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The optimal surgical techniques for pituitary tumors

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In this paper, the currently used and well evaluated techniques for the surgery of pituitary tumors will be reviewed. Since the first surgical approaches to pituitary tumors more than 100 years have elapsed. Various surgical techniques have been developed, refined and standardized. Most of these tumors are to date treated via transsphenoidal approaches. Many pituitary adenomas, particularly, smaller, enclosed ones, can be completely excised and a selective adenomectomy is usually attempted. It leads to remission of hormonal oversecretion and also to recovery of pituitary function in many patients. The resection of pseudocapsule around the adenoma seems to improve the operative results further. Transcranial approaches, employing craniotomies, are still needed in some patients with pituitary adenomas and in many of those harbouring craniopharyngiomas. The operative techniques will be described and briefly commented. Moreover, the application and usefulness of several technical developments will be reviewed, such as the use of the endoscope, magnetic resonance imaging, fluorenscent dyes and neuronavigation. The use of the intraoperative Doppler probe, ultrasound and the value of intraoperative hormonal measurements will be briefly discussed. There is sufficient evidence that the best and optimal outcome in terms of tumor resection and correction of hormonal oversecretion as well as the lowest rate of complications are obtained in centers of excellence with sufficiently experienced, specialized surgeons and a high patient load.
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Introduction

For the majority of patients with pituitary tumors, surgery is still the initial treatment of choice to date [1,2]. Only in prolactinomas, it is accepted that medical treatment with dopamine agonists is the primary treatment. The operative techniques and strategies have undergone a century of developments and were paralleled by advances in imaging and also medical therapeutic options [3]. After complete excision of hormone secreting tumor tissue, the source of hormonal oversecretion is ideally eliminated or at least to the utmost degree reduced. Hardy coined the term selective adenomectomy and with it referred to the very targeted resection of only pathological tissues with preservation of the normal gland [4]. The operating microscope and the endoscope are both ideally suitable as adequate visualization tools to differentiate between normal and pathological tissues. Pituitary tumors are mainly pituitary adenomas, but of course, also craniopharyngiomas and other, much less frequent neoplasms within and adjacent to the sella region occur.

Transsphenoidal approaches to pituitary tumors

The vast majority of all space occupying pituitary tumors are to date approached and resected via the transsphenoidal route. Since the first transsphenoidal operation which a patient survived, more than a century has elapsed. However, only the introduction of the operating microscope and the use of the roentgenologic image intensifier paved the way for widespread use of this operation. The transsphenoidal approach has many variants, and includes direct perinasal, sublabial or paraseptal corridors with or without the use of a nasal speculum or dissection of the nasal mucosa. One disadvantage of the transsphenoidal approach is the deep and narrow working corridor. Specific instruments are needed, designed just for this kind of surgery. For visualization, to date, there are basically two options. One is the use of the operating microscope with which virtually all neurosurgeons are familiar since they need it for a huge spectrum of lesions and most intracranial pathology. The use of a nasal speculum is mandatory for transsphenoidal microsurgery. Alternatively, an endoscope can be used for visualization in which a speculum is usually not needed. Whereas the light source is localized outside of the head in microsurgery, in endoscopic surgery light source and lens are introduced into the sphenoid sinus and into the tumor cavity, respectively. With both visualization tools the sellar floor is identified. Apart from anatomical landmarks, there is always the option of intraoperative fluoroscopy or neuronavigation guidance, to ascertain proper orientation. Diamond drills are used to create access through the bone of the skull base and sellar floor. This is particularly cumbersome in patients with incompletely pneumatized sphenoid sinus or in young children, in whom the sphenoid sinus is not yet developed. In these instances, neuronavigation is certainly helpful. Through an incision or fenestration of the sellar dura, tumor resection is performed, usually by using curettes of various angles and sizes and microforceps. A generous exposure allows for adequate access and the opportunity to manipulate structures with microinstruments. Invasion of the cavernous sinus restricts very much the chance to resect a tumor completely. In microadenomas, the normal gland and the medial wall of the cavernous sinus are usually the adjacent structures. The usual intraoperative estimate of tumor resection in pituitary macroadenomas is the visualization and degree of descent of the arachnoid of the opticochiasmatic cistern. It might be covered by a thin layer of normal pituitary tissue. The Knosp-Scale allows for a preoperative assessment of the probability of parasellar invasive tumor growth based on magnetic resonance imaging [5]. This has prognostic significance for the chance to resect a pituitary tumor completely and consequently also to achieve endocrine remission in hormonally secreting pituitary adenomas [6]. In extrasellar expanding tumors like craniopharyngiomas resection of the clivus or the anterior skull base might be needed to obtain the ability to resect such tumors completely. With the introduction of the endoscope those, so called “extended” transsphenoidal approaches have been more and more deployed. When the most possible radical resection of the tumor has been accomplished, meticulous hemostasis is performed. One problem of this approach is the closure of the osseous defect of the sellar floor, particularly if cerebrospinal fluid (CSF) leaks and especially in extended transphenoidal approaches. There are several techniques described for the reconstruction of the skull base, including gelfoam, autologous transplants, like fat, fascia, or bone, fibrin glue, direct suturing, the use of a muco-periosteal flap, and others.

