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Clinical Article

Objective criteria for successful transsphenoidal removal of suprasellar nonfunctioning pituitary adenomas. A prospective study

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Summary

Background. Despite ample experience with transsphenoidal surgery, objective data on which suprasellar tumour expansion and growth pattern allows for radical adenoma resection are still sparse. Hence, we have performed a prospective study to establish the predictive value of tumour dimension and shape for the intra-operative descent of the diaphragma, the completeness of tumour resection and the outcome of patients harbouring pituitary adenomas with suprasellar extension.

Method. Included in the study were 105 patients with nonfunctioning pituitary adenomas and suprasellar extension who underwent primary transsphenoidal surgery between January 1998 and December 2005. The precise suprasellar extension, the degree of dumbbell-shape, the configuration of the adenomas and the depth of the pituitary fossa were evaluated. Completeness of resection was assessed by MRI at 3 months postoperatively.

Findings. The mean cranio-caudal diameter of the tumours was 28.0 mm (range 9.2–57.8 mm). On average, the suprasellar extension measured 11.9 mm (range 2.1–25.8 mm). Total removal of the suprasellar tumour was accomplished in 83% (87 of 105) of the patients. A second operation for residual adenoma was only indicated in 2 cases. The vertical intracranial extension was the strongest independent predictor of subtotal resection ($p < 0.001$). Irregular and multilobular configuration was a second highly-significant and independent predictor for incomplete resection ($p < 0.003$). In contrast, dumbbell-shape and shallow pituitary fossa were not independent predictive factors for incomplete tumour resection. The complication rate was very low. None of our patients suffered postoperative rhinorrhea, meningitis or visual deterioration.

Conclusions. One-stage transsphenoidal surgery allows total or near-total resection of most suprasellar pituitary adenomas with low surgical morbidity. Quantitative assessment of tumour dimension and configuration contributes to establishing guidelines for the selection of the appropriate approach and prediction of surgical outcome.

Keywords: Transsphenoidal surgery; nonfunctioning pituitary adenoma; suprasellar extension; outcome.

Introduction

Only 3 years separated the first transcranial operation of a pituitary adenoma by Victor Horsley in 1904 from the first transsphenoidal operation performed by Hermann Schloffer in 1907 [26, 30, 33]. Schloffer's patient died in the postoperative course from a suprasellar tumour remnant causing hydrocephalus. Schloffer admitted that he had underestimated the suprasellar extension (SSE) of the tumor [24, 34]. The competition between these principle operative techniques continued until the late 1960s. With the introduction of radiofluoroscopic intra-operative control and microsurgery by Guiot and Hardy, transsphenoidal surgery gained world-wide acceptance and recognition [13, 14, 26]. Today, the transsphenoidal approach is utilized in up to 99% of pituitary adenomas [1, 39].

Unlike in Schloffer's era, our decision in choosing the appropriate approach is facilitated by modern imaging techniques which provide precise definition of tumour extension and shape. With the advent of computerized tomography (CT) and magnetic resonance imaging (MRI), suprasellar adenomas were classified into grade A-D depending on the intracranial extension [28]. However, it has been suggested that it is not so much the size but rather the configuration that affects the selection of the appropriate approach. It has been proposed that suprasellar adenomas are amenable to transsphenoidal removal if they are symmetrical and rounded in shape and located strictly in the midline above an enlarged sella

turcica [12, 13]. A dumbbell-shaped adenoma, a multilobular adenoma, an asymmetrical SSE, an irregular shape and a normal-sized pituitary fossa with a predominant suprasellar portion are considered indications for transcranial surgery [7, 32, 36, 39, 40]. Such descriptive features of adenomas provide a basis for clinical decision-making. However, they represent endpoints of a continuous scale of tumour configurations rather than distinct tumour entities.

Despite ample experience with transsphenoidal surgery, objective data on which tumour expansion and growth pattern allows for radical adenoma resection are still sparse. To provide objective evidence for the usefulness of transsphenoidal surgery, we have evaluated pre-operative MRI and quantitatively assessed morphological features of adenomas with SSE. We have studied the feasibility of transsphenoidal removal, the radicality of tumour removal and the resulting morbidity in relation to SSE and shape in 105 patients with nonfunctioning pituitary adenomas.

Methods and materials

Patient selection

Between January 1998 and December 2005, 170 newly-diagnosed nonfunctioning pituitary adenomas were surgically treated by the first author at the Departments of Neurosurgery in Freiburg (before September 2004) and in Tuebingen. 165 patients (97%) underwent primary transsphenoidal surgery, while only 5 patients were primarily treated by craniotomy.

