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The current role of transcranial surgery in the management of pituitary adenomas

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Abstract The aim of this study was to determine the factors influencing the use of a transcranial (TC) approach in pituitary adenomas and suggest a decision-making tree for the surgical strategy. The data for 23 (4.6 %) patients who underwent TC surgery from amongst 494 pituitary adenomas were retrospectively analyzed. Eight factors on magnetic resonance imaging (MRI) that could predict a difficult transsphenoidal (TS) surgery were noted. Adverse findings at TS surgery leading to a 2nd stage TC surgery were documented. Eighteen of the 23 cases were giant adenomas. Thirteen patients underwent TC surgery alone or as an initial approach when combined with TS while 10 underwent 2nd stage TC surgery following a TS approach. Most cases in the first group had 3 or more radiological factors in combination with a small sella. The 2nd group had higher sellar tumor volumes and fewer unfavourable radiological factors that led to the initial use of the TS approach. A hard, fibrous consistency or a significant residue obscured from the surgeon's view, and difficulty in hemostasis were additional factors prompting the use of a TC approach. Tumor excision ≥90 % could be achieved in 13 cases (56.5 %). Post-operative RT was administered in 12 patients. There were 2 deaths (8.7 %) and the major morbidity rate was 43 %. Despite advances in endoscopic surgery the TC approach may be required in 5 % of cases. A study of the preoperative MRI for factors that predict difficulty with the TS approach might encourage the surgeon to consider a TC surgery either as an initial approach or combined with a TS surgery.

Keywords Pituitary adenoma · Transsphenoidal · Transcranial

Abbreviations

TC	Transcranial
TS	Transsphenoidal
MRI	Magnetic resonance imaging
T4	Thyroxine
FTC	Free thyroxine concentration
TSH	Thyroid stimulating hormone
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
GH	Growth hormone
IGF-1	Insulin-like growth factor
OGTT	Oral glucose tolerance test
PACS	Picture archiving and communication system
ICA	Internal carotid artery
FLAIR	Fluid attenuated inversion recovery
CT	Computed tomography
ACoA	Anterior communicating artery
$ETCO_2$	End tidal CO_2
CSF	Cerebrospinal fluid
RT	Radiation therapy
SRT	Stereotactic radiation therapy
SD	Standard deviation

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Introduction

The goals of pituitary tumor surgery are adequate decompression of the optic apparatus and maximal resection of the tumor. The TS route achieves these goals effectively in the majority of cases with low morbidity and mortality and currently pituitary surgeons favour this route for the excision of pituitary adenomas [1–3]. With the advent of endoscopy, better instrumentation, angled telescopes and experience with the expanded endoscopic TS approach there has been a decline in the necessity for TC surgeries for pituitary adenomas in the last two decades. Previous indications for the TC route such as hour-glass tumors and fibrous tumors may not be indications anymore because of the versatility of the endoscopic approaches [4–6]. However, the TC route still has a role to play in about 1–10 % of primarily giant adenomas [1, 7, 8] and neurosurgeons who deal with large numbers of pituitary tumors annually may need to use this technique fairly frequently. Apart from giant adenomas that have universally been recognised to be difficult tumors from the standpoint of extent of excision, need for radiation and complications, smaller tumors with peculiar tumor anatomy may present difficulty during TS excision warranting an approach from above. Preoperatively, we study the MRI carefully for tumor anatomy and intuitively make a decision to operate either TS or TC but our preferred approach is the TS route. Zada et al. [4] seem to prefer the TS route in their analysis of 250 cases of suprasellar tumors consisting of pituitary adenomas, meningiomas, craniopharyngiomas and chordomas. They describe 13 cases in whom an open craniotomy was considered in the preoperative discussion but in whom a TS surgery was finally done or a craniotomy was required subsequently for a complication. They speak of eight factors that when taken into consideration preoperatively might predict problems with the TS approach and influence the surgeon to go trancranially as an initial procedure. These factors were: suprasellar extension beyond the floor of the third ventricle with edema in hypothalamus and intraventricular extension, lateral extension beyond the cavernous sinus, retrosellar extension, tumor consistency, brain invasion and cerebral edema, previous surgery and/or radiation therapy, involvement of the arteries of circle of Willis, and encasement of the optic apparatus or invasion of the optic foramina laterally. The presence of one or more of these factors resulted in an increased frequency of subtotal resection and/or complications. In this study, we reviewed the preoperative MRI and intraoperative findings in 23 cases from 494 pituitary adenomas in which the TC approach was utilized. We used some of the radiological features suggested by Zada et al. [4] along with extension of the tumor lateral to the supraclinoid ICA, asymmetric subfrontal tumor extension, a small sella in relation to entire tumor volume and diaphragmatic constriction of the tumor at its waist with the aim of reconstructing the decision-making tree that led us to employ the TC surgery alone or in combination with the TS approach.

Methods

Between January 2004 and August 2012 we operated on 494 pituitary adenomas. In this study, we include only those 23 patients (4.6 %), in whom TC surgery alone or staged with the TS approach was used in specific situations. The medical records of these patients were retrospectively analysed and biochemical data was obtained from the institutional computerised clinical results database. All patients were evaluated in the Neurosurgery and Endocrinology departments. Visual acuity and field charting were done by the Ophthalmology department with a Humphrey's Field Analyser, preoperatively and at each postoperative visit. Hormonal assessments included Thyroxine (T4), Free Thyroxine concentration (FTC), Thyroid stimulating hormone (TSH), Serum Cortisol, Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin and Growth hormone (GH) levels for all patients. For growth hormone tumors, normal IGF-1 (Insulin-like growth factor) levels corrected for age and gender and 1 h post-glucose suppression GH <0.4 ng/ml were used as remission criteria for acromegaly [9]. Tumor tissue was fixed in 10 % buffered formalin, routinely processed and embedded in paraffin. 5 μm sections were stained with hematoxylin and eosin and all tumors were immunostained for the full spectrum of pituitary hormones.

Radiological evaluation

Radiological images were reviewed from our Picture archiving and communication system (PACS) by a radiologist (SEM). All patients had preoperative MRI and the following features considered to be unfavourable for the TS route were noted: (1) Relative volume of the sella: The volume of the tumor was calculated on contiguous post-gadolinium MRI sections by outlining the tumor on all slices that showed the tumor and the sum of the areas was calculated. This was multiplied by the slice thickness. The cases that had imaging from elsewhere were scanned into the PACS system and a similar process of calculating the volume was followed. The sellar volume was calculated separately and expressed as a percentage of the total tumor volume. The preoperative tumor volume could not be assessed in 1 patient. (2) extension of the tumor lateral to the supraclinoid internal carotid artery (ICA), (3) asymmetric subfrontal tumor extension, (4) tumor reaching the foramen of Monro, (5) encasement of subarachnoid

arteries, (6) tumor predominantly within the cavernous sinus, (7) diaphragmatic constriction of the waist of the tumor and (8) brain T2 FLAIR changes. In addition we documented tumor invasion into the sphenoid and ethmoid sinuses and into the clivus.

Our postoperative imaging policy was to do a plain axial computed tomography (CT) and contrast coronal scan at 1 week and an MR image at 3–6 months that was repeated annually thereafter. In those patients in whom a substantial residue was left behind in the cavernous sinus and in whom no further surgical excision was planned the extent of excision was based on the CT scan and the patient referred for radiotherapy. Extent of excision was classified as radical when there was no evidence of residual tumor on the post-operative imaging, subtotal when tumor residue was $\leq$10 % of preoperative tumor volume and partial when >10 % of tumor was left behind.