Practice points: *The transsphenoidal approach is ideally suitable for all intrasellar pituitary tumors and for those in whom the connection between the intra- and extrasellar tumor portions is sufficiently wide. Both, the operating microscope and the endoscope are perfect visualization tools for this operation. The term "extended" in this context refers to a larger skull base resection than simply the sellar floor. Extended approaches enlarge the spectrum of lesions via the transsphenoidal approach.*

Research agenda: *While the approaches themselves are fairly standardized, the ideal closure technique of the skull base defect is still a matter of controversy. It should be as simple as possible and reduce the number of CSF leaks to a minimum. Whether at all and for how long a lumbar drainage would be helpful in this context is also not yet fully elucidated.*

Transcranial approaches to pituitary tumors

Transcranial approaches are still needed for tumors which are mainly localized outside of the sella or if the sella turcica is inadequately expanded in respect to the size of the lesion. Standardized craniotomies are used, which are performed close to the skull base so that brain retraction is avoided. Depending on the localization of the tumor fronto-lateral, fronto-temporal (*pterional*) or basal midline craniotomies are performed. The drainage of cerebrospinal fluid and/or resection of sphenoid bone creates sufficient space to microsurgically dissect the carotid artery and is branches as well as the optic nerves and chiasm, respectively [2,7]. The arachnoidal planes within the optico-chiasmatic cistern are detached from the surface of the tumor. Usually, already at this stage an attempt is made to identify the infundibulum. Once the course of the major arteries of the anterior circulation is identified, the capsule of the tumor is incised and the lesion resected in a piecemeal fashion. One might be aware that the tumor capsule in pituitary is the compressed and flattened pituitary gland. There are several corridors through which the tumor can be dissected: between the ipsilateral carotid artery and the optic nerve, between both optic nerves, lateral of the branches of the carotid artery and through the lamina terminalis [8,9]. A careful dissection under direct vision and maintenance of anatomical cleavage planes seems crucial. The tumor may be traced posteriorly until the arteries of the posterior cerebral circulation are dissected. The authors prefer a pterional craniotomy for anteriorly located suprasellar lesions and a midline fronto-basal craniotomy with subsequent interhemispheric dissection for lesions that extend posteriorly to the clivus level. In the latter situation, the olfactory nerves need to be dissected and relieved from their arachnoidal sheets. In tumors with intraventricular extension, paramedian or medial frontal craniotomies may be needed which allow transventricular exposure and resection of the tumor or a restricted corpus callosotomy. In pituitary adenomas these are rarely needed. However, in individual craniopharyngiomas these are the ideal approaches since they allow intraventricular dissection under direct microscopic vision. The transcranial approaches allow a relative radical resection of the intracranial portion of a pituitary tumor. However, the major challenge is the risk of damage to the surrounding structures, such as blood vessels, the visual pathways, the infundibulum, pituitary gland and the hypothalamus. In craniopharyngiomas with huge extension into the 3rd ventricle, there is a significant risk of severe hypothalamic injury which has to be taken into account by preoperative planning of the possible degree of resection.

