

# Combined simultaneous transcranial and transsphenoidal resection of large-to-giant pituitary adenomas

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## Abstract

**Background** While large-to-giant pituitary adenomas (PAs) may be safely removed by experienced surgeons through a single route, the procedure is technically challenging. We present the outcome of a simultaneous combined transcranial and transsphenoidal approach and discuss its applications.

**Methods** A retrospective review was conducted on 12 consecutive patients. Surgical complications, visual and endocrinological functions, and tumour control were reviewed.

**Results** There were four men and eight women, with a mean age of 47.6 years. All but one patient had non-functioning PAs. The mean tumour height was 4.1 cm (range: 2.3–5.5). The predominant presenting symptoms were visual field loss in eight patients, headache in three patients and mental confusion in one patient. There was no operative mortality. Post-operative cerebrospinal fluid leakage occurred in one patient. Five of the eight patients who presented with visual field loss achieved full recovery, and three had partial improvement. Two patients developed permanent diabetes insipidus after surgery. Panhypopituitarism occurred in one patient. Gross total removal (GTR) was achieved in five, and subtotal removal (STR) in seven patients. Seven patients received post-operative external irradiation. All patients who had GTR remained tumour-free and all those with STR had stable diseases after a mean follow-up period of 53.1 months (range: 14.1–92.1).

**Conclusion** The simultaneous ‘above and below’ approach is a safe and effective surgical strategy for large-to-giant PAs, particularly when expertise in endoscopic transsphenoidal surgery is unavailable. Its use, however, should be limited to a carefully selected group of patients, and tailored to individual user’s expertise and experience.

**Keywords** Pituitary adenoma · Transsphenoidal · Craniotomy · Surgical approach · Complications

## Introduction

Surgery for large-to-giant pituitary adenomas (PAs) is technically challenging. Although the transsphenoidal approach has been widely adopted as a safe and effective method for the removal of the majority of PAs, large lesions may still present with considerable difficulties [1, 5, 8, 12, 13, 35]. Some of the large PAs may have a fibrous consistency or an ‘hour-glass’ configuration, rendering complete removal through the transsphenoidal route alone difficult and hazardous. With incomplete removal, a residual suprasellar tumour mass may be complicated by haemorrhages at the early post-operative period, resulting in acute hydrocephalus or optic nerve compression. The transcranial approach is effective for the removal of a suprasellar tumour mass but provides only limited visualization of the intrasellar region. Since some of the large PAs may be highly vascular, a direct transcranial attack may be associated with significant bleeding within the intradural space. Previous studies have reported high operative mortality and morbidity rates using the transsphenoidal or the transcranial approach alone [9, 14, 31, 32].

Several alternative approaches have been described, including the extended endoscopic transsphenoidal approach

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[4, 17], the staged transsphenoidal approach [1], the staged transcranial-transsphenoidal approach [2], the combined endoscopic transsphenoidal transventricular approach [10, 24, 25], and the simultaneous combined transcranial and transsphenoidal approach [2, 7, 19]. The latter, in particular, has the advantage of achieving radical tumour removal in a single setting of general anaesthesia. We report our experiences with this simultaneous ‘above and below’ technique, and discuss its advantages and limitations.

## Materials and method

A retrospective study was conducted on 12 consecutive patients who underwent simultaneous combined microscopic transsphenoidal and transcranial surgery for the removal of PAs between January 2000 and December 2008. The diagnosis of PA was made on magnetic resonance imaging (MRI) and confirmed histologically. All giant PAs (>4 cm in height) were approached with this technique during the study period. For large PAs (>2 cm and <4 cm in height), this approach was used when there was significant lateral suprasellar or third ventricular tumour extension, and/or an hourglass configuration.

The anatomical classification of PA described by Wilson et al. [34] was adopted. The relationship of the PA to the sella and sphenoidal sinus was graded as I (normal sella), II (enlarged sella), III (localized sellar perforation), IV (diffuse sellar destruction), and V [cerebrospinal fluid (CSF) or blood-borne spread]. Extrasellar extension was staged as 0 (none), A (occupying cistern), B (third ventricular obliteration), C (grossly displaced third ventricle), D (intracranial parasellar extension), and E (extradural parasellar extension).

Patients’ pre-operative and post-operative (6-month) visual and endocrinological functions, and surgical complications were reviewed. The first follow-up MRI was performed three months after surgery. Gross total removal (GTR) and subtotal removal (STR) were defined as the absence or presence of contrast-enhancing lesions on the first post-operative MRI, respectively. Thereafter, MRI was performed 12-monthly for patients with GTR, and 6-monthly for those with STR. Tumour control and the patients’ Karnofsky Performance Score (KPS) were assessed upon the latest follow-up.

## Surgical technique

The tumour was approached both transcranially and transsphenoidally under a single setting of general anaesthesia. Prophylactic broad spectrum antibiotics (ceftriaxone and metronidazole) were given on induction and continued for 3 days post-operatively. Each of the transsphenoidal and

transcranial phases had its own surgeon, scrub nurse, operating microscope and set of instruments. The transsphenoidal surgeon stood on the right side of the patient while the transcranial surgeon was seated at the head end. The two operative fields were separate by a vertical drape to minimize contamination.

The transcranial approach was conducted through the anterior interhemispheric route (ten patients) or the subfrontal route (two patients). The patient’s head was positioned using a Mayfield clamp in the neutral position for the former, or turned to the side for the latter. The transsphenoidal phase was performed using either the sublabial transseptal route (ten patients) or the transnasal route (two patients).