Surgery

We prefer the TS approach for pituitary adenomas. The 494 patients underwent 507 procedures; an endoscopic assisted microscopic TS surgery was done in 314 cases. We changed in 2009 to a complete endoscopic TS technique and have done 183 cases thereafter. Twenty-three patients underwent TC surgery alone (10 cases) or in addition to TS surgery (13 cases). Transcranially, the pterional route was most commonly used, but more recently we have favoured the medial subfrontal approach. Dolenc's epidural approach [10] was used for tumors with a predominant component in the cavernous sinus.

Operative technique of the medial subfrontal approach

Under general anaesthesia the patient is positioned supine with the head fixed in a Mayfield clamp, extended to allow the frontal lobe to fall away from the anterior skull base and with no head rotation. A right frontal craniotomy including the supraorbital rim and extending to the midline is done. The orbital roof is rongeured to increase the basal exposure. The dura is opened in a curvilinear fashion close to the base and CSF released from the lateral sylvian fissure following which the right frontal lobe is retracted after freeing the olfactory tract from the orbital surface of the frontal lobe. An anterior interhemispheric dissection enables separation of the frontal lobes bringing the anterior communicating artery (ACoA) into view. Corridors to the tumor include the interoptic, optico-carotid or carotico-oculomotor spaces (Fig. 1). A safe technique for tumor removal entails remaining within the tumor capsule, that is, in the plane between the tumor and adenohypophysis thus ensuring that there is no damage to the arterial supply to the optic apparatus and hypothalamus. The brisk bleeding that is often encountered can be controlled with gelfoam and cottonoids.

Endoscopic transsphenoidal technique

Our endoscopic exposure is via both nostrils and we drill off the sella floor up to the edge of the ICAs on both sides but stop short of the tuberculum sellae. The dura is opened as a flap based superiorly and the anaesthesiologist, based on studies done at our institution, raised the intracranial pressure by elevating the $ETCO_2$ or injecting saline via a lumbar subarachnoid catheter [11, 12]. In two cases we used the extended endoscopic TS approach. The first was in a 70-year-old gentleman who had a 4.5 cm non-functional pituitary adenoma with a large subfrontal extension in the interhemispheric fissure (Fig. 2a) with no asymmetric extension onto the sides. We were able to achieve a radical excision (Fig. 2b). The second was in a 33-year-old man in whom we found a highly fibrous tumor at an initial endoscopic TS approach (Fig. 2c). Although our intraoperative impression was that of a radical excision, we were not entirely sure, as a fold of arachnoid bulged into the field from anteriorly. His vision did not improve postoperatively and the immediate postoperative MRI showed a substantial residue superiorly (Fig. 2d). Since the residue was in the midline we did an extended endoscopic approach at the same admission and were able to excise the tumor completely because of the expanded view at the second surgery (Fig. 2e).

The following complications were considered major post-operative morbidities: vision deterioration, hematoma/hemorrrhagic infarct requiring surgery, ocular motor nerve paresis, hydrocephalus requiring surgery and post-operative cerebrospinal fluid (CSF) rhinorrhoea. The decision on administration of adjuvant radiation therapy (RT) was based on the histopathology, size of the residue and progression of disease.

Results

There were 15 male and 8 female patients. The median age was 42 years (range 13–60 years). The commonest presentations were decreased vision (95 %) and headache (40 %). Less common presenting symptoms included altered sensorium, diplopia, apoplexy, diabetes insipidus, seizure, gait and memory disturbance, acromegaly, CSF rhinorrhoea and hemiparesis. 18 patients had severe visual impairment in at least one eye. Fourteen patients had preoperative hypopituitarism requiring hormonal replacement. Eighteen of the 23 cases had giant adenomas with maximum tumor diameter >4 cm. Hydrocephalus was seen in 4 patients of whom one required a preoperative

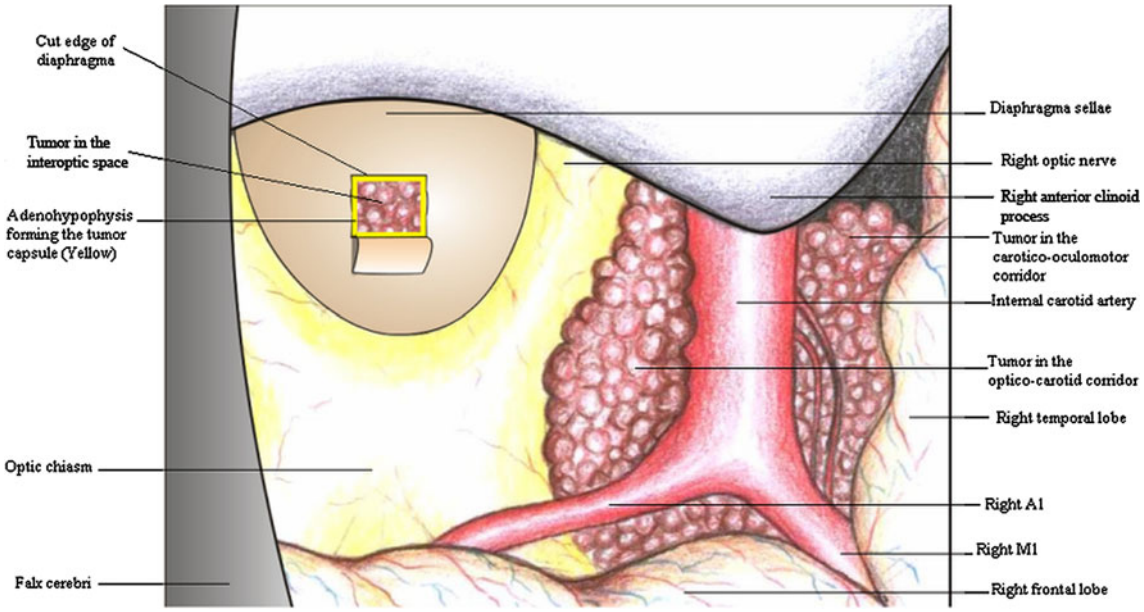

Fig. 1 This diagram shows the microscopic view following a right medial subfrontal approach. Note the diaphragma sellae lifted up by tumor in the interoptic space and the tumor seen after cutting the diaphragm. The adenohypophysis is seen as a thin layer under the diaphragma sellae, forming the capsule of the tumor. The tumor has invaded the diaphragm laterally and is presenting in the optico-carotid and carotico-oculomotor corridors

ventriculoperitoneal shunt. Eleven tumors were invasive. There were 9 gonadotroph adenomas, 7 null cell adenomas, 4 silent corticotroph adenomas, 2 growth hormone adenomas and 1 pituicytoma. MIB-1 labelling index ranged from 1 to 15 %.

Tables 1 and 2 are a detailed description of radiological and intraoperative findings in 23 cases that might be useful in predicting the need for a TC surgery versus a TS approach.

