guideline, neither image-guided surgery nor intraoperative imaging are able to replace the experience of the surgeon as the decisive factor for the success of the operation.

Perioperative management

No.	Recommendations	Consensus
5.9	If secondary adrenal insufficiency is present or suspected, adequate glucocorticoid substitution **shall** be performed. The perioperative substitution of hydrocortisone in the resection of pituitary tumors **should** be performed according to a standardized local protocol.	Strong
5.10	In case of possible or proven postoperative adrenal insufficiency, patients **shall** be adequately informed before discharge from hospital about the required medication and the necessity of a need-based adaptation (see also **Recommendation 8.1** and **Recommendation 8.2**).	Strong
5.11	In case of pre- or postoperative evidence of hypothyroidism, corticotropic insufficiency **shall** be excluded before starting a substitution therapy; otherwise, it may clinically unmask. For diagnosis as well as dose titration of the thyroid hormone substitution therapy, fT4 (and not the, in this case, frequently suppressed or inadequately low TSH) **shall** be taken into account.	Strong
5.12	In order to detect a possible syndrome of inadequate antidiuretic hormone (ADH) secretion (SIADH) and/or diabetes insipidus early, serum electrolytes **shall** be determined regularly after surgery until at least the 10th postoperative day, and patients **shall** be informed in appropriate detail.	Strong
5.13	After a neurosurgical intervention, the possible occurrence of cerebrospinal fluid fistulas, meningitis, and visual disturbances **shall** be paid attention to.	Strong
5.14	Short-term postoperative imaging of the sellar region is usually unnecessary and **should** be reserved for certain questions (e. g., to assess the size of intraoperative tumor remnants, newly occurring visual disturbances or neurological deficits with regard to postoperative bleeding or vascular injury). The first regular imaging control **should** be performed 3–6 months after surgery.	Strong

Short explanation

A variety of perioperative substitution regimens has been described in the literature, differing in glucocorticoid dose and duration of administration. Common substitution regimens for the immediate perioperative phase are 50 mg or 100 mg hydrocortisone intraoperatively and 50 mg or 100 mg hydrocortisone over 24 hours by perfusion. Thereafter, the dose is gradually decreased until a maintenance dose is reached.

On discharge from hospital, a daily hydrocortisone dose of 15–30 mg is usual (about 2/3 in the morning and 1/3 at noon; alternatively, division into 3 daily doses is possible). This maintenance

dose then has to be kept unchanged until postoperative endocrine re-evaluation (i. e., 6–12 weeks after surgery) and has to be adapted in situations of increased need.

Postoperative electrolyte alterations due to a disorder of antidiuretic hormone (ADH) release by the posterior pituitary lobe are frequently observed. They are of central importance for the early postoperative management of patients after pituitary surgery. Diabetes insipidus centralis due to a lack of ADH usually occurs in the first postoperative days. The syndrome of inadequate ADH release (SIADH) as the opposite disorder usually occurs with a delay of several days after surgery. Accordingly, close supervision of electrolytes is reasonable at least until the 10th postoperative day. More details on the management of postoperative diabetes insipidus centralis or SIADH are given in the full version of this guideline in the Appendix.

An MRI examination provides more reliable results if it is not performed immediately, but rather not earlier than 3–6 months after the operation. One of the reasons is that, after this period of time, an assessment of the size of residual tumor tissue is less complicated by post-operative changes and artifacts [16].

Recommendations for residual and recurrent tumors

No.	Recommendations	Consensus
5.15	In case of residual or recurrent tissue of a hormone-inactive pituitary tumor, observation ("wait and scan"), re-operation, and radiotherapy **shall** be considered (if possible, in a multidisciplinary case conference with endocrinological, neurosurgical, (neuro-) pathological, (neuro-) radiological, ophthalmological, and radiotherapeutic participation).	Strong
5.16	The radiotherapy of residual/recurrent tissue of hormone-inactive pituitary adenomas **can** be performed by radiosurgery depending on the individual patho-anatomical conditions.	Strong
5.17	Radiotherapy of residual/recurrent tissue of hormone-inactive pituitary adenomas **can** be performed by fractionated radiotherapy. Radiation therapy of pituitary adenomas that are not eligible for radiosurgery (e. g., in the vicinity of the optical system) **should** be fractionated.	Strong
5.18	In case of postoperative tumor growth and after exhaustion of surgical and radiotherapeutic options, treatment of hormone-inactive pituitary adenomas with dopamine agonists **can** be considered in individual cases. For somatostatin analogues, evidence is insufficient in this indication.	Strong
5.19	As first-line chemotherapy for aggressive pituitary adenomas with documented tumor growth and lack of surgical or radiotherapeutic treatment options, monotherapy with temozolomide **should** be performed.	Strong

Short explanation

The most reasonable step for recurrent adenomas is a multidisciplinary discussion of the case and an individualized decision.

In large recurrent adenomas with an invasive component, the concept of surgical tumor debulking with subsequent radiotherapy may also be pursued. In the case of progressive residual findings of hormone-inactive pituitary adenomas, radiotherapy achieves high control rates of about 90 % after 10 years.