Practice points: *Most neurosurgeons are familiar with microsurgical transcranial approaches to midline lesions, such as pituitary tumors. The dissection needs to be careful and meticulous since cerebral arteries and cranial nerves are to be directly exposed and manipulated.*

Selective adenomectomy and recovery of normal pituitary function

Accurate differentiation of tissues is a prerequisite for selective resection of the adenoma or other tumors and for the preservation of the normal pituitary gland. Such a selective tumor extraction obviously alleviates intrasellar pressure without loss of endocrine function. Damage to the gland or infundibulum seems to be responsible for the development of hypopituitarism and central diabetes insipidus. In contrast to earlier studies, which only addressed deterioration or preservation of (frequently already deficient) pituitary function, more recent endocrinological functional studies document that improvement of previously impaired pituitary function may result as a sequel of selective adenomectomy. Interestingly, this recovery outnumbers by far the rate of new deficiencies caused by transsphenoidal operations [10–13]. Even the most sensitive functions, like growth

hormone secretion, can recover. Only in transcranial operations, pituitary function recovers infrequently and new losses of function occur in a substantial proportion of patients [12]. In craniopharyngiomas the prevalence and incidence of both, hypopituitarism and central diabetes insipidus are much higher than in pituitary adenomas.

Practice points: *With identification and careful handling of the normal pituitary gland and infundibulum, surgically induced hypopituitarism is a rare event. In contrast, in many patients restoration of normal intrasellar pressure is followed by at least partial recovery of pituitary function. To preserve the infundibulum and normal pituitary, respectively, in craniopharyngiomas is much more difficult.*

Research Agenda: *The factors which determine the potential of the normal pituitary to recover are as yet not perfectly clear.*

Enlarged adenomectomy and pseudocapsule dissection

Previously, mainly micro-curettes and tiny forceps were used to extract the tumor in a piecemeal fashion just like an internal decompression [1,2,14]. Many years ago, it was already noticed that many, but not all, pituitary adenomas are surrounded by a compressed, thin layer of normal pituitary tissue. Histologically, this tissue also referred to as pseudocapsule. It has been shown to contain sparse tumor cells [15]. Thus, also resecting this skin-like cover of the tumor promised to result in a more radical resection. The term "enlarged adenomectomy" refers to resection of a small rim of normally appearing pituitary tissue around the tumor cavity. Oldfield and Vortmeyer, first tried intraoperatively to develop and dissect the pseudocapsule around microadenomas of the pituitary in patients with Cushing's disease instead of their internal piecemeal removal [15,16]. However, the dissection around the pseudocapsule of tumor is also possible in larger tumors, although not in all tumors completely around the entire lesion. It seems that there is a slightly higher rate of intraoperative CSF leaks, but no higher threat to pituitary function as compared to selective piecemeal resections [17,18]. In parasellar invasion, the tumor is rather traced through preexisting perforations than by deliberately opening the cavernous sinus in a sharp and aggressive fashion [14]. The availability of radiosurgery has decreased the need to dissect vigorously within the cavernous sinus and risk an injury of the intracavernous carotid injury.

Moreover, in small tumors, which are not directly depicted even by most sophisticated magnetic resonance imaging, strategies were developed to search through an apparently normal pituitary gland that shows no obvious abnormality on the surface. An exposure of the entire pituitary gland, between both cavernous sinus, is needed in such situations. Oldfield [15] proposed linear, parallel, sagittal incisions throughout the entire gland after meticulous hemostasis has been achieved. This technique requires skill and experience, but is probably the most promising way to intraoperatively detect and resect minute tumors.

Practice points: *Obviously, an extended resection of pituitary adenomas, including a small layer of not obviously pathological tissue, increases the rate of surgical success in secreting pituitary tumors. Tiny tumors can only be found if the gland is sectioned systematically.*

Intraoperative imaging

A neurosurgical theatre with access to a magnetic resonance (MR) scanner allows acquisition of MR images during a surgical procedure [19]. Usually, in such instances, when the most radical or even total resection of a tumor is suspected intraoperatively, the operation is interrupted and images are obtained. The intraoperative MRI objectively reveals the extent of tumor resection, and in case of residual and resectable tumor tissue being depicted, and localize the residuel mass in the operative field and more radical resection ideally proven by further intraoperative MR-images (Table 1) [20–32]. Meanwhile, there are several studies from different expert centres throughout the world which have shown that intraoperative MR-imaging provides the advantage of not only improving the extent of pituitary tumor resection but also of increasing the amount of complete tumor excisions in primary and especially in re-do procedures (Fig. 1) [20,30,33–35]. The immediate intraoperative feedback may speed up the learning curve of the surgeons and serves as an excellent quality control. High field systems ($\geq$1.5 Tesla) provide a better resolution and thus allow a better depiction of structures, particularly in the parasellar space in comparison to low-field ($\leq$0.5 Tesla) systems [35,36]. It is obvious that the rate of

Table 1
Results of intraoperative high field MR imaging (1.5–3 T) on the extent of pituitary adenoma resection: A review of the pertinent literature.