Transcranial surgery alone or as initial procedure when combined with transsphenoidal surgery

Ten patients were managed with a craniotomy alone and three had a subsequent TS surgery for tumor residue as a staged procedure. The mean maximum tumor diameter was 4.6 cm (SD 1.3 cm) and the mean tumor volume was 39.3 cm^3 (SD 21.6 cm^3). The mean sellar tumor volume was 2.6 cm^3 (SD 2.3 cm^3). The majority of these patients had at least three of the unfavourable factors for the TS route present, in fact 7 patients had four or more present. It is evident that the large tumor size in this group seems to predispose to the presence of more unfavorable factors, however the smaller tumors less than 30 cm^3, namely Cases 1, 2, 9, 11 and 13, demonstrated factors such as extension above and lateral to the ICA (Fig. 3a), vessel encasement (Fig. 3b), predominant location in the cavernous sinus (Fig. 3c) and T2 flair changes (Fig. 3d). Case 11 had a tumor volume of only 23 cm^3 but had an unusual suprasellar tumor configuration as it extended to the foramen of Monro (Fig. 4a). We felt that at TS surgery early decompression of the inferior half of the tumor would trap a significant volume of suprasellar residue between folds of arachnoid and therefore opted for the TC route. As a staged procedure the portion in the sella and sphenoid sinus were removed transsphenoidally and she underwent stereotactic radiation therapy (SRT) for the right cavernous sinus residue (Fig. 4b). Case 13 was a highly vascular pituicytoma in whom we chose the TC route because of the small sella. Retrospectively we found that there were T2 FLAIR hyperintensities along the left optic tract (Fig. 3d). There was no improvement in his vision and six months after the surgery his MRI showed a significant tumor residue that prompted us to attempt an endoscopic TS excision. Only a partial excision could be achieved, again on account of the vascularity and he was sent for RT. Case 7, a patient with acromegaly had a giant tumor (Fig. 5) with a small sella, a constriction of the tumor by the diaphragma sellae and extensions of the tumor to the foramen of Monro and lateral to the supraclinoid ICA. She suddenly deteriorated in the ward with altered sensorium and decreased vision suggestive of an apoplexy. She was operated transcranially as an emergency because we were not sure if we would be able to remove the entire tumor transsphenoidally through the small sella. At surgery, the infarcted tumor was completely excised and her postoperative MRI showed a 98 % tumor volume excision. Since her postoperative GH level was 11.2 ng/ml and IGF-1 level was 962 ng/ml she was

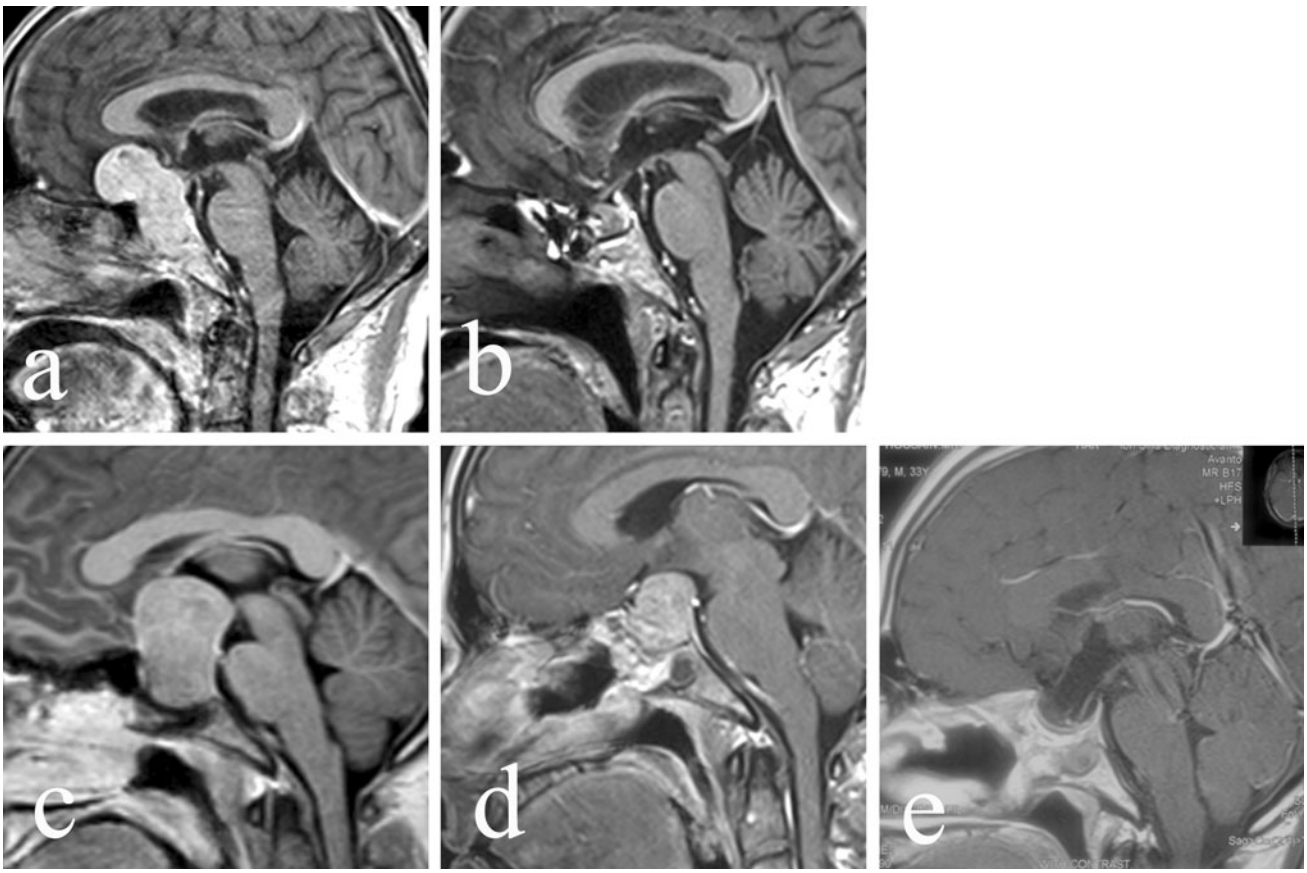

Fig. 2 **a** Gadolinium enhanced T1w sagittal MRI showing a 4.5 cm Hardy's grade D pituitary macroadenoma with subfrontal extension. **b** Post-operative contrast T1w sagittal MRI following an extended endoscopic TS surgery showing no residual tumor. **c** Gadolinium enhanced T1 w sagittal MR image showing a 4 cm Hardy's grade C macroadenoma, reaching the foramen of Monro. At an endoscopic transsphenoidal excision, the tumor was found to be highly fibrous and the postoperative image shows significant suprasellar residue (**d**). After a 2nd stage extended endoscopic approach the contrast T1w sagittal MR image shows no residual tumor (**e**)

advised postoperative SRT. Cases 2 and 3 had tumor predominantly in the cavernous sinus for whom a Dolenc epidural approach to the cavernous sinus was done. Only a 60 % excision could be achieved in both cases and they were given adjuvant RT.

There were two deaths in the immediate postoperative period in this group. One patient, Case 8 developed a right middle cerebral arterial territory infarct and Klebsiella sepsis. He also developed deep vein thrombosis and died secondary to possible pulmonary embolism. Case 9 had a silent corticotroph adenoma with tumor predominantly in the right cavernous sinus and infiltration through the roof of the cavernous sinus into the suprasellar and ambient cisterns (Fig. 6a). Although he had a large sella component we chose to go transcranially on account of the vessel encasement. We did a subtotal excision leaving behind tumor within the cavernous sinus and around the supraclinoid ICA. This patient developed a delayed subarachnoid hemorrhage (Fig. 6b) after being discharged from the hospital 2 weeks after surgery and died. The cause of death was presumed to be due to the aggressive nature of the tumor with infiltration into the major vessels.