Radiosurgery is a highly conformal, single-session radiotherapy with steep dose gradients. In hormone-inactive pituitary tumors, single doses of 12Gy or more are effective, and edge doses of up to 16Gy have been described in clinical cohorts.

The decision between single-session radiosurgery and hypofractionated radiosurgery is – also in consideration of conventional fractionated radiotherapy – based on the anatomical situation, especially the proximity to the optical system and the size of the target volume. For tumors that do not fall below a minimum distance from the optical system (optic nerve and optic chiasm) of 2 mm, single-stage radiosurgery is more appropriate. In case of contact (without compression) or a distance of less than 2 mm, hypofractionated radiosurgery may be performed [17].

Tumors that are not delimitable (i. e., they are diffusely infiltrating), walling around the optical system or symptomatic tumor masses constitute contraindications for radiosurgery.

Although there are no comparative studies that have investigated the response rates of fractionated radiotherapy vs. radiosurgery, numerous retrospective cohort analyses show approximately comparable control rates of both procedures in hormone-inactive pituitary adenomas. In the case of large tumors that are no longer accessible to stereotactic radiosurgery or in cases of critical proximity to the optical structures, especially the optic chiasm, fractionated radiotherapy is the method of choice to avoid the effects of high single doses to the optical system.

Usually, fractionated radiotherapy uses doses between 45Gy and 54Gy in 5 fractions of 1.8Gy to 2Gy per week over a period of 5 to 6 weeks.

Due to the limited number of subjects and the lack of further randomized studies on the use of drug therapy of hormone-inactive adenomas, the authors of the guideline do not consider the data situation robust enough to make a general recommendation. However, in case of so-called aggressive adenomas the situation is slightly different. These tumors are characterized by radiologically invasive growth and an unusually rapid growth rate, or they show a clinically relevant growth despite optimal standard therapies. In these rare tumors, temozolomide is treatment of choice following a recent recommendation of the European Society of Endocrinology [13].

Pathology

No.	Content	Consensus
6.1	Surgically resected tissue from a pituitary tumor **shall** be processed and evaluated according to the criteria of the the currentlx valid World Health Organization (WHO) classification for tumors of endocrine organs and tumors of the central nervous system.	Strong
6.2	For the histopathological work-up of pituitary adenomas, antibodies against the pituitary hormones (growth hormone (GH), prolactin, TSH, ACTH, FSH, LH, alpha-subunit), the three pituitary transcription factors (pituitary-specific positive transcription factor 1 (PIT-1), T-box factor pituitary (T-PIT), steroidogenic factor 1 (SF-1)), the estrogen receptor, and the proliferation marker Ki-67 **shall** be held available in the laboratory according to the WHO classification.	Strong
6.3	Since the identification of certain hormone-producing as well as transcription factor-positive pituitary adenomas is of prognostic relevance, the hormone and transcription factor subtypes **shall** be mentioned in the written pathology report.	Strong
6.4	For hormone-negative, transcription factor-positive adenomas, the following diagnoses **shall** be applied according to the WHO classification: – Hormone-inactive PIT-1 positive pituitary adenoma (a more precise classification as GH-prolactin or TSH adenoma is not reliably possible) – Hormone-inactive gonadotroph pituitary adenoma (SF-1 positive adenoma) – Hormone-inactive corticotroph pituitary adenoma (T-PIT positive adenoma)	Strong
6.5	In addition to the histological classification of a pituitary tumor, its clinical significance and aggressiveness **shall** be assessed according to the WHO classification. This requires clinical information on the endocrine activity of the tumor and radiological findings regarding spread and invasiveness.	Strong
6.6	If aggressiveness criteria are present, according to the WHO classification, the addition "with characteristics of aggressiveness" **shall** be included in the written pathology report (after the hormone and transcription factor subtype).	Strong
6.7	Immunohistology with detection of somatostatin and dopamine receptors **can** be helpful for planning the pharmacotherapy. If a therapy with temozolomide is considered for aggressive pituitary adenomas and carcinomas, O-6-methylguanine-DNA-methyltransferase (MGMT) determination **can** be included.	Strong
6.8	Currently, a molecular genetic examination of hormone-inactive pituitary adenoma tissue **cannot** be recommended due to a lack of clinical consistency.	Strong

Short explanation

In this regard, the currently valid World Health Organization (WHO) classification for endocrine tumors and tumors of the central nervous system [18, 19] has become established worldwide in recent years and, thus, represents the basis for neuropathological workup. In the diagnosis of pituitary tumors, a good flow of information between the treating medical disciplines (including neurosurgery, endocrinology), and (neuro-) pathology is essential for the consistent application of the classification recommended by the WHO. Essential information for the (neuro-) pathologist, especially for the assessment of the aggressiveness of a pituitary adenoma, are tumor size, tumor extent or invasiveness in the preoperative MRI, and details on clinical presentation.

The group of clinically non-functioning pituitary tumors includes the "silent" adenomas that do not lead to clinically measurable hormone hypersecretion despite immunohistochemically detectable hormone production, the hormone-negative, transcription factor-positive adenomas, and the hormone- and transcription factor-negative null-cell adenomas.