Authors	Year	Field strength	Number of patients	Suspected residual tumor on iMRI	Eligible for further resection	Complete resection on further MRI	Total complete resection at end of procedure	Intraoperative MRI lead to further tumor resection
Nimsky C et al. [20] (Erlangen)	2006	1.5 T	n = 106	36 of 85 (42%) 21 of 21 (100%)	29 of 36 (81%) 8 of 21 (38%)	21 of 29 (72%) (Intended residual)	49 + 21 of 106 (66%)	29 + 8 of 106 (35%)
Meng XH et al. [21] (Beijing)	2011	1.5 T	n = 30	12 of 30 (40%)	10 of 12 (83%)	8 of 10 (80%)	18 + 8 of 30 (87%)	10 of 30 (33%)
Szerlip NJ et al. [22] (New York)	2011	1.5 T	n = 53	33 of 53 62 (62%)	28 of 33 (85%)	13 of 28 (46%)	20 + 13 of 53 (62%)	28 of 53 (53%)
Kuge A et al. [23] (Yamagata)	2013	High-field	n = 35	12 of 35 (34%)	3 of 12 (25%)	3 of 3 (100%)	23 + 3 of 35 (74%)	3 of 35 (9%)
Berkmann S et al. [24] (Erlangen)	2014	1.5 T	n = 85	48 of 85 (56%)	40 of 48 (83%)	19 of 40 (48%)	37 + 19 of 85 (66%)	40 of 85 (47%)
Fomekong E et al. [25] (Brussels)	2014	3.0 T	n = 73	30 of 73 (41%)	8 of 30 (27%)	8 of 8 (100%)	43 + 8 of 73 (70%)	8 of 73 (11%)
Li J et al. [26] (Nanjing)	2015	1.5 T	n = 30	12 of 30 (40%)	9 of 12 (75%)	6 of 9 (67%)	18 + 6 of 30 (80%)	9 of 30 (30%)
Sylvester PT et al. [27] (St.Louis)	2015	1.5 T	n = 156	112 of 156 (72%)	56 of 112 (50%)	13 of 112 (12%)	44 + 13 of 156 (37%)	56 of 156 (36%)
Serra C et al. [28] (Zürich)	2016	3.0 T	n = 51	35 of 51 (69%)	30 of 35 (86%)	18 of 30 (60%)	16 + 18 of 51 (67%)	30 of 51 (59%)
Zaidi HA et al. [29] (Boston)	2016	3.0 T	n = 20	8 of 20 (40%)	5 of 8 (63%)	4 of 5 (80%)	12 + 4 of 20 (80%)	5 of 20 (25%)
Netuka D et al. [30] (Prague)	2016	3.0 T	n = 105 n1 = 80 n2 = 25	38 of 105 (36%) 15 of 80 (19%) 25 of 25 (100%)	22 of 40 (55%) 12 of 15 (80%) 10 of 25 (40%)	9 of 22 (41%) 9 of 12 (75%) (Intended residual)	61 + 9 of 105 (67%) 61 + 9 of 80 (88%)	22 of 105 (21%) 12 of 80 (15%) 10 of 25 (40%)
Zhang H et al. [31] (Beijing)	2017	1.5 T	n = 137	45 of 137 (%33)	23 of 45 (51%)	19 of 23 (83%)	92 + 19 of 137 (81%)	23 of 137 (17%)
Hlaváč M et al. [32] (Günzburg)	2019	1.5 T	n = 111	78 of 111 (70%)	56 of 78 (72%)	10 of 56 (18%)	33 + 10 of 109 (39%)	56 of 111 (50%)