Pre-operative coronal and sagittal MRI scans were prospectively scanned (ScanJet 6100C/T; Hewlett-Packard, Palo Alto, CA) into a personal computer at a 180–200 dpi resolution. Postoperative MRI was routinely scheduled 3 months postsurgery and thereafter the patients presented at the outpatient neurosurgical department for re-evaluation. At the 3-month postoperative follow-up visit, coronal and sagittal postoperative MRI sections were again scanned and documented for the study.

One hundred and five patients out of 165 primary transsphenoidal cases with suprasellar adenomas presenting with complete postoperative MRI results at the 3-month follow-up visit, were eligible for the study. Clinical data and surgical complications were prospectively assessed. Each patient underwent pre-operative ophthalmological evaluation and re-evaluation 3 months after surgery.

Operative technique and surgical details

All patients were operated upon in the supine position with the surgeon standing behind the patient's head. Before 2001, a sublabial or pernasal transseptal approach was used. From 2001 onward, a direct transnasal approach was used ("septum pushover" technique). This technique was retained because it is less invasive and, in our opinion, far better tolerated by patients. The pituitary fossa was opened wide and the basal and lateral adenoma removed. Thereupon, the suprasellar tumour was expected to descend into the pituitary fossa. If the suprasellar tumour did not spontaneously enter the fossa, intracranial venous pressure was enhanced by increasing the end-expiratory venous pressure (Valsalva manoeuvre) up to 13–15 cm H_2O as tolerated by the patient. If this failed to bring the diaphragma into vision, bilateral jugular vein compression was applied. Extensive manipulations with surgical instruments above the sella entrance were avoided in every patient. Whenever the tumour cavity was not fully visible, the surgeon employed angulated mirrors or an endoscope (so-called endoscopy-assisted microsurgery). Removal of tumour above the sella entrance was only performed under direct vision. If a thin diaphragma sellae was observed after tumour removal, the sella was closed with fascia lata from the thigh. A prophylactic postoperative lumbar drainage was inserted and CSF was continuously drained over a 5-day period if an intra-operative CSF leak was encountered. Details of each surgical procedure were documented in the surgical report. In particular, the applied manoeuvres of removing the

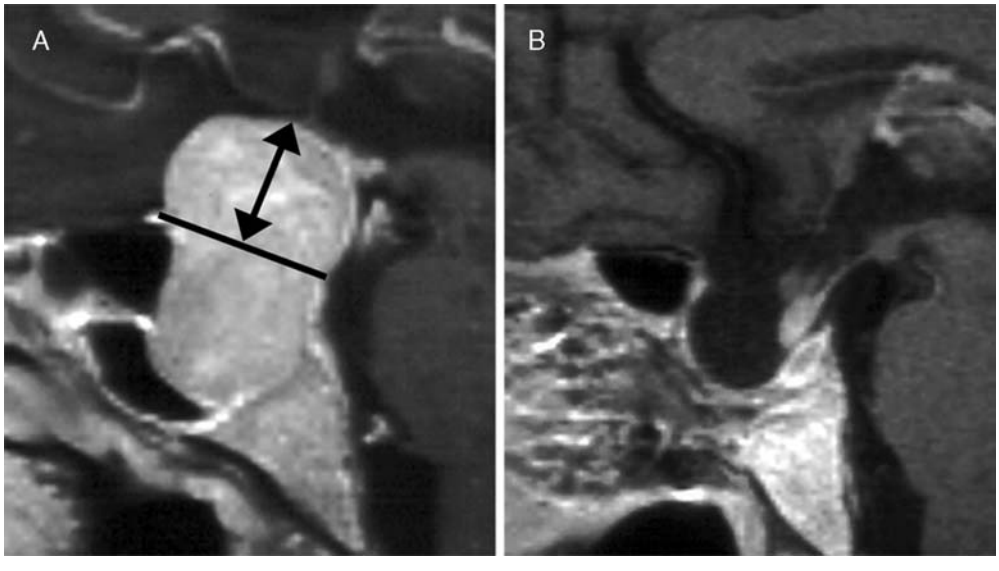

Fig. 1. (A) Pre-operative MRI of a nonfunctioning adenoma: Measurement of the suprasellar extension (SSE) on the midsagittal section. The line is drawn between the tuberculum sellae and dorsum sellae and delineates the sella entrance. The arrow depicts the SSE of the adenoma. (B) Postoperative MRI following transsphenoidal surgery

suprasellar tumour and the success from the surgeon's point of view were documented in each case.