The determination of the pituitary adenoma subtype is based on structural and immunohistological differences as shown in ▶ **Table 4**.

The hormone-negative, but transcription factor-positive adenomas, are either endocrine-inactive/"silent" or endocrine-active and then, if detected, represent the critical correlate for the explanation of pituitary hyperfunction. Thus, PIT-1-positive adenomas are able to explain GH-, prolactin- or TSH-hyperfunction without detection of the expected hormone. Likewise, T-PIT-positive, ACTH-negative adenomas account for ACTH-hyperfunction (in the sense of Cushing's disease or Nelson's syndrome). Finally, SF-1-positive, FSH-, and LH-negative adenomas represent gonadotroph adenomas.

The aggressive adenomas of the new nomenclature of 2017 [13, 19] are characterized by a faster growth and a higher recurrence rate. Therefore, the clinician has to provide the pathologist clinically relevant information.

If somatostatin analogues, dopamine agonists or temozolomide are clinically eligible for the treatment of aggressive hormone-inactive adenomas, immunohistochemical staining with antibodies against the somatostatin receptors (SSTR) SSTR2a and SSTR5, the dopamine receptors as well as the determination of O-6-methylguanine-DNA-methyltransferase (MGMT) expression have proven to be helpful. Although sporadic mutations have been described in up to 60 % of corticotropic adenomas (mainly USP8 and USP48 mutations) and in about 40 % of somatotroph adenomas (mainly GNAS mutations) [20, 21], there are no pathogenetically relevant mutations to be frequently found in hormonally inactive adenomas. In principle, molecular pathological detection of mutations has no therapeutic consequences at present and is therefore only carried out within the framework of research projects.

▶ **Table 4** WHO classification of pituitary adenomas of 2017.

	Immunohistochemistry		Aggressive	Main function	Possible function
Tumor type	**Hormones and receptors**	**Transcription factor**			
Somatotroph adenomas					
Densely granulated GH adenoma	GH, possibly PRL, a-SU, ER negative	PIT-1		Acromegaly	
Sparsely granulated GH adenoma	GH, possibly PRL, a-SU, ER negative	PIT-1	Yes	Acromegaly	Silent
Undifferentiated GH adenoma	GH, possibly PRL, ER negative	PIT-1	Yes	Acromegaly	Silent
Lactotroph adenomas					
Densely granulated PRL adenoma	PRL, ER positive	PIT-1		Hyperprolactinemia	
Sparsely granulated PRL adenoma	PRL, ER positive	PIT-1	Macroadenomas in men	Hyperprolactinemia	Silent
Acidophil stem cell adenoma	PRL, (GH), ER positive	PIT-1	Yes	Hyperprolactinemia	Acromegaly
Undifferentiated PRL adenoma	PRL, ER positive	PIT-1	Yes	Hyperprolactinemia	Silent
Mixed GH-Prolactin adenomas					
Densely granulated GH/PRL adenoma	GH, PRL, ER positive	PIT-1		Acromegaly	Hyperprolactinemia
Sparsely granulated GH/PRL adenoma	GH, PRL, ER positive	PIT-1		Acromegaly	Hyperprolactinemia
Mammosomatotroph adenoma	GH, PRL, ER positive	PIT-1		Acromegaly	Hyperprolactinemia
Thyrotroph adenomas					
TSH adenoma	TSH (PRL)	PIT-1		TSH-hyperfunction	Silent
Undifferentiated TSH adenoma	TSH, PRL	PIT-1		TSH-hyperfunction	Hyperprolactinemia
Plurihormonal adenomas					
Plurihormonal PIT-1 positive adenoma	GH, PRL, TSH, others	PIT-1	Yes	Inactive	Hyperprolactinemia
T-PIT or SF-1 positive adenoma	Various combinations	T-PIT or SF-1	Unclear		
Corticotroph adenomas					
Densely granulated ACTH adenoma	ACTH	T-PIT		Cushing's disease	Silent → aggressive
Sparsely granulated ACTH adenoma	ACTH	T-PIT		Cushing's disease	Silent → aggressive
Crooke's cell adenoma	ACTH	T-PIT	Yes	Cushing's disease	Silent
Gonadotroph adenomas				Inactive	
FSH or LH or FSH/LH adenoma	FSH and/or LH	SF-1			
a-SU adenoma	a-SU	SF-1		Inactive	
Hormone and transcription factor-negative tumors	Negative	Negative		Inactive	
Null-cell adenoma	Negative	Negative		Inactive	

Abbreviations: ACTH, adrenocorticotropic hormone; a-SU, alpha subunit; ER, estrogen receptor; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PIT-1, Pituitary-specific positive transcription factor; PRL, prolactin; T-PIT, T-PIT-box factor pituitary; TSH, thyroid-stimulating hormone; SF-1, Steroidogenic factor 1.