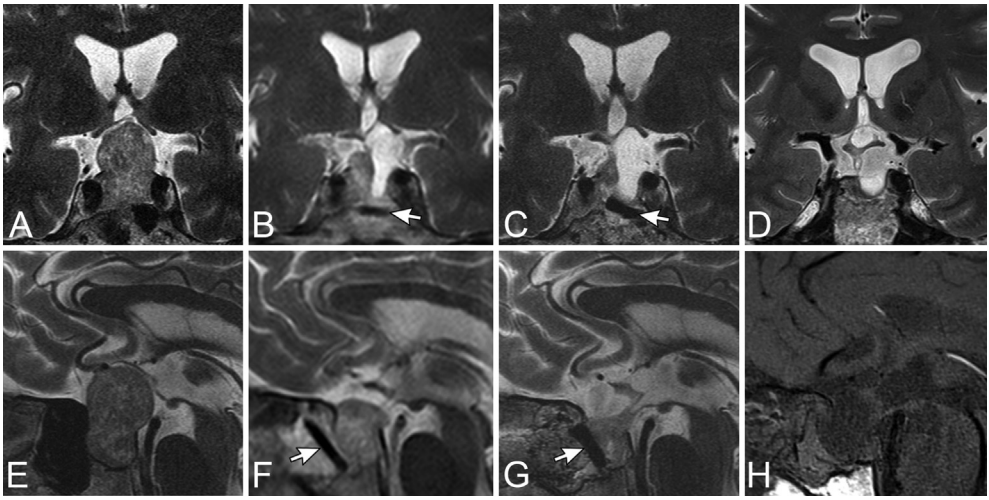

Fig. 1. An intra-, suprasellar non-functioning macroadenoma in a 68-year-old male patient with mainly visual deficits. Preoperative T2-weighted sequences in coronal (A) and sagittal (E) section shows that the chiasma was compressed by the tumor. The first intraoperative MRI was performed after satisfactory resection with the arachnoid descending to the sellar floor, and a small piece of bone wax (arrow) was placed on the arachnoid herniation as a marker. The residual tumor was demonstrated in the first intraoperative coronal (B) and sagittal (F) T2-weighted sequences, thus a further resection was indicated, followed with another iMRI. An intraoperative total resection was achieved according to the second intraoperative coronal (C) and sagittal (G) T2-weighted sequences. The 3-month follow-up MRI (D: T2-weighted in coronal section, H T1-weighted in sagittal section) confirmed the complete resection with descended chiasma.

complete resections reported depends on the selection of patients and cases [20,30,37]. In patients with hormonally secreting tumors, such as in acromegaly, the improvements are less impressive since "complete" MR guided and documented resections cannot be equated with normalization of hormonal oversecretion as defined by current guidelines [38]. In craniopharyngiomas, other factors than the depiction of residual tumor, i.e. the threat of hypothalamic injury, limit the resectability of these tumors. Whereas the intraoperative acquirement of the MR-images using high-field scanners only takes some minutes, sterile draping and also positioning the patient within the scanner additionally may prolong the surgical procedure. Generally speaking, the acquisition time is shorter the higher the magnet strength. Miniaturized intraoperative ultrasound probes and computerized tomography are alternative techniques for intraoperative imaging and estimation of tumor resection, but lack a high resolution. Caution is advised in the interpretation of intraoperative images, since the tumor cavity can be partially obstructed with blood, fluid or materials used for hemostasis [39]. The major disadvantages are the high cost for installation an intraoperative MR-system, shielding of the operative theatre and maintenance, which hitherto limited the widespread use of this technology [34].

Practice points: *Since magnetic resonance imaging depicts pituitary neoplasms with the highest resolution and for this reason is the standard diagnostic tool for pituitary tumors, it is obvious that also the extent of resection is ideally assessed intraoperatively with MRI. There are several setups available which offer reasonable protocols. The technology delivers immediate feedback about the degree of tumor resection and might speeds up the learning curve of the surgeon. The disadvantages are the high costs for acquisition and maintenance of the systems.*

Research agenda: *Develop and assess scanning sequences which allow to ideally differentiating between intratumoral hemorrhage and residual pituitary tumor. Improve head coil devices.*