MRI evaluation

Preoperative tumour extension was measured using an image-processing software program available in the public domain (ImageJ; National Institutes of Health, Bethesda, MD). The cranio-caudal size of the adenoma was measured. A line was drawn on the mid-sagittal image from the tuberculum sellae to the upper end of the dorsum sellae to define the sella entrance [31]. The maximal suprasellar extension (SSE) perpendicular to that line was measured on the midsagittal section (Fig. 1). The distance from the sella entrance to the floor of the pituitary fossa defined whether the sella was shallow or enlarged and excavated. Both the absolute depth of the pituitary fossa and the depth in relation to SSE were assessed.

The adenomas were evaluated for a constriction at the sella entrance or dumbbell shape. A narrowing may exist at the level of the sella entrance due to a small pituitary fossa, a short interclinoid distance or a narrow distance between the intradural carotid arteries (Fig. 2) [31]. The horizontal diameter of the adenoma at the level of narrowing and constriction was measured on midsagittal or coronal section and compared with the greatest suprasellar horizontal diameter (Fig. 2). The ratio (suprasellar diameter divided by smallest diameter at adenoma waist) was calculated. No narrowing was found if the ratio was equal to or below 1.

An independent neuroradiologist (U.E.) evaluated the tumour configuration. It was judged whether the suprasellar portion was monolobular, regularly shaped, symmetrical and rounded or whether it was multilobulated, asymmetrical, or irregular. Postoperative MRI was used to judge the extent of tumour removal (U.E.). Total removal was confirmed if no intrasellar or suprasellar adenoma was found on postoperative MRI three months after surgery. The evaluation was "blinded" without knowledge of operative details. Cavernous sinus invasion was found preoperatively in 21% of the cases (22 out of 105). As the study focused on removal of suprasellar adenomas, radicality of tumour removal from within the cavernous sinus was not addressed.

Fig. 2. Dumbbell-shaped nonfunctioning pituitary adenoma: The lower arrow depicts the measure of the tumour waist and narrowing. The upper arrow shows the measure of the maximal suprasellar horizontal diameter

Statistical analysis

Statistical analysis was performed with SPSS (Version 11.0 for Windows). The variables affecting the success at total tumour removal were assessed by a logistic regression analysis. A probability value of 0.05 was selected as denoting statistical significance. Multiple logistic regression analysis was used to determine which variables independently predicted total resection.

Results

The mean pre-operative cranio-caudal adenoma size was 28.0 mm (range 9.2–57.8 mm; median 26.8 mm). On average, the suprasellar extension (SSE) above the sella entrance was 11.9 mm (range 2.1–25.8 mm; median 11.4 mm). A rounded and smooth shape of the suprasellar portion was observed in 87 adenomas (Fig. 3). Eighteen adenomas exhibited an irregular or multilobulated suprasellar shape (Fig. 4).

In 87 out of 105 (83%) adenomas, the suprasellar adenoma was completely removed by transsphenoidal surgery. Radical resection was confirmed by postoperative MRI. Most residual tumours were minor in size. Eight of 18 (44%) residual tumours had completely descended to the floor of the pituitary fossa by the time of postoperative MRI and six minor residual adenomas were located at the level of the pituitary stalk and sella entrance (Fig. 4). Only 4 residual adenomas showed SSE. The suprasellar residual tumour necessitated transcranial surgery in only one patient. One other patient underwent transsphenoidal re-operation to remove a descended, but still significant residual adenoma with SSE. The remaining 16 patients with residual adenomas were kept under observation because of the small size of the remaining adenoma found on postoperative MRI.

Figure 5 shows SSE of the adenomas in relation to the manoeuvres required to remove the suprasellar portion. In the majority of cases, the diaphragma spontaneously descended into the pituitary fossa. All tumours with SSE below 10 mm were totally removed without additional manoeuvres. However, the diaphragma spontaneously descended in some cases with even greater SSE up to 22 mm. Valsalva manoeuvre and/or jugular vein compression allowed total removal in 20 additional adenomas. A 10-mm SSE turned out to be a suitable cut-off value, with a 100% predictive value of total removal below this cut-off level. An overlap of complete and incomplete removal is observed above 10-mm intracranial extension.