Follow-up

General aspects

No.	Content	Consensus
7.1	Patients with evidence of a germline mutation **should** be made aware of the possibility of a genetic counseling.	Strong
7.2	After a neurosurgical intervention on the pituitary gland, the patient **shall** be advised that certain everyday and leisure activities have to be avoided for a limited period of time.	Strong
7.3	Patients **shall** be specifically asked about psychosocial consequences and concomitant effects of pituitary tumors. The use of questionnaires **can** be helpful.	Strong

Short explanation

A germline mutation needs to be considered especially if the patient is ≤ 30 years old at first diagnosis of the pituitary adenoma, if other tumors are known besides the pituitary adenoma, or if there is a familial cluster of pituitary adenomas [22].

Certain activities as well as physical exercise are to be avoided after a neurosurgical intervention, at least for a certain period of time. An overview of recommendations for the postoperative course after transsphenoidal interventions that were given as examples by several German neurosurgeons is provided in ▶ **Table 5** [23].

▶ **Table 5** Action recommendations after routine or extended transsphenoidal access.

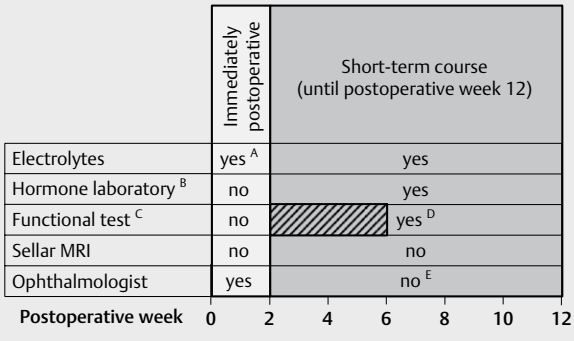
Activity	Recommended latency (weeks) after routine transsphenoidal access			Recommended latency (weeks) after extended transsphenoidal access		
	Variation	Median	Recommendation	Variation	Median	Recommendation
Daily activities						
Blow nose	<1–8	3	3[A]	1–12	4	4[A]
Wash hair	<1–1	<1	<1	<1–2	<1	<1
Sauna visit	1–4	4	4	2–12	4	4
Play wind instrument	3–12	6	6[B]	3–26	8	6[B]
Flying	<1–8	1.5	1[C]	<1–8	2.5	2[C]
Heavy lifting	<1–8	4	4	1–26	6	6
Drive a car	<1–12	1	<1[D]	<1–12	4	2[G]
Use a CPAP device	<1–12	3.5	3[A]	<1–12	4	4[A]
Have sexual intercourse	<1–4	1	1	<1–8	3.5	2
Sports activities						
Nordic walking	<1–4	2	2	<1–6	3	3
Jogging	<1–6	4	3	<1–12	5	4
Breast stroke	1–8	4	4	2–12	6	6
Crawl	1–8	4	4	2–12	6	6
Diving	4–26	8	12[E]	6- Ø	12	12[E]
Tennis	<1–8	4	4	4–12	7	6
Soccer	<1–8	4	4[F]	4–12	8	8[F]
Competitive sports	4–12	6	6	6–12	12	10
Occupational activities (8 hours/day)						
Sitting activity	<1–3	1.5	2	<1–4	2	3
Physical activity	<1–6	3.5	4[A]	2–12	6	6[A]

Results were derived from a survey conducted in 14 German neurosurgeons (with a total of about 1,000 transsphenoidal operations per year). In the column "Variation" the data of the neurosurgeons participating in the survey are listed with their respective range ("from…to…"). [A] longer after intraoperative cerebrospinal fluid flow; [B] starting point for gradual increase of activity; [C] exclusion of intracranial air (within the skull), e. g., by computed tomography is a prerequisite; [D] provided hyponatremia is excluded and patient feels well; [E] statement of the responsible surgeon is binding; [F] no headballs; [G] provided the brain surface was neither involved by the tumor nor by the surgery; Ø = never (for further information refer to the corresponding original paper). Table modified according to [23]. Abbreviations: CPAP, continuous positive airway pressure.

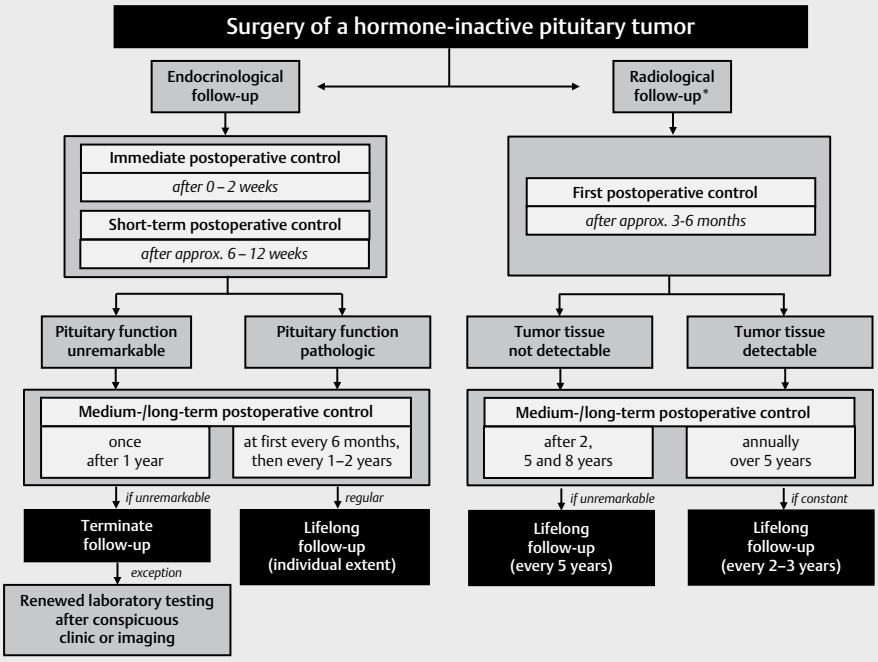
Patients with hormone-inactive pituitary macroadenomas have been shown to suffer from an impaired quality of life as compared to age-matched healthy controls even after successful surgery or radiotherapy. A positive influence of accompanying psychosocial care (e. g. cognitive behavioral interventions) on the treatment and follow-up care of a pituitary adenoma seems to be obvious, but has not yet been verified specifically for this clinical picture (▶ **Fig. 1**, ▶ **Fig. 2** and ▶ **Table 6**).