Transsphenoidal surgery followed by transcranial approach

Seven patients underwent a staged TS + TC and three had concurrent TS + TC at the same sitting. The mean maximum tumor diameter was 4.5 cm (SD 1.4 cm) and the mean tumor volume was 34.5 cm^3 (SD 21.1 cm^3). The mean sellar tumor volume was 6.9 cm^3 (SD 5.3 cm^3). From Table 1 it is evident that the TC approach was performed in Cases 16, 17 and 18 because of an intraoperative finding at the initial TS surgery (highly fibrous tumor in two cases, bulging arachnoid folds obscuring suprasellar residue in one) and a postoperative hematoma in Case 19. Cases 14, 15 (Fig. 7) and 20 underwent unsatisfactory TS surgery as an initial approach requiring a TC surgery later. In retrospect, they had unfavorable radiological features for the TS approach namely, extension lateral to the supraclinoid ICA in Cases 14 and 15 and a small sella,

Table 1 Details of the 13 patients who underwent transcranial surgery alone or as an initial procedure when combined with transsphenoidal surgery

Case no.	Surgery	Sella volume as % of total tumor volume	Tumor volume (cm^3)	Sphenoid sinus/ ethmoid sinus tumor/ clival involvement	Tumor extension lateral to supraclinoid Internal carotid artery	Asymmetric subfrontal extension	Tumor extension up to Foramen of Monro	Encasement of subarachnoid vessels	Tumor predominantly in cavernous sinus	Waist sign	Brain T2 flair changes	Transsphenoidal findings	Final extent of excision and final outcome
1	TC	9	29	No	Yes	No	No	Right IC	No	No	No	–	95 %, HP, TCA
2	TC	7	25	No	No	No	No	No	Yes	No	No	–	61 %, DI, 6th nerve paresis, RT, TCA
3	TC	3	46	No	No	No	No	No	Yes	No	Yes	–	62 %, VW, 6th nerve paresis, VP shunt, SRT, TCA
4	TC	5	42	No	Yes	Yes	No	Right IC, MC, A1	No	No	Yes	–	77 %, VW, SRT, TCA
5	TC	2	82	No	Yes	Yes	Yes	Bilat A1 and A2	No	No	Yes	–	98 %, HP, DI delayed CSF rhinorrhoea repaired, RT, TCA
6	TC	2	68	No	Yes	Yes	Yes	Bilat A1	No	No	Yes	–	92 %, HP, S
7	TC	4	36	No	Yes	No	Yes	No	No	Yes	No	–	98 %, DI, SRT, TCA
8	TC	9	47	No	Yes	No	Yes	No	No	Yes	Yes	–	Subtotal, Died
9	TC	19	11	No	Yes	No	No	AChorA, PCoA	Yes	No	Yes	–	Subtotal, Died
10	TC	5	38	No	Yes	No	Yes	Bilat A2	No	No	No	–	Subtotal, EVD for transient hydrocephalus, no follow-up
11	TC + TS	43	23	Yes	No	No	Yes	Bilat A1	No	No	No	–	81 %, S, SRT, TCA
12	TC + TS	6	58	No	Yes	No	No	Bilat A1	No	No	No	–	100 %, HP, TCA
13	TC + TS	9	6	No	No	No	No	No	No	No	Yes	Pituicytoma—highly vascular	10 %, SRT, TCA

NA not available, *HP* new onset hypopituitarism, *VW* vision worsened, *DI* diabetes insipidus, *S* postoperative seizures, *RT* radiation therapy, *SRT* stereotactic radiation therapy, *EVD* external ventricular drain, *TCA* tumor control achieved, *AChorA* anterior choroidal artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery

Table 2 Details of the 10 patients who underwent transsphenoidal surgery followed by transcranial approach

Case no.	Surgery	Sella volume as % of total tumor volume	Tumor volume (cm^3)	Sphenoid sinus/ ethmoid sinus tumor/ clival involvement	Tumor extension lateral to supraclinoid Internal carotid artery	Asymmetric subfrontal extension	Tumor extension up to Foramen of Monro	Encasement of subarachnoid vessels	Tumor predominantly in cavernous sinus	Waist sign	Brain T2 flair changes	Transsphenoidal findings	Extent of excision, complications, adjuvant therapy and final outcome
14	TS + TC	NA	NA	No	Yes	No	No	No	No	No	No	Residue suprasellar	NA, RT, TCA
15	TS + TC	15	55	Yes	Yes	No	No	MCA, AChorA, PCA	No	No	No	Residue suprasellar	85 %, DI, 3rd nerve paresis, SRT, TCA
16	TS + TC	17	18	No	No	No	No	No	No	No	No	Fibrous tumor	100 %, TCA
17	TS + TC	22	50	No	No	No	No	No	No	No	Yes	Fibrous tumor	47 %, venous infarct operated,RT, no follow-up
18	TS + TC	17	52	Yes	No	No	Yes	No	No	No	No	Arachnoid pouch obscured suprasellar residue	98 %, DI, TCA
19	TS + TC	35	7	No	Yes	No	No	No	No	No	Yes	Postoperative hematoma	51 %; HP, VW, on follow-up
20	TS + TC	5	14	No	No	No	No	No	No	Yes	Yes	Suprasellar residue	90 %, TDI, TCA
21	Combined	45	33	Yes	Yes	Yes	No	Left A1	No	Yes	Yes	Significant subfrontal residue left side	90 %, HP, S, SRT, TCA
22	Combined	23	64	Yes	No	No	Yes	Bilat A1	No	No	No	Difficult hemostasis	96 %, meningitis repacking for CSF rhinorrhoea SRT, TCA
23	Combined	24	18	No	Yes	No	No	No	No	No	Yes	Significant suprasellar residue	37 %, HP, no follow-up

NA not available, *HP* new onset hypopituitarism, *VW* vision worsened, *DI* diabetes insipidus, *S* postoperative seizures, *RT* radiation therapy, *SRT* stereotactic radiation therapy, *EVD* external ventricular drain, *TCA* tumor control achieved, *AChorA* anterior choroidal artery, *PCoA* posterior communicating artery, *MCA* middle cerebral artery, *IC* internal carotid artery