A second useful cut-off level is 20 mm SSE. In all adenomas with intracranial extension up to 20 mm, total or near-total descent of the diaphragma was encountered

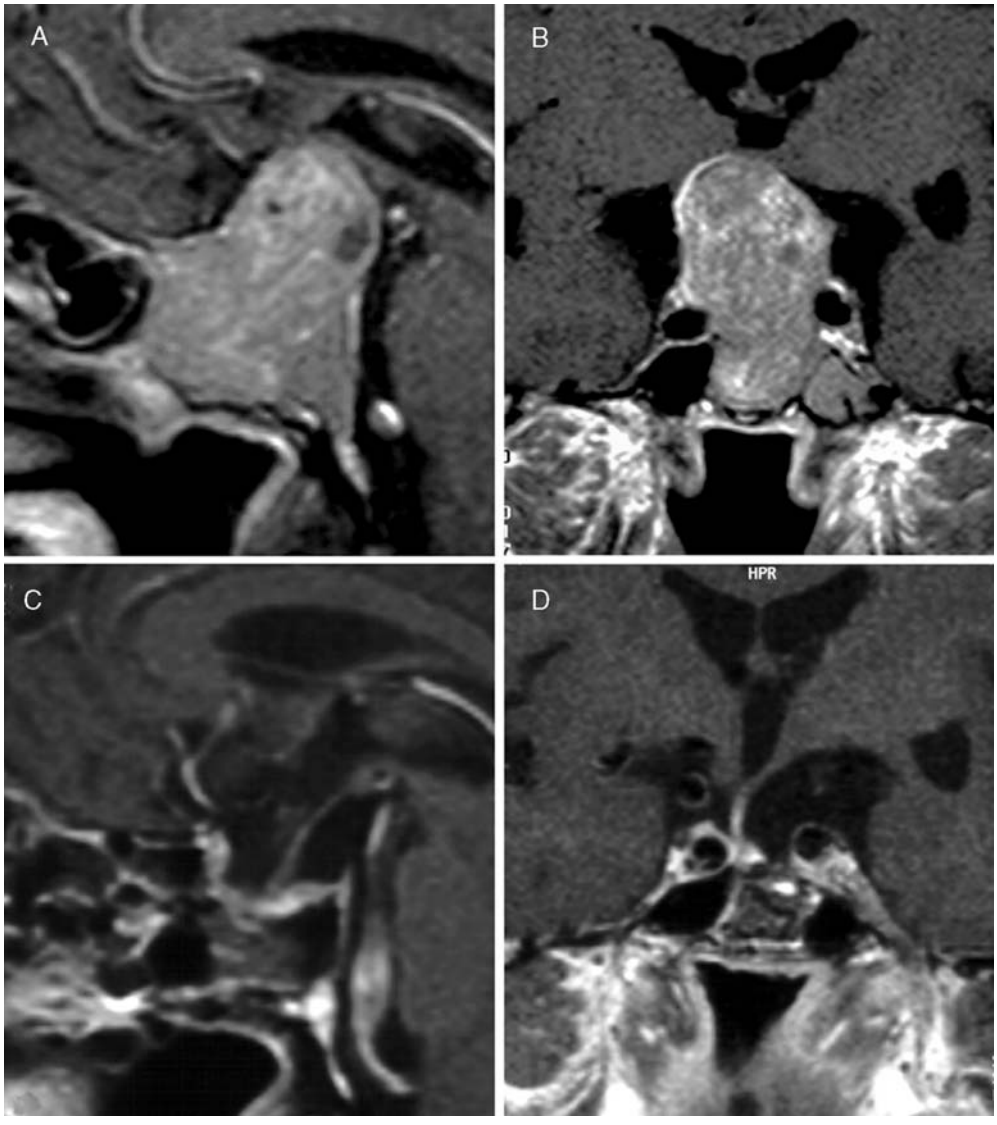

Fig. 3. Nonfunctioning pituitary adenoma with rounded and smooth suprasellar extension before and after transsphenoidal surgery. Pre-operative MRI: (A) Midsagittal view and (B) coronal view. Postoperative MRI (C) Midsagittal view and (D) coronal view showing total removal

intra-operatively (Fig. 5). SSE exceeded 20 mm in all 5 cases with obvious intra-operative evidence of partial resection due to incomplete descent of the diaphragma sellae.

SSE was the most significant independent predictor of surgical success. With increasing suprasellar expansion, the likelihood of radical removal decreased ($p < 0.001$).

In 9 cases, intra-operative findings and postoperative MRI were discordant with an intra-operatively totally descending diaphragma in the central part but evidence of a small residual adenoma on postoperative MRI. This finding suggests that a small residual adenoma remained in the lateral fold of the diaphragma (Fig. 5).