Immediate postoperative course (until about 2 weeks after surgery)

After surgical resection of a pituitary adenoma, the concrete follow-up is determined mainly by the time of postoperative evaluation. The perioperative and immediate postoperative course (up to about 2 weeks after surgery) is already discussed in **Chapter 5** on therapy (and there specifically in **Recommendations 5.9–5.14**).



▶ **Fig. 1** Proposal for postoperative follow-up of patients in the first 12 weeks after surgery for a hormone-inactive pituitary tumor. **A** regularly until at least the 10th postoperative day; **B** TSH, fT4, fT3, cortisol, IGF1, LH, FSH, estradiol or total testosterone depending on sex; **C** dynamic function tests for the diagnostic workup of a possible corticotropic insufficiency (see reasoning to Recommendation 4.2); **D** after 6 weeks at the earliest, better after 8, and at the latest after 12 weeks; **E** if preliminary examination is inconspicuous and if there are no clinical features, no further clinical examination is necessary in the 1st half-year. Abbreviations: MRI, magnetic resonance imaging.



▶ **Fig. 2** Proposal for postoperative follow-up care of patients with hormone-inactive pituitary tumors. * In principle, magnetic resonance imaging is the examination procedure of choice, in case of contraindications computed tomography may be used. Provided that there is no obvious visual impairment and imaging follow-up by magnetic resonance imaging is performed regularly, ophthalmological follow-up examinations may be omitted if there are no radiological indications of tumor contact with the visual path.

▶ **Table 6** Assessment intervals for size-stable pituitary adenomas without endocrine abnormalities.

	First control after initial diagnosis		**Further controls**	
	Time point	**Content**	**Time point**	**Content**
Microadenoma	after 12 months	– hormonal evaluation – sellar MRI	– initially after 24 and 36 months – further controls according to individual – assessment (discuss length of intervals)	– hormonal evaluation – sellar MRI
Macroadenoma without contact to structures of the anterior visual tract	after 6 months	– hormonal evaluation – sellar MRI	– annual re-evaluations over 3 years (i. e., 4 controls in total, incl. initial control) – further controls according to individual assessment (discuss length of intervals)	– hormonal evaluation – sellar MRI
Macroadenoma with contact to structures of the anterior visual tract	after 3–6 months	– hormonal evaluation – sellar MRI – ophthalmologist	– annual re-evaluations over 3 years (i. e., 4 controls in total, incl. initial control) – further controls according to individual assessment (discuss length of intervals)	– hormonal evaluation – sellar MRI – ophthalmologist
For the approach in pregnant patients, refer to **Chapter 9** and specifically to **Section "Pregnant Patients"**.				

Short-term postoperative course (until about 6–12 weeks after surgery)