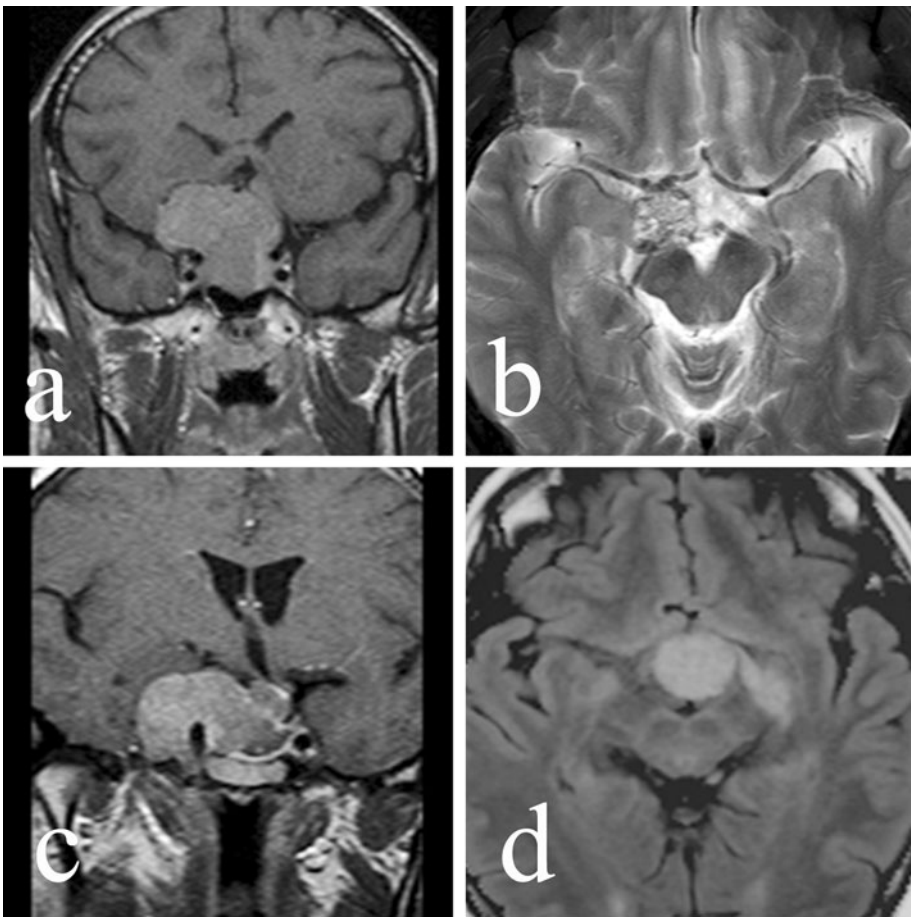

Fig. 3 **a** Gadolinium enhanced T1w coronal MR brain image of *Case 1* showing a 4 cm Hardy's grade D tumor with asymmetric suprasellar extension above and lateral to the right supraclinoid ICA. **b** T2w axial MR brain image of *Case 9* showing encasement of the right posterior communicating and anterior choroidal arteries. **c** Gadolinium enhanced T1w coronal MR brain image of C*ase 2* showing a 4 cm invasive macroadenoma with tumor predominantly in the right cavernous sinus, encasing the cavernous ICA. **d** Axial T2 FLAIR image of C*ase 13* showing edema in the left optic tract adjacent to the suprasellar tumor. The histopathology was reported as a pituicytoma

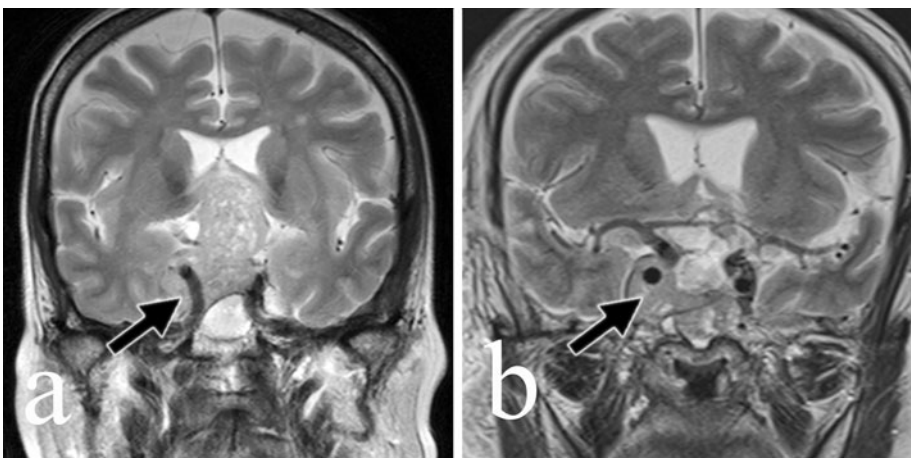

Fig. 4 **a** T2w coronal MR brain imaging of C*ase 11* showing predominant vertical growth of the tumor up to the foramen of Monro. Note the tumor invasion into the right cavernous sinus (*arrow*). **b** Post-operative T2 weighted coronal MRI showing residual tumor in the right cavernous sinus (*arrow*) for which the patient underwent SRT

diaphragmatic constriction and T2 FLAIR changes in Case 20. It may be argued that the TC surgery could have been done concurrently with the TS approach in these cases. Case 14 was 28 weeks pregnant leading us to choose the shorter TS approach as the initial procedure and a TC surgery after the baby was delivered. Cases 21, 22 and 23 were concurrent TS and TC surgeries in large tumors with 5 unfavourable factors in Case 21 and two each in Cases 22 and 23. All three had good outcomes.

Outcomes

Follow-up was available in 18 patients with a mean duration of 23.5 months. Tumor volume excision $\geq$90 % could be achieved in 13 of the 23 cases (56.5 %). The mean tumor volume excision rate was 77.2 % (SD 25.6 %). Vision improvement occurred in 13 patients (56.5 %).

Post-operative RT was administered in 12 patients (4-conventional RT, 8-SRT). Post-operative residual tumor