As shown in Fig. 6, irregular or multilobulated adenomas are less likely to be totally removed. Complete suprasellar removal was accomplished in 80 out of 87 (92%) symmetrical and rounded adenomas. All rounded adenomas with SSE up to 15 mm were successfully removed. In contrast, only 7 out of 18 (39%) irregular or multilobulated adenomas were totally removed. Irregular shape was a significant independent predictor of incomplete tumour resection ($p < 0.003$).

Figure 7 shows the correlation of SSE and degree of dumbbell-shape and narrowing at the level of the sella entrance. Dumbbell shape was correlated with SSE. Dumbbell shape was negatively correlated with total tumour resection in the univariate analysis. However, it

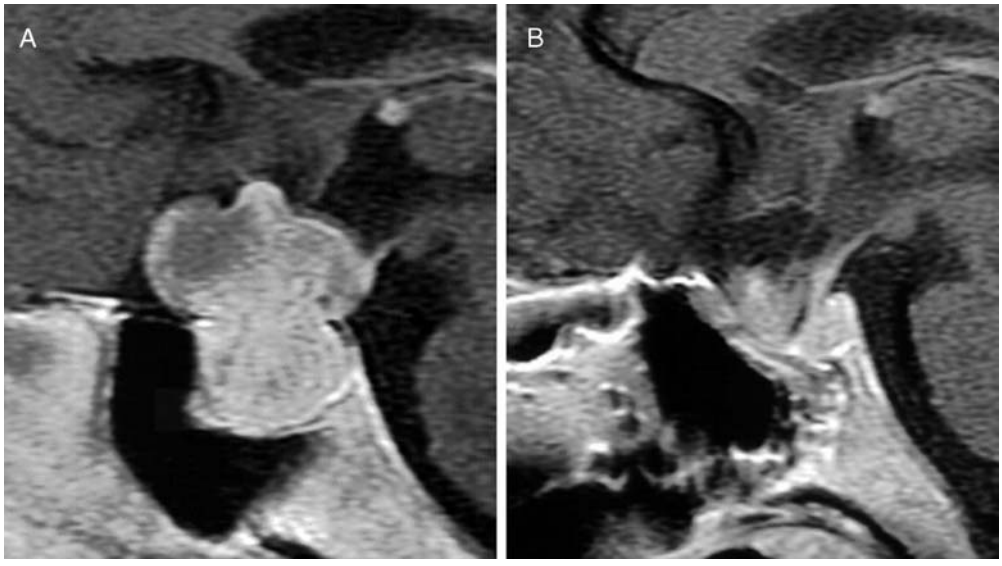

Fig. 4. Multilobulated nonfunctioning pituitary adenoma before and after transsphenoidal surgery. (A) Pre-operative MRI (midsagittal view). (B) Postoperative MRI (midsagittal view) showing residual adenoma at the sella entrance

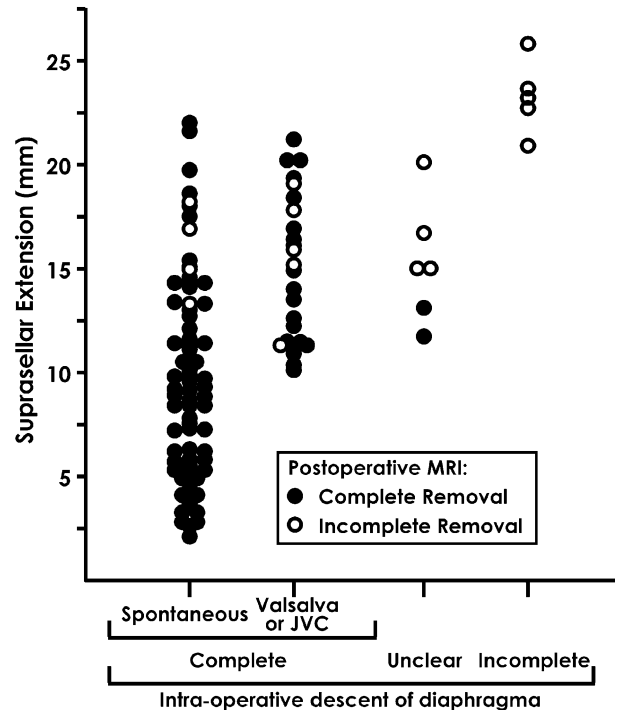

Fig. 5. The graph shows the correlation of suprasellar extension and intra-operative success of removing the suprasellar adenoma and forcing the diaphragma sellae into the pituitary fossa. JVC = Jugular vein compression