No.	Content	Consensus
7.4	Postoperative follow-up **shall** be closely monitored and performed according to local multidisciplinary standards. If local multidisciplinary standards are lacking, the procedure shown in (▶ **Fig. 1**, ▶ **Fig. 2** and ▶ **Table 6**) **can** be applied.	Strong
7.5	Within the first 3 months postoperatively, a detailed endocrinological follow-up **shall** be performed. Endocrinological laboratory tests **shall** include a morning-time measurement of TSH, fT4, fT3, cortisol, IGF-1, LH, FSH, as well as total testosterone (in men) or estradiol (in premenopausal women) in all patients. Secondary adrenal insufficiency **shall** be definitively excluded after 6 weeks at the earliest and 12 weeks at the latest, e. g., by suitable dynamic function test (see also **Recommendation 4.3**). If diabetes insipidus is suspected, the urine osmolality **should** be determined and, if necessary, a corresponding functional test **should** be performed.	Strong
7.6	In case of a proven insufficiency of the corticotropic and thyrotropic axes, treatment **should** be mandatory. For other pituitary hormone insufficiencies, a substitution therapy **should** be considered (see also **Recommendation 5.9**, **Recommendation 5.10**, and **Recommendation 5.11**). Regarding an adequate training of patients, see also **Recommendation 8.1** and **Recommendation 8.2**.	Strong
7.7	Provided that there is no obvious impairment and radiological follow-up by magnetic resonance imaging is performed regularly, ophthalmological follow-up examinations **can** be dispensed with if there is no radiological evidence of tumor contact with the visual path.	Strong
7.8	If postoperative pituitary function is sufficient, detailed biochemical diagnostics **should** be performed 1 year after surgery. If the results are again inconspicuous, further endocrine follow-up care **should** be terminated. If pituitary insufficiency becomes apparent, endocrine follow-up care **should** be carried out initially every 6 months and later on every 1–2 years for the rest of the patient's life.	Strong
7.9	A first MRI control **should** be performed 3–6 months postoperatively. If no residual or recurrent tumor is detected, the next MRI control **should** be performed 2 years after surgery. If the course is inconspicuous, the neuroradiological control intervals **should** then be further extended (to every 3 years, thus, re-imaging is done 5 and 8 years after the operation). If there is still no evidence of recurrence after 8 years of follow-up imaging, long-term follow-up imaging **should** only be performed every 5 years. If a residual tumor is detected in the first postoperative MRI control, further imaging **should** initially be performed annually for 5 years. If the results are stable, the control interval **can** then be extended (e. g., to every 2–3 years). In all cases, lifelong radiological follow-up care **should** be offered.	Strong
7.10	If a tumor recurrence or a relevant growth of postoperatively remaining tumor tissue is suspected, concrete recommendations for further procedures **shall** be determined (if possible, in a multidisciplinary case conference with endocrinological, neurosurgical, (neuro-) pathological, (neuro-) radiological, ophthalmological, and radiotherapeutical participation).	Strong
7.11	In case of stable long-term impairment of the visual function as well as missing residual/recurrent tumor, the necessity of regular ophthalmological follow-up **should** be evaluated. If new ophthalmological deficits occur or a possible tumor contact to the visual pathway is present (e. g., suspicious findings in a control MRI), an ophthalmological examination **shall** be arranged promptly. Depending on the long-term course of the disease, shorter or longer control intervals **should** also be considered, if appropriate.	Strong

Short explanation

In the case of hormone deficiency conditions that are already known preoperatively or have newly arisen in the course of the underlying disease, it is advisable to initiate appropriate diagnostics shortly after surgery in order to be able to adequately adapt or start a necessary substitution therapy. In the full version of this guideline (see Appendix) detailed considerations on diagnostic and therapeutic management of pituitary insufficiency are provided. Suggestions for postoperative diagnostics are summarized in ▶ **Fig. 1**.

Medium and long-term postoperative course

Regular follow-up examinations are necessary also in the long-term course. The individual control interval depends, e. g., on preoperative findings (i. e., tumor size, presence and extent of hormonal impairment), the surgical outcome (i. e., complete or partial resection), and the postoperative course.

Short explanation

Concrete recommendations regarding the ideal intervals of imaging controls are difficult to give due to the very limited data available so far. ▶ **Fig. 2** provides an orientation.

According to current data, recurrence is observed in 10–33 % of cases after pituitary surgery alone, whereby the risk is significantly lower if no residual tumor tissue is detectable in the postoperative MRI.

The contents of long-term ophthalmological follow-up care basically correspond to the recommendations for ophthalmological diagnostics in the short-term postoperative course, and are therefore not discussed here in detail.

Follow-up care after radiotherapeutic interventions

No.	Content	Consensus
7.12	After radiotherapy, regular radiotherapeutic follow-up involving magnetic resonance imaging **shall** be performed.	Strong
7.13	After radiotherapy of hormone-inactive pituitary tumors, endocrine follow-up **should** be performed throughout the patient's life. The intervals of the ophthalmological follow-up **should** be determined individually.	Strong

Short explanation

For Germany, the obligation for permanent radiotherapeutic aftercare by a competent and expert physician results from German law and regulations (e. g., the Radiation Protection Act and the current guideline "Radiation Protection in Medicine") and serves for quality assurance of the radiation application. Therefore, after radiotherapy, a life-long clinical radiotherapeutic follow-up care has to be performed.

Pituitary axis insufficiencies usually occur with a considerable latency to radiotherapy, the majority after 2–4 years; however, up to 30 % of post-therapeutic insufficiencies manifest significantly later than 5 years after radiotherapy. Long-term endocrine controls are, therefore, necessary. These are initially to be carried out every 6–12 months and may be extended over time, depending on the findings.

Likewise, radiogenic damage to the optical system may occur with a significant delay, although the overall incidence is very low.

Follow-up care of patients without previous pituitary surgery

Regarding the sole follow-up of non-functional pituitary adenomas only few prospective data are available, and many recommendations are therefore expert opinions. Guidance is provided by the published recommendations of the Endocrine Society [6]. Suggestions for assessment intervals for size-stable pituitary adenomas without endocrine abnormalities are given in ▶ **Table 6**.