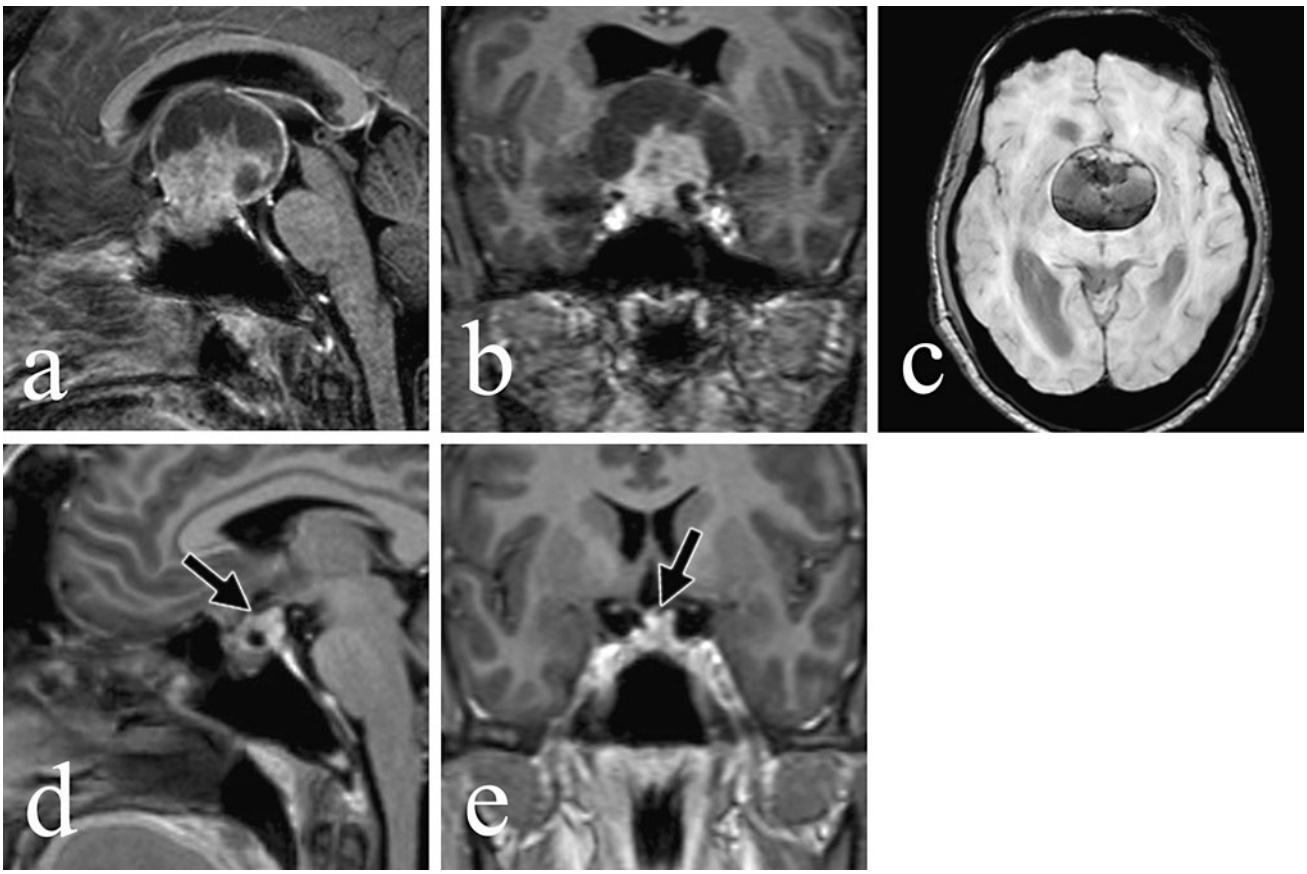

Fig. 5 Gadolinium enhanced T1w MR imaging sagittal (**a**), coronal (**b**), susceptibility weighted imaging sequence (**c**) of C*ase 7* shows a 4 cm giant adenoma with apoplexy in whom the sella was small. Follow-up MRI [T1w sagittal (**d**) and T1w coronal (**e**) with gadolinium] at 20 months, showed a small suprasellar residue (*arrows*). The histopathology showed an atypical sparsely granulated growth hormone secreting pituitary adenoma. The postoperative GH and IGF-1 levels were high and she underwent SRT for the residual tumor

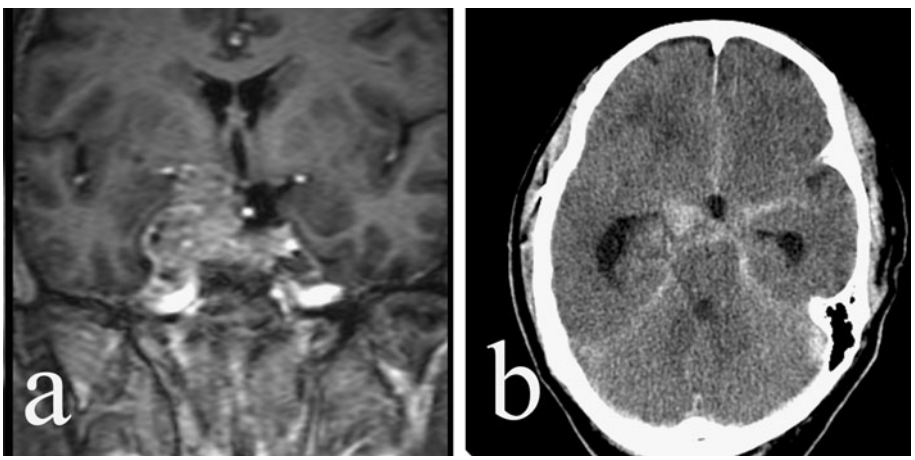

Fig. 6 **a** Gadolinium enhanced T1w coronal MR brain image of C*ase 9*, an invasive corticotroph adenoma, showing a 3.5 cm tumor predominantly in the right cavernous sinus and also encasing the right supraclinoid ICA after infiltrating through the roof of the cavernous sinus. **b** Two weeks postoperative plain CT brain showing a delayed subarachnoid hemorrhage—the patient died after a week

completely resolved after RT in 2 patients. At the last follow-up tumor control had been achieved in all patients. Both the functional tumors in this series were growth hormone secreting adenomas. We could achieve disease control in one patient (Random GH- 0.5 ng/ml with an age-sex normalized IGF-1 of 66.1 ng/ml). In the other patient

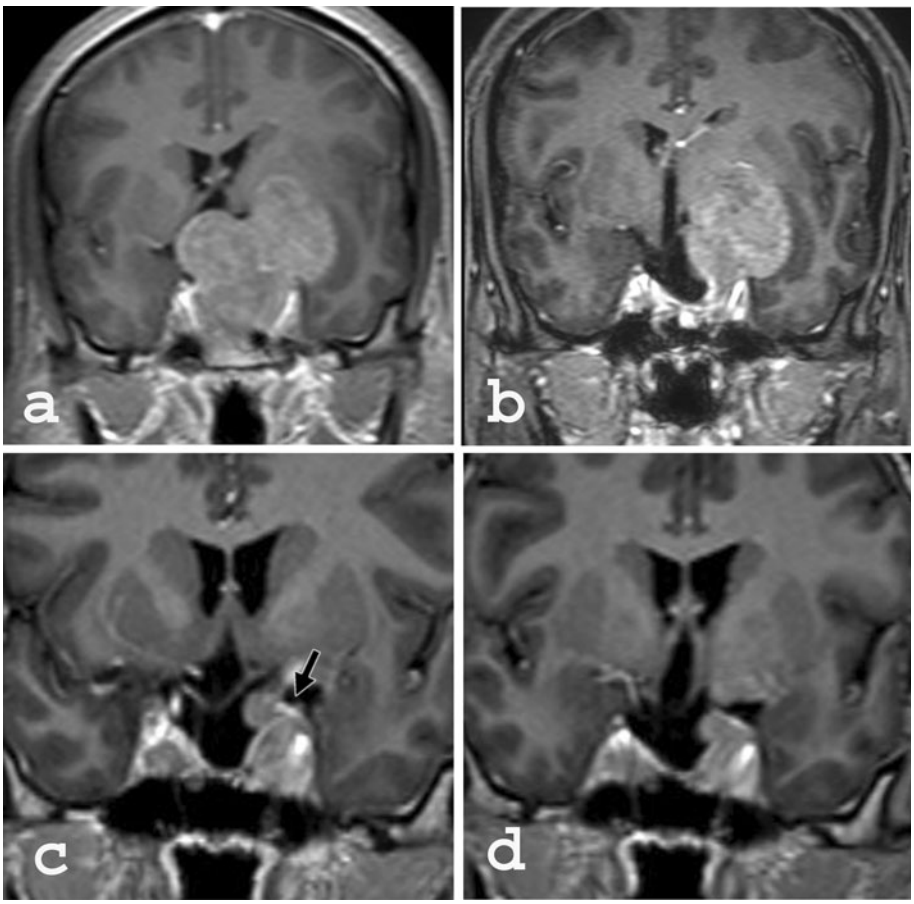

Fig. 7 This 37-year-old male (*Case 15*) presented with decreased vision in both eyes for 2 months. T1w gadolinium enhanced coronal MR image showing a 6 cm pituitary adenoma, volume 55 cm^3 with an asymmetric suprasellar extension to the left side (**a**). Three months following TS surgery and removal of the sella and suprasellar portions of the non-functional adenoma the T1w MR image with contrast showed residual suprasellar tumor on the left side—volume 35.8 cm^3 (**b**). The histopathology was reported as a gonadotroph adenoma. After a left frontotemporal craniotomy and excision of this residue the T1w contrast MR image shows residual tumor in the left cavernous sinus—volume 8.2 cm^3 (**c**). Note the tumor emerging from the roof of the cavernous sinus (*arrow*). He was given SRT and the MR image 6 months later shows mild reduction in tumor size (**d**)

the serum GH level reduced from a preoperative value of 149 ng/ml to 11.2 ng/ml at 24 months with a high concomitant IGF-1 level of 962 ng/ml. This patient underwent SRT for the small suprasellar residue (Fig. 4).