Intraoperative visualization

The development of modern operating microscopes allows visualization of the deep-seated structures through the nasal tunnel with much better illumination and resolution [14]. However,

the introduction of the endoscope opened new dimensions [40]. Since the eye of the surgeon is virtually introduced into the sphenoid sinus or tumor cavity, a closer view, even better illumination and a more panoramic appreciation of the environment of the skull base is provided [41]. The surgeon's view is no more restricted by the straight beam of light and the blades of the speculum. Thus, particularly the lateral portions can be properly visualized and a direct insight into the cavernous sinus is possible. This advantage of the endoscope was utilized to refine Knosp's classification of parasellar tumor extension as related to invasion [5]. The endoscope can either be used for purely intraoperative visualization or as an adjunct tool in microscopic transsphenoidal surgery [42]. Whenever it is felt that the lateral, anterior or posterior visualization could be improved, it can be employed, in an "endoscope-assisted" operation. There is sufficient data, that more tumor tissue can be extracted and also the rate of complete tumor excisions increased, if the endoscope is used for such purpose [43]. The "second look" with the endoscope was more efficacious and thus useful in macroadenomas and less valuable in smaller tumors. Alternatively, purely endoscopic surgery can be performed without the microscope and a nasal speculum [41,44,45]. There are some disadvantages [46,47] and advantages. Excellent normalization rates in secreting pituitary adenomas have been reported in small and large patient series [6,30,48]. However, the few direct comparisons of microscopic and endoscopic surgeons sharing patients in centers of excellence did not reveal a significant difference in hormonal normalization rates or complications [42,49,50]. Since the endoscope allows almost unlimited visualization, "extended transsphenoidal approaches" were devised with extensive openings of the skull base, such as anterior fossa, clival and parasellar windows of access to intracranial tumor extensions [51–54]. The conventional contraindications for transsphenoidal approaches were thus challenged, but several technical problems still limit the widespread use of these approaches. One is the difficult reconstruction of the skull base, another one the relatively high rate of CSF fistulae and even more important the need of acquisition of specific skills with the endoscopic operation technique [55]. After all, instead of looking through the lenses of the microscope one sees the situs depicted on a screen [47].

Practice points: *Since paranasal sinus surgery is to date globally performed endoscopically, it seemed logical to employ the endoscope also for transsphenoidal surgery. Its use is well established. It offers a panoramic view and also insights into portions of the operative field which cannot be visualized with the operating microscope. The results reported in terms of tumor resection, normalization of hormonal oversecretion and complications match very well with transsphenoidal microsurgery. Endoscopic extended transsphenoidal surgery competes with transcranial operations.*

Flourescence optical imaging

Besides of visualization advances of normal and pathological structures with visible light based on developments of operating microscopes and endoscopes, recently there are efforts to additionally use fluorescence signal, which require specific light filters. The use of indiocyanine green (ICG), injected during the surgery, allows the identification of the carotid artery by a strong signal, at least, when the major artery is directly exposed, such as in parasellar invasive tumors [56]. Moreover, the normal pituitary enhances more than an adenoma, which might help with the differentiation of tissues [57]. After the injection of ICG there are time-dependent but clearly recognizable fluorescence intensity changes, which correspond to different tissues [58]. In another study, flourescein sodium salt (FNa) was used with the yellow 560 filter and proved useful to differentiate between pituitary adenoma, normal pituitary gland and particularly scar tissue [59]. In glioma surgery, the utility of 5-aminolevulinic acid (5-ALA), administered the day before the operation, is already established. This substance has net proven to be useful in pituitary operations [60]. A brilliant idea seems to be targeting receptors which the tumor expesses, with flourescent dyes. In a pilot study the folate receptor alpha (FRα) was labelled in operations of non-functioning pituitary adenomas [61]. A potential application could be the documentation of residual microadenomas, which is the weakness of intraoperative magnetic resonance imaging. The techniques of fluorescent optical imaging can be used in both, microscopic and endoscopic operations. However, there are some limitations in the use of the two fluorescence methods, such as the visibility requires exposure of the structures, potential allergic reactions, and a spectrum of possible interpretations which depends on the injection-to-visualization time [58].

Practice points: *Optical fluorescence imaging using special dyes is practically feasible during endoscopic and microscopic transsphenoidal operations. Depending on the agent, it might be used to directly visualize the carotid artery and help to differentiate normal and pathological stuctures within the sella region. However, it is still in an experimental stage.*

Research agenda: *The few reports that still only deliver preliminary data need to be confirmed in larger series and supplemented by outcome informations. It has still to be proven whether adenomectomy can be more selective and/or radical with or without the use of these techniques.*