No.	Content	Consensus
7.14	For microadenomas, endocrine follow-up **shall** initially be performed after approx. 12 months and then once a year for 3 years. In case of consistently inconspicuous findings, subsequent examination intervals are determined individually. For macroadenomas, endocrinological follow-up **shall** initially be performed after 3–6 months and then once a year for 3 years. In case of consistently inconspicuous findings, subsequent examination intervals are determined individually.	Strong
7.15	For microadenomas, radiological follow-up by MRI of the sellar region **shall** initially be carried out once a year for 3 years. In case of consistently inconspicuous findings, subsequent examination intervals are determined individually.	Consensus
7.16	For macroadenomas without contact to structures of the anterior visual path, radiological follow-up by MRI of the sellar region **shall** initially be carried out after about 6 months and then once a year for 3 years. In case of consistently inconspicuous findings, subsequent examination intervals are determined individually. For macroadenomas with contact to structures of the anterior visual path, a radiological follow-up by MRI of the sellar region **shall** initially be carried out after about 3–6 months and then once a year for 3 years. In case of constantly inconspicuous findings, further examination intervals are individually determined.	Strong
7.17	In case of radiological detection of pituitary tumors with contact to or compressing the optic tract, a visual field examination and, optionally, an optical coherence tomography (OCT) **shall** be performed as an obligatory procedure. In patients with a pituitary lesion that does not reach the structures of the visual system and who regularly receive follow-up care by MRI imaging, an ophthalmological examination **can** be dispensed with.	Strong

Short explanation

Frequently, pituitary microadenomas are not accompanied by any relevant clinical or biochemical alterations. In contrast, a clinically relevant restriction of pituitary function was described in macroadenomas (including the gonadotropic axis in about one in three women and up to 40 % of men). Data regarding the ideal imaging intervals for pituitary adenomas are limited. Upon initial detection of a macroadenoma, sellar imaging is to be induced in the long term, as tumor growth within 4–5 years occurs in up to 50 % of cases. In addition, pituitary apoplexy within 5 years is observed in about 10 % of cases [24].

Some authors recommend neither radiological nor endocrine long-term follow-up in the case of incidental microadenomas < 5 mm [16]. Some members of the guideline committee are

of the opinion that in the subgroup of very small, clinically inactive microadenomas, follow-up is not absolutely necessary and, if the findings are stable in size, no further imaging is required after 12 months.

In the case of asymptomatic hormone-inactive macroadenomas, refraining from lifelong MRI controls needs to be discussed if size constancy is documented over a longer period of time. There is no evidence for or against imaging controls in the available literature. However, in case of impairment of the anterior optic tract, we recommend to continue the imaging control.

Consulting and Training of Patients

No.	Content	Consensus
8.1	Patients with non-functioning pituitary tumors (and also, if possible, their reference persons) **shall** be counseled regarding the characteristics by which a deficiency of vital hormones (e. g., cortisol, thyroid hormones, and ADH) and/or a syndrome of inadequate antidiuresis **can** be recognized and how they are treated.	Strong
8.2	If secondary adrenal insufficiency is suspected or has already been diagnosed, patients **shall** receive an emergency card and an emergency kit. In addition, these patients **should** be trained (ideally together with a reference person) using structured training and treatment programs (with regular repetition throughout the course of the disease)	Strong
8.3	Patients with non-functioning pituitary adenomas **shall** be provided with relevant medical documents (e. g., discharge letter, investigational reports). Patients (and also, if possible, their reference persons) **shall** be informed by the responsible medical staff that further treatment in a center or practice specialized in pituitary diseases is advisable.	Strong
8.4	Patients with non-functioning pituitary tumors (and also, if possible, their reference persons) **shall** be made aware of disease-related patient organizations (including self-help groups) by the responsible medical staff (e. g., physicians, endocrinology assistants).	Strong

Short explanation

Rare diseases are frequently recognized late or misinterpreted. It is therefore essential that all patients with pituitary macrotumors or former surgery or radiation of the sellar region (and their reference persons) are sufficiently informed about possible symptoms of pituitary insufficiency so that they consult an endocrinologist for diagnosis at an early stage if needed. As especially the failure of the corticotropic and thyrotropic axis is frequently able to lead to (life-threatening) complaints, education on these two conditions is most necessary. An emergency card allows for rapid identification of affected patients by healthcare professionals. In addition, in the first days and weeks after a surgical intervention in the sellar region, affections of the posterior pituitary lobe (including disturbances of the water balance) may occur.

Parallel to this guideline, a separate **patient brochure** has been produced, which addresses the specific aspects of the guideline and in particular patient education.

In general, it appears very reasonable that patients receive all relevant medical documents concerning their own medical history.

Support in self-management by a self-help group is a great relief for many patients.

Special Patient Groups

Patients with involuntary childlessness

No.	Content	Consensus
9.1	In case of an involuntary childlessness associated with a clinically non-functioning pituitary tumor and consecutive hypogonadotropic hypogonadism, involvement of a fertility center **should** be offered.	Strong
9.2	Prior to a planned pregnancy, surgical resection **should** be discussed in the case of tumors (especially if they are larger than 1 cm) that could potentially impair visual function during the course of the pregnancy. Patients who do not undergo pituitary surgery **shall** have regular ophthalmological examinations during pregnancy (at least every 3 months).	Strong

Short explanation

Hormone-inactive pituitary adenomas may cause cycle disturbances/amenorrhea, reduced libido and fertility and, consequently, involuntary childlessness. However, appropriate hormonal stimulation therapy is usually able to restore fertility.