Complications

Both the mortalities were in the pure TC group. Major morbidity rate in our series was 43 %. Three patients had worsening of vision post-operatively. Two patients had 6th nerve paresis and one patient had 3rd nerve paresis that improved partially in all at the last follow-up. One patient needed repacking for immediate post-operative CSF rhinorrhoea and delayed CSF rhinorrhoea occurred 3 years following TC surgery and RT for a patient with a giant gonadotroph adenoma, which was successfully repaired transsphenoidally. Diabetes insipidus occurred in 6 patients, 2 of whom required long term replacements. Seven patients developed new onset hypopituitarism requiring replacement drugs. One patient required a ventriculoperitoneal shunt 3 months after TC surgery.

Discussion

Radiological tumor characteristics hindering a radical transsphenoidal excision

Small sella

Our findings indicate that we preferred to use the TC approach upfront when the sella was relatively small compared to the rest of the tumor. This might not be an absolute indication for a TC approach since it may be possible to extend bone removal across the tuberculum sellae and planum and get to the tumor above the diaphragma sellae [6]. For functional adenomas a combined approach is probably necessary to radically excise tumor in the sella regardless of sella size.

Tumor above and lateral to the supraclinoid internal carotid artery

Frequently tumors may extend lateral to the supraclinoid ICA as was seen in 14 of our 23 cases, a feature more common in but not limited to giant adenomas. This

Fig. 8 Gadolinium enhanced T1w axial (**a**) and coronal (**b**) MR images of the brain of C*ase 21* showing a 4.8 cm macroadenoma with asymmetric left subfrontal extension and asymmetric left suprasellar extension respectively. Note the extension into the left cavernous sinus (*arrow*) in **b**. We did a concurrent endoscopic TS and TC surgery. The postoperative gadolinium enhanced T1w image shows no suprasellar residue (**c**), but there is residual tumor in the left cavernous sinus (*arrow*) (**d**). SRT was administered for this residue

represents an asymmetric lateral extension that makes their removal challenging despite the availability of angled telescopes because of the risk of trauma to vessels and the subsequent inability to control hemorrhage. In these cases, although we staged TS with TC in some cases, it might be argued that the surgeon could assess the extent of tumor removal after the TS surgery using intraoperative MRI [13] and then employ a TC approach at the same sitting if there is a large residue.

Asymmetric subfrontal extension

Subfrontal extension per se is no longer an indication for a TC approach as these tumors can be dealt with effectively through an extended endoscopic TS approach (Fig. 2 a, b). On the other hand when the subfrontal extension is not into the inter-hemispheric fissure but is asymmetrically off onto one side, lateral and anterior to the anterior clinoid process with encasement of the A1 vessels, we feel that excision and hemostasis through the TS route is difficult, in spite of the availability of angled endoscopes and therefore advocate a craniotomy at the same sitting as a safe strategy (Fig. 8).

Tumor reaching the foramen of Monro

Large Hardy's stage C tumors are not a homogenous group of tumors and many authors have recommended a staged TS surgery for these challenging tumors to allow the suprasellar residue to descend into the sella [14, 15]. In an earlier study we found that when more than 50 % of the suprasellar portion of the tumor is out of the line of TS vision the chances of a radical excision are reduced particularly when tumor consistency is unfavourable [3]. Although raising the $ETCO_2$ levels may help in the descent of these tumors, especially those that are soft, bulging of the arachnoid pouch often obscures the surgeon's view precluding a radical excision, particularly when the width of the tumor is narrow. Aspiration of CSF from the lumbar subarachnoid drain at this point in the surgery keeps the arachnoid pouches away and reduces the incidence of an intraoperative CSF leak [16]. Giant adenomas with large suprasellar extension reaching the foramen of Monro, are intimately related to the perforator vessels and to the hypothalamus as they lift up the floor of the third ventricle [4, 17]. Pulling on the suprasellar residue from below may result in intraventricular hemorrhage or a rupture of

perforator vessels. These tumors often require a second stage TS surgery or TC surgery depending on the degree of descent of the residual tumor at follow-up [14, 15]. Thus, a large vertical suprasellar extension and/or an irregular lobulated suprasellar portion are strong indicators of a subtotal TS surgery in these tumors [18].

Encasement of subarachnoid arteries

This tumor characteristic, that can be identified on the preoperative MRI, increases the risk of damage to branches from the circle of Willis and associated vasospasm [4]. Encasement of vessels are well seen on thin slice T2 weighted MRI and a close study of the coronal images in particular, depict encasement of the A2 vessels in giant tumors that elevate the floor of the third ventricle. Axial images provide good information regarding the A1, posterior communicating arteries and anterior choroidal arteries. Traction on the tumor can pull the encased vessels and cause remote hemorrhage—a TC route may be safer in this setting.

Presence of tumor predominantly in the cavernous sinus

This is a particularly difficult group of tumors and are not amenable to radical excision on account of the encasement of the carotid arteries and involvement of the cranial nerves [4]. Of the three such cases in our series operated by the Dolenc's epidural approach, one died and we could achieve only a 60 % excision in the other two. Based on these findings, we would recommend a more conservative approach to these tumors and suggest a TS approach to decompress the optic apparatus, if vision is compromised, followed by RT.

Diaphragmatic constriction/'waist' sign

Dumb-bell tumors (due to diaphragmatic constriction), may not descend into view during a TS surgery necessitating either a staged TS surgery or a craniotomy. Aggressive traction from below may be transmitted superiorly placing small vessels on the superior capsule at risk for rupture. It is likely that increased experience with extended endoscopic approach may encourage neurosurgeons to attempt a TS excision as a first stage to avoid a TC approach in such patients.

Brain T2 FLAIR changes

Tumor invasion through the capsule and infiltration into the adjacent brain may be indicated by this radiological finding [4]. These authors suggest that the risk of postoperative hemorrhage is higher with a TS approach in such cases and recommend a TC approach in the presence of this finding. Based on the recommendations of Zada et al. [4] we could have anticipated the postoperative suprasellar haematoma in Case number 19 due to the presence of T2 FLAIR changes in the brain.

Fibrous tumor at TS surgery

It is well known that tumor consistency plays an important role in determining the ease of resection via the TS route [15, 19]. For instance a giant adenoma might be amenable to a gross total resection when the tumor is soft and easily removed in the suction. On the other hand fibrous and gritty tumors, seen in 5–7.5 % of large pituitary adenomas [20], are difficult to debulk despite the use of dissectors, curettes and vigorous movements of the suction tip that could prove to be dangerous. Inadequate removal might merit a TC approach, however this is not an absolute indication as widening the exposure through an extended TS approach [4, 21–23] allows the surgeon to approach the tumor from above the diaphragma sellae allowing the application of CUSA and scissors [6]. This is exemplified in one of our cases operated via the endoscopic extended TS approach (Fig. 2c, d, e). Snow et al. [24] found T2 weighted imaging to be a good preoperative predictor for firm tumors to decide on the surgical approach. However, we did not find MRI characteristics to be useful in predicting consistency [25].

Post-operative apoplexy in suprasellar residue after TS surgery

Postoperative deterioration of vision or altered sensorium following TS surgery is usually secondary to a tumor bed hematoma that may be due to trapped suprasellar residue between the folds of arachnoid which undergoes hemorrhagic necrosis and expands with disastrous consequences [26, 27]. This makes a strong case for a TC excision of the residue at the same sitting [20, 28]. We used this technique in three of our cases in this series. In one of these patients with a large suprasellar component, the tumor was highly vascular and haemostasis proved to be very difficult prompting us to pack the sella with gelfoam and turn a craniotomy immediately to remove the suprasellar residue successfully.