Neuronavigation

Neuronavigation utilizes preoperative MR or computerized tomography (CT) images to guide the surgery in a three-dimensional (3D)-anatomical orientation. The more minimally invasive the procedures are, the less anatomical structures are available for intraoperative orientation [62]. Particularly in anatomical variants, such as a poorly pneumatized or ill-developed sphenoid sinus, vascular anomalies and especially during reoperations, where it lacks anatomical landmarks, any additional support is very much appreciated [63,64]. Defects in the skull base, scars and cisternal herniations are reasons, why re-interventions are technically more difficult [65]. The shape and location of crucial structures can be extracted from images, based on preoperative investigations and the localization within the real operative field can be confirmed by a pointer or superposition of the relevant contours (such as the course of the intracavernous carotid artery) (Fig. 2). Only little brain shift is expected at the level of the skull base. Thus, the locations as indicated by the system can be trusted once an accurate registration process of the preoperative dataset has been achieved [42,66]. Although, in contrast to intraoperative imaging, navigation systems cannot depict residual tumor, but it seems that they increase the comfort of the surgeon and the safety of the patient. There are complex lesions that only became surgically accessible since navigation systems are available [67].

Practice points: *Neuronavigation not only replaces intraoperative fluoroscopy, it also avoids radiation exposure within the operating theatre*, it. *It is essentially useful in transsphenoidal and transcranial operations*, *particularly if there is a lack of reliable anatomical landmarks or structural variants*. *The most sophisticated way of neuronavigation is augmented reality features.*

Research agenda: *The reliability of neuronavigation depends on the accuracy of the data*. *Thus*, *plausibility checks are mandatory*. *Which structures are ideally suitable during pituitary surgery and when the check procedure should be performed*, *is yet to be systematically determined*. *Moreover*, *there are no comparisons between different systems available*.

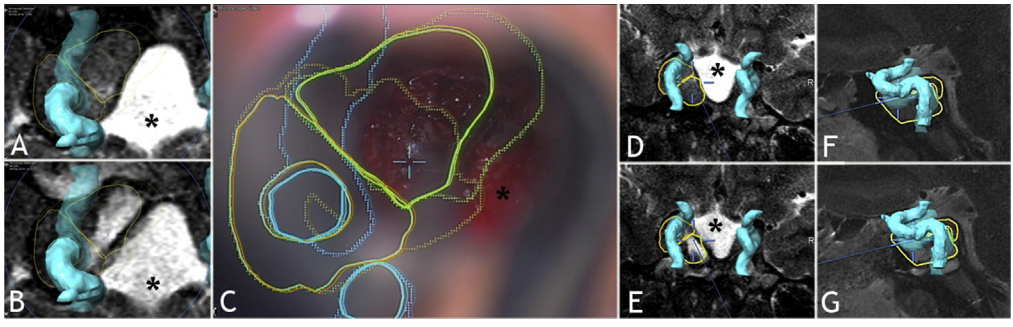

Fig. 2. Recurrent hormone secreting adenoma in a 43-year-old male patient with invasion of the left cavernous sinus. The 3D data set of the intraoperative MRI provides important information such as tumor volume (yellow: removable tumor, orange: cavernous invasion tumor), the course of the carotid arteries (blue), and the arachnoid herniation (asterisk). The microscopic depth view based on preoperative T2-weighted imaging (A) and intraoperative updated T2-weighted imaging (B) shows the complete resection of the removable tumor and partial of the cavernous invasion from the view of the surgeon. The intraoperative microscopic view (C) with the corresponding navigation reveals the surgical field and the intact arachnoid herniation. The standard neuronavigation in coronal section (D: preoperative T2-weighted, E: intraoperative T2-weighted) and in sagittal section (F: preoperative T2-weighted, G: intraoperative T2-weighted) demonstrated the anatomic relationship in standardized orientation.

Other technical gadgets

Although there are no specific ultrasound systems devised for transsphenoidal surgery, attempts have been made to scan the sella region with ultrasound systems positioned at the sellar floor level. Pituitary adenomas are mostly hyperechoic masses in ultrasound images. Some surgeons not only visualized the tumor itself, but also the interface with the normal pituitary. They also detected small tumors in patients with Cushing's disease with the ultrasound probe [68,69]. However, the inconsistencies of the findings, the difficult image interpretation, the relatively low resolution and the requirement of specific ultrasound skills, made this technique less popular in recent years [42]. Doppler probes are commonly used to localize the carotid arteries at the level of the sellar floor. They are considered extremely useful in reducing the risk of damage to the carotid arteries, particularly when the tumor infiltrates the cavernous sinus [70], since the carotid artery is mostly invisible by direct light [71].