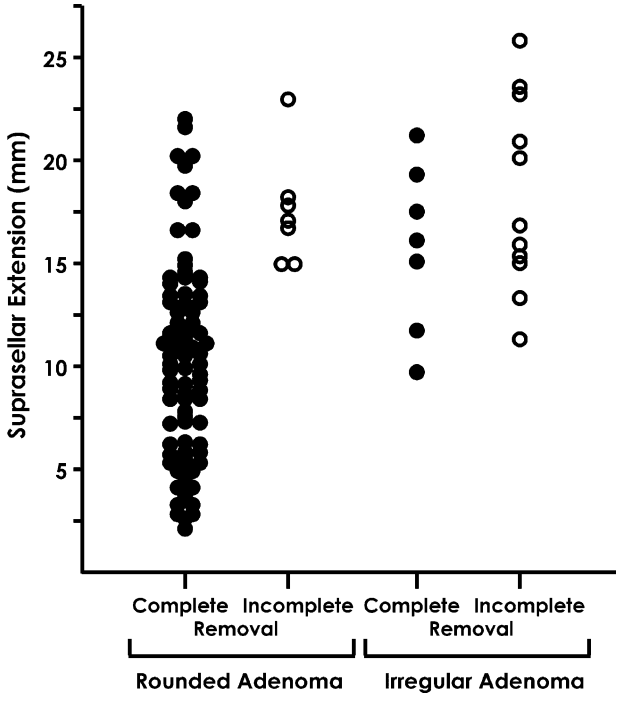

Fig. 6. The graph shows the extent of transsphenoidal tumour removal of rounded or irregular/multilobulated adenomas in relation to the suprasellar extension

lost its predictive value in the multivariate analysis. Similarly, a shallow pituitary fossa was no independent predictor of incomplete tumour resection.

The complication rate was very low. The surgical mortality was 0%. Two out of 105 patients had supradiaphragmatic bleeding observed during routine postoperative CT that did not require operative revision. One patient developed a wound infection of his thigh where fascia lata was removed for closure of the sella. No other complications occurred in our series. None of the patients

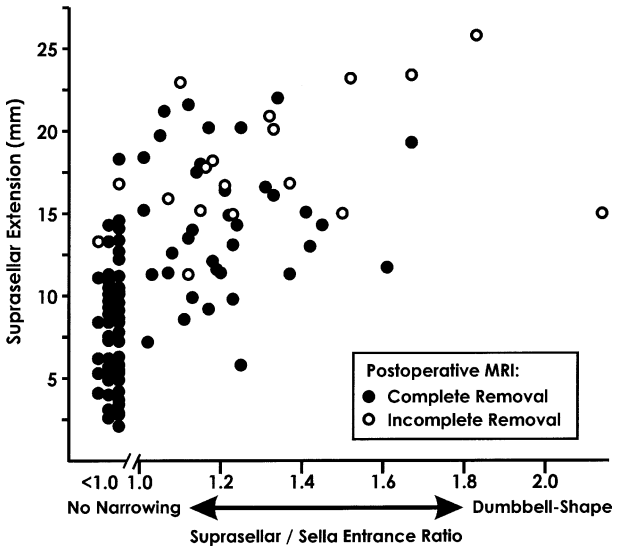

Fig. 7. The scatterplot shows the correlation of suprasellar extension and dumbbell-shape of nonfunctioning pituitary adenomas

suffered postoperative rhinorrhea, meningitis or visual deterioration.

Discussion

Frequency of using the transsphenoidal approach in pituitary surgery

Transsphenoidal surgery is the prevailing operative technique for removal of pituitary adenomas. Today, it is used in 96–99% of all cases [39, 40]. In Cushing's disease, the vast majority of patients harbour minute microadenomas and the transsphenoidal approach is indicated in virtually every patient [2, 35]. Similarly, patients suffering from acromegaly generally become symptomatic because of GH oversecretion. Most of the underlying adenomas are still relatively small in size and suitable for transsphenoidal removal [11]. With the introduction of dopamine-agonists (DA) in the early 1970s, medical treatment became the treatment of choice for prolactinomas [6]. In particular, a surgical cure is unlikely in macroadenomas with suprasellar extension (SSE). Consequently, DA therapy is preferred in large prolactinomas [29].