Prior to a planned pregnancy it is advantageous to surgically resect hormone-inactive pituitary macroadenomas or large microadenomas, since tumors may grow during pregnancy. This applies especially to tumors that are located in relative proximity to the visual pathway. Without surgery, at least regular ophthalmological and, if necessary, radiological controls are to be arranged in order to detect a potential threat to the visual pathway as early as possible.

Pregnant patients

9.3	If there is a clinical need for imaging of the sellar region during pregnancy, this **should** be done by means of native magnetic resonance imaging. A contrast medium **should** only be administered in justified exceptional cases.	Strong
9.4	If surgery in the sellar region becomes necessary during pregnancy, it **should** be performed in the 2nd trimester, if possible.	Strong
9.5	During pregnancy, hormone parameters are often difficult to interpret. Before any hormonal evaluation of pregnant women, it **shall** therefore be determined whether the planned diagnostic test has any meaningful therapeutic consequences.	Strong
9.6	If a hormone-inactive pituitary tumor is present during pregnancy, thyroid gland levels **shall** be measured once per trimester, irrespective of any pre-existing thyroid pathologies. In case of pre-existing hypothyroidism, an immediate escalation of the levothyroxine dose is regularly required after confirmation of pregnancy, thereby addressing the increased thyroid hormone requirement and ensuring sufficient child development. If hypothyroidism is highly suspected and the laboratory findings are inconclusive, further diagnostics **shall** be applied (including determination of thyroid autoantibodies and thyroid ultrasound), followed by the initiation or adaptation of a substitution therapy with levothyroxine, if necessary.	Strong
9.7	While the substitution dose of hydrocortisone in case of known adrenal insufficiency usually does not need to be adjusted during pregnancy (at least in the first and second trimester), the dose **shall** be adequately increased during the birth process.	Strong

Short explanation

Diagnosis and therapy of pituitary adenomas in pregnancy are challenging. Typical physiological changes may complicate or delay the recognition of the underlying disease, while therapeutic options are limited.

The determination of prolactin and alpha-subunit in the context of pregnancy is generally not useful due to the physiologically elevated values in this scenario.

Contrast medium is usually not administered, since severe pathologies are often detectable without contrast medium and contrast medium-induced fetal damage may occur.

Since the volume of the pituitary increases during pregnancy (due to hyperplasia of the prolactin-producing cells), a relevant space requirement may develop. Consecutive symptoms may be (partial) pituitary dysfunctions and/or a chiasmal syndrome.

In the case of severe visual disturbances or the occurrence of a pituitary apoplexy surgical intervention may be necessary. The 2nd trimester is the most appropriate time for surgery, as fetal organogenesis has already been completed and compression of the vena cava during the procedure is not yet a probable complication (other than in advanced pregnancy).

If secondary hypothyroidism is suspected or already known, only fT4 is used to assess thyroid function or to determine the required substitution dose. The American guidelines recommend to measure total T4 that appears to be particularly useful if the fT4 values are implausible. However, total T4 is nowadays rarely available in Germany.

Patients with known adrenal insufficiency usually do not require an adjustment of the hydrocortisone substitution dose if the course of the pregnancy is uncomplicated; a slight dose escalation might be necessary in the 3rd trimester [25–27]. In the context of childbirth, however, an adequate dose escalation is essential.

Patients with relevant morbidity or frailty

9.8	Before any diagnostics in frail and multimorbid patients, it **shall** always be considered whether possible therapeutic consequences can be drawn. Before any surgery, a risk assessment **shall** be carried out.	Strong
9.9	Especially in (severely) obese patients the increased risk of cerebrospinal fluid fistulas **should** be considered postoperatively.	Strong
9.10	Patients with hormone-inactive pituitary tumors under therapy with platelet aggregation inhibitors or oral anticoagulants are at an increased risk of bleeding and require a special risk assessment and preparation before any surgical intervention. An early multidisciplinary exchange regarding the therapeutic procedure **should** always be aimed at.	Strong

Short explanation

To estimate the overall risk of general anesthesia, various scores have been used. One of the best known was proposed by the American Society of Anesthesiologists (ASA) [28]. By division of the physical condition into six groups, the so-called ASA classification allows a simplified risk assessment.

A special feature is the increased risk of cerebrospinal fluid fistulas in obese patients, which increases with higher body mass index.

For patients taking oral anticoagulants, general rules for surgical procedures apply. Multidisciplinary consultation and determination of the perioperative anticoagulation regimen is always to be sought. Preoperative discontinuation of oral anticoagulants and postoperative prophylaxis with low-molecular-weight heparins are generally appropriate. These recommendations are not specific to the perioperative management of patients with pituitary adenomas, but are derived from other (neuro-) surgical operations [29].

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Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. A detailed list of all reported potential conflicts of interests is given at https://www.awmf.org/fileadmin/user_upload/Leitlinien/089_D_Ges_fuer_Endokrinologie/089–002i_S2k_Diagnostik-Therapie-hormonaktiver-Hypophsenaddenome_2020–02.pdf

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