Intraoperative hormone measurements

Since hormonal parameters determine remission or persistence in patients who undergo pituitary surgery for hormonally secreting pituitary adenomas, attempts were made to intraoperatively determine the decrease of oversecreted hormone with a short half-life, such as growth hormone (GH) and adrenocorticotropin (ACTH), respectively. The underlying pathophysiological concept is easy to understand in that with resection of all secreting tissue the tumoral source is supposed to be completely eliminated. In a successful operation, the respective hormones should drop to subnormal levels within 10 half-life periods. Abe and Lüdecke [72] reported on an impressive improvement of their surgical results in acromegaly with intraoperative GH determinations. However, Valdemarsson et al. [73] found different serum hormone half-lives between those patients with and without remission. Moreover, in several of their patients, they could not even calculate half-lives. Otani et al. [74] measured GH in blood samples before surgery, before tumor resection and thereafter, every 20 minutes and could only correlate remission and failure with the GH level changes at 20 minutes after the supposed tumor resection. Most authors admit that there are many technical and organizational problems with intraoperative hormone measurements. Mathematical models are required which, to a certain degree; predict the extent of resection based on two or several intraoperative measurements. The technique is time consuming and requires a specific setup with laboratory facilities and rapid GH or ACTH determinations. The surgeon has to wait for the results before he can draw conclusions whether to terminate or continue the procedure. Thus, the procedure has not managed to be included in the routine practice of pituitary surgery [42].

Practice points: *Some authors report more favorable outcomes in patients with acromegaly and Cushing's disease, respectively, if intraoperative determinations of growth hormone or ACTH were performed. The protocols extend the operation time significantly, since the surgeon has to wait for the results of hormonal determinations. The time required to document normalization is too long if the magnitude of the hormonal excess is high. Furthermore, it can only be executed in specific settings.*

Research Agenda: *Several factors with this paradigm are not perfectly clear. There are doubts that the half lifes of hormones secreted by pituitary tumors are identical. Moreover, mathematical models to predict later normalization from only the slope between two or a few measurements need to be developed.*

Intraoperative tissue assessment

The use of intraoperative tissue-based assessment to guide the resection of PA is still limited in the literature. Erfe et al. [75] evaluated the real-time ACTH concentration in the resected tissue during surgery by using ACTH-antibody assay in Cushing disease in 14 patients and revealed notable long term disease remission rate with 85.7% and acceptable long-term hormonal deficiencies with 29%. It provided a more accurate lateralization than preoperative MRI, but somehow prolonged surgical time and potentially sacrificed pituitary function by continuously tissue sampling. Martirosyan et al. [76] reported their experience with rapid intraoperative histological assessment by using confocal scanning microscopy for the guidance of further decision-making.

Currently, the operative options and indications have been carefully modified and standardized with consent worldwide. A more optimal surgical treatment would likely to be supported by revolutionary technology providing better localization, visualization, and oriented tumor elimination with minimal interference based on detailed studies in molecular and genetic levels.

Complications

As already mentioned, pituitary surgery bears the risk of both serious and less serious complications. Over the years, with more standardized techniques, improved equipment and with gained experience, the rate of complications has decreased, which certainly is a major advance. A survey, mainly conducted in the United States convincingly demonstrated the relationship between surgical experience of the individual surgeon and the rate of complications [77]. Selected series of experienced centers impress with low mortality and low cumulative complication rates [11,12]. However, insurance data from the United States seem to reveal the countrywide reality better, with also a dependency on the caseload of the center but much higher frequencies of untoward effects [78]. Thus, there is a real need to define centers of excellence [79].

Conclusions

MR-imaging, operative techniques, surgical equipment and strategies in pituitary surgery have undergone a dramatic improvement throughout the last decades. There are optimal techniques suitable for the various types of tumors. They depend on the size, localization, shape and nature of the tumor and on the experience of the individual surgeon with a specific technique. Ideally, the surgeon has all the technical equipment available and acts within an interdisciplinary team. The normalization rates in the treatment of hormone secreting tumors are convincing. Likewise, the complication rates decreased in recent years. Apart from the factors defined by the tumor, surgical experience and caseload play an important role achieving optimal results. There is still an ongoing technical development, that will certainly be further refined. Neuronavigation, intraoperative imaging and endoscopy will probably even gain increasing importance in the future.

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