In contrast, nonfunctioning pituitary adenomas are often large in size at the time of diagnosis. They usually become symptomatic with symptoms due to a space-occupying lesion. Among presenting symptoms, a chiasmal syndrome prevails followed by endocrine deficiency. A chiasmal syndrome only occurs with a considerable SSE which usually exceeds 10 mm [18]. Therefore, surgical treatment of nonfunctioning adenomas is often challenging and a transcranial approach is required more often than in functioning pituitary adenomas [41].

The frequency of using the transsphenoidal or transcranial technique for nonfunctioning adenomas varies among different series [7, 28, 36–41]. It depends on patient selection but also on the preference of the surgeon and his experience with transsphenoidal or transcranial surgery. When looking at the literature, the indication for transsphenoidal surgery is generally descriptive and not based on quantitative and objective criteria. Furthermore, MRI studies confirming the rate of radical resection in suprasellar adenomas are sparse. Hence, we have performed a prospective study to establish the predictive value of tumour size and shape for the intra-operative descent of the diaphragma, the completeness of tumour resection and the outcome of patients harbouring suprasellar pituitary adenomas.

Predictive factors for removal of suprasellar adenomas

When discussing the limitations of transsphenoidal surgery, irregular or asymmetrical tumour shape is more frequently addressed than SSE [12, 32, 36, 40]. Our study confirms that not only the shape and configuration of a suprasellar adenoma but also the vertical intracranial extension is a significant predictor of completeness of tumour resection. The absolute intracranial extension was even a more significant predictor of surgical success than irregular or multilobulated shape of the adenoma. Adenomas with SSE have previously been divided into grade A (moderate SSE up to 10 mm), grade B (large SSE up to 20 mm), grade C (very large SSE up to 30 mm) and grade D (huge SSE in excess of 30 mm) [28]. In our study, all adenomas of grade A were readily removed during transsphenoidal surgery. In grade B adenomas, the diaphragma entered the pituitary fossa with complete or nearly-complete resection in all cases. With grade C adenomas, the risk of incomplete resection increased. A 39.5% risk of residual or recurrent adenoma has been described for grade C and D adenomas [28]. Our study demonstrates that Valsalva manoeuvre or jugular vein compression is often required to completely deliver the intracranial mass into the pituitary fossa if SSE exceeds 10 mm. Intracranial pressure is already increased due to supine positioning which is further enhanced by Valsalva manoeuvre and jugular vein compression [19, 28]. Hence, we do not use intrathecal injection of air or saline which might be indicated when operating in a semi-sitting position [32, 39, 41].

An irregular suprasellar adenoma and a multilobulated adenoma suggests perforation the diaphragma sellae or a very thin diaphragma. Our study shows that irregular and multilobulated suprasellar expansion is a second important independent predictor of incomplete resection. Despite the negative predictive value of irregular shape, our study supports the notion that even irregular and multinodular adenomas should be operated on first by transsphenoidal surgery. In 39% of these irregular cases, total removal was accomplished. A second operation was required in only 2 out of 18 (11%) irregular or multilobulated cases and was performed by a transsphenoidal and transcranial approach, respectively. Intending to avoid excessive suprasellar manipulations, we had no complications with transsphenoidal surgery in such difficult cases.

A dumbbell-shape might also prevent safe intrasellar delivery of the suprasellar mass [32, 36, 39, 40]. This can be true for rare adenomas with a perforated diaphragma sellae. More often, we see a dumbbell-shape due to the short interclinoid distance or the anatomically-narrow space between the carotid arteries (Fig. 2). Our study shows that a dumbbell shape is more pronounced with increasing vertical suprasellar expansion. However, a dumbbell shape is not an independent prognostic factor for incomplete resection. The study further provides evidence that the dumbbell shape is not a specific entity. We rather observe a continuous scale of constriction at the sella entrance (Fig. 7).

It has been claimed that the use of the transsphenoidal approach is also dependent on the size of the pituitary fossa [21, 36]. A normal-sized pituitary fossa is more frequently encountered in non-adenomatous lesions (i.e. craniopharyngiomas, hypophysitis) than in macro-adenomas [16, 17]. We rarely found a normal-sized pituitary fossa in our series of nonfunctioning macro-adenomas, and a shallow fossa was not an independent factor for incomplete tumour removal.

Fibrous and firm tumour consistency are also considered when discussing the appropriate approach. MRI signal intensity might provide information on tumour consistency [36]. Difficulty in removing fibrous adenomas by a transsphenoidal procedure has been reported in the literature [32, 36]. However, firm tumours might be equally resistant to radical transcranial resection. In our experience, the firm capsule sometimes facilitates the transsphenoidal removal of a fibrous suprasellar adenoma because it can be gently peeled off the diaphragma sellae after internal decompression of the adenoma.