Complications of the transcranial approach

The shift towards the TS approach has naturally resulted in fewer publications on TC surgery for pituitary adenomas in the last two decades. We have tabulated the results in various series [29–47] describing mortality rates with the TC approach for giant adenomas and large pituitary adenomas (Table 3). In experienced hands, the TC approach for small pituitary adenomas is safe—Symon and

Table 3 Mortality rates in transcranial surgery for pituitary adenomas

Author	Years	No. of procedures	Mortality (%)
Mortality rates in transcranial surgery for giant pituitary adenomas			
Symon et al. [29]	1979	16	18.7
King et al. [30]	1996	5	20
Mortini et al. [31]	2007	26	3.8
D'Ambrosio et al. [32]	2009	11	0
Sinha and Sharma [33]	2010	163	4.3
Mortality rates in transcranial surgery for pituitary adenomas of all sizes			
Bakay [34]	1950	232	35 (with suprasellar extension)
			6.4 (without suprasellar extension)
Horrax et al. [35]	1952	113	14.1
Tonnis et al. [36]	1953	264	10.4
Baker [37]	1960	150	5.3
Elkington and McKissock [38]	1967	260	10
Ray and Patterson [39]	1971	165	1.2
Kunc [40]	1973	300	12.9
Wirth et al. [41]	1974	199	6.9
Kunicki et al. [42]	1975	114	4.8
Symon and Jakubowski [43]	1979	101	0.99 (giant tumors excluded)
		117	
			3.4 (giant tumors included)
Valtonen and Myllymäki [44]	1986	111	11.7
Guidetti et al. [45]	1987	84	6
Suzukawa [46]	1989	111	1.8
Van Lindert et al. [47]	1991	53	5.7

Jakubowski [43] reporting a mortality rate of 0.99 % in a premicrosurgical series that excluded giant adenomas—their mortality rate for giant adenomas was about 18 % [29]. In the microsurgical era, van Lindert et al. [47] had a mortality rate of 5.7 % with TC pituitary surgery in a series that included all sizes of pituitary adenomas. As expected giant adenomas have higher reported operative mortality rates ranging from 4.6 to 18.7 % [29, 31, 48–50] and morbidity rates from 10.4 to 23.2 % [48, 49, 51]. Recent studies indicate that minor surgical morbidity can be as high as 75 % following TC surgery for giant adenomas with major morbidity in about 35 % [31] emphasizing the challenge that these tumors pose to neurosurgeons.

Improving safety of pituitary surgery

Knowledge of pituitary adenoma anatomy is vital to achieving a radical and safe excision of these tumors that typically grow from within the confines of the sella into the suprasellar cistern by elevating the diaphragma sellae. Thus they usually remain within a capsule that consists of the normal compressed adenohypophysis and the dura of the diaphragma sellae [52]. It is only when the tumor invades through the capsule that it lies in contact with the arachnoid and important arteries with brain invasion in focal areas that may cause brain edema as seen on the T2 FLAIR images [4]. This finding might be helpful in deciding to employ the TC route to prevent postoperative hemorrhage and intractable cerebral edema [4]. Our TS tumor removal strategy is based on an intracapsular excision rather than an extracapsular excision as proposed by Hashimoto et al. [19]. Traditional TC surgery for pituitary adenomas involves the same extracapsular excision strategy that frequently results in excessive intraoperative haemorrhage that is difficult to tamponade. We have successfully applied the intracapsular excision strategy in which the surgeon remains within the tumor and never attempts to dissect the capsule away from the suprasellar structures. Thus, the tumor capsule provides a shell within which gelfoam and cottonoids help tamponade brisk tumor haemorrhage. We have repeatedly found that a piecemeal removal at the tumor-capsule interface even preserves the thin

adenohypophysis. Nevertheless our mortality rate is significant with two patients (8.7 %) suffering from hemorrhagic infarct and middle cerebral artery infarct respectively. This is comparable to the mortality described for TC surgery for giant tumors [29–33].

Giant pituitary adenomas

It is difficult to achieve tumor control in giant adenomas through surgery alone with a radical excision being achieved in 4.3–29.65 % [31, 49–51, 53]. Adjuvant RT plays a major role in the management of these tumors following the debulking surgery with improved tumor control rates with this combined therapy [31, 54]. Similarly partial excision or debulking has been shown to improve the hormonal control with somatostatin analogs in acromegaly, especially in large and invasive tumors [55, 56]. We manage residual tumors based on the size of the residue and the histopathology. Repeat surgery is offered to a patient with a significant accessible tumor residue while SRT is administered for the cases with inaccessible residual tumor in functional adenomas, tumor residue more than 1 cm in a non-functioning tumor or if the residue shows growth on serial imaging. In non-functional tumors, we prefer to wait and watch, if the residue is less than 1 cm in size particularly when the MIB-1 labelling index is <3 %. In our series with the combination of debulking surgery and RT, we could achieve tumor control in all patients.

As Zada et al. [4] stress, the radiological features described above are by no means rigid indications for applying the TC approach, instead reviewing the preoperative MRI and the patients clinical condition with these features in mind would alert the surgeon to potential difficulties with the TS approach and a possible subtotal resection. In countries such as ours where patients face financial problems with repeated reviews and imaging, applying the following strategy for this difficult subset of pituitary tumors, most of which are giant adenomas, might enable a more complete and safe tumor removal through a TS with or without a TC approach at the same admission.

An endoscopic TS approach efficiently deals with the vast majority of pituitary adenomas and it is only a minority of patients, 4.7 % in our series, in whom an extended TS approach or a TC surgery is required. At TS surgery, if the tumor is fibrous and access to the suprasellar component is limited by a diaphragmatic constriction or if there is a significant suprasellar residue it should be possible to expand the approach by drilling off the tuberculum sellae and planum sphenoidale and accessing the tumor from above the diaphragma sellae [6]. If this proves unsuccessful a TC approach may be planned concurrently rather than staged as there is a risk of hemorrhage in the residue. When the tumor has enlarged the sella, invaded into the sphenoid/ethmoid sinuses or clivus and the suprasellar component extends above and lateral to the supraclinoid ICA, a combined TS + TC surgery should be planned particularly in giant adenomas when there is encasement of subarachnoid arteries or extensive brain T2 FLAIR changes. When the sella is relatively small in comparison with the suprasellar component along with at least one of the other unfavorable radiological features it might be prudent to consider a TC approach up front—the sellar component may be removed with angled curettes with endoscopic assistance.

Conclusions

In the surgical management of pituitary adenomas, transsphenoidal surgery with or without expanded approaches is preferred but a transcranial surgery may be required in about 5 % of cases despite technological advances in endoscopic pituitary surgery. A detailed study of the preoperative MRI for factors that predict difficulty with the transsphenoidal approach might encourage the surgeon to consider a transcranial surgery either as an initial approach or combined with a transsphenoidal surgery. In giant tumors this strategy to reduce tumor bulk followed by adjuvant radiotherapy should offer the best results with regard to tumor control and patient safety.

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Ethical standards The authors declare that there were no ethical issues related to this study and have complied with the current laws of our country.

Conflict of interest The authors declare that they have no conflict of interest.

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