Acute paranasal sinus infection, co-existence of pituitary adenoma and adjacent aneurysm and intrasellar ''kissing'' carotid arteries have been described as further indications for transcranial surgery [7, 40]. These circumstances are rare and were not observed in our series.

Techniques used in transsphenoidal surgery

We used a minimally-invasive procedure. While a transseptal approach was used earlier, the septal push-over technique has been gaining in acceptance and we have used it routinely since 2001.

Extended transsphenoidal approaches are increasingly described in the literature [8, 15, 22, 23, 27]. The disadvantage of the extracapsular approach to suprasellar tumours is the risk of meningitis and CSF rhinorrhea [9, 21]. We have therefore performed the extracapsular transtuberculum sellae approach only in supradiaphragmatic small non-adenomatous lesions and in two recurrent adenomas but not in the series presented here. Additionally, most of our tumors were large, which is a relative contra-indication for using the extracapsular transsphenoidal technique [21].

Staged operations with two or multiple transsphenoidal resections have been proposed [32]. However, re-operation was only required in 2 of our patients. The other residual adenomas were usually minor in size and were kept under observation given the slow growth rate often found in small tumour remnants [17].

The authors employ endoscopy-assisted microsurgery to visualize the suprasellar space in large adenomas and to visualize a non-descending diaphragma sellae or suprasellar residual tumour. Removal of suprasellar residual tumour under direct endoscopic view might have contributed to the low morbidity and avoidance of intracranial complications. Pure endoscopy has become an alternative to the microsurgical technique [4, 20]. A low morbidity has also been described when using the endoscopic technique [3]. There is still an ongoing debate, whether microscopy or endoscopy yields superior resection results. A comparative study with objective assessment of tumour expansion as done in our study could answer this unsolved issue.

Complications and outcome

Massive suprasellar expansion has been considered a contra-indication for a transsphenoidal approach [39]. Other authors recommend transsphenoidal surgery even in very large adenomas [41]. The morbidity and mortal-

ity is higher following transcranial surgery [9, 10, 37, 38]. In experienced hands, the complication rate of transsphenoidal surgery is low [5]. Takakura and Teramoto [38] found that initial transsphenoidal surgery improves outcome in huge pituitary adenomas. The impressive series of Jules Hardy with transsphenoidal surgery for giant pituitary adenomas demonstrates favourable results [28]. The transsphenoidal technique also had clear preference in our series of nonfunctioning adenomas. The morbidity of our series was very low with no case of meningitis or rhinorrhea. The success rate for total removal was favourable justifying a minimally-invasive transsphenoidal microsurgical technique even in the presence of large adenomas with major intracranial extension. Given the results of our study, we feel confirmed in our concept of performing an initial transsphenoidal procedure in huge adenomas even if a certain risk of subtotal or partial removal can be anticipated.

Conclusions

In conclusion, our study intends to provide objective criteria for predicting the success of transsphenoidal surgery. Quantitative assessment of tumour dimension and configuration contributes to establishing guidelines for the selection of the appropriate approach. Irregular and multilobulated shape and vertical suprasellar expansion are highly-significant and independent predictors for incomplete transsphenoidal removal of suprasellar pituitary adenomas. In contrast, shallow pituitary fossa and dumbbell-shape are not independent variables affecting the success of tumour removal. Given the high rate of radical removal and the low morbidity, transsphenoidal surgery is the favoured technique for initial surgery, even in the presence of major intracranial adenoma expansion.

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Comments

This is an interesting study in which the authors have evaluated in a prospective fashion shape and size factors of pituitary macroadenomas which influence the ability to remove the tumor. They reviewed 105 cases, of which 87 had complete removal of their tumor.

They note, not surprisingly, that the amount of suprasellar extension (SSE) was the most significant predictor of complete removal (especially greater than 20 mm). Multilobulated adenomas, those with irregular shape were also less likely to be removed completely. Dumbbell shape was negatively correlated with complete removal on a univariate analysis yet failed to be a significant statistical factor in the multivariate analysis.

While most of the results here are intuitive, this reviewer believes that it merits publication with some revision. The authors have developed a practical approach to looking at the MR appearance of the tumor and hence predicting complete removal.

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This is an excellent paper, that includes important information for the neuroendocrine neurosurgeon. The prospective study is well conducted, the manuscript is well written and the messages of the paper are very clear and supported by the results. The related literature is cited appropriately. The illustrations and graphs are easily to understand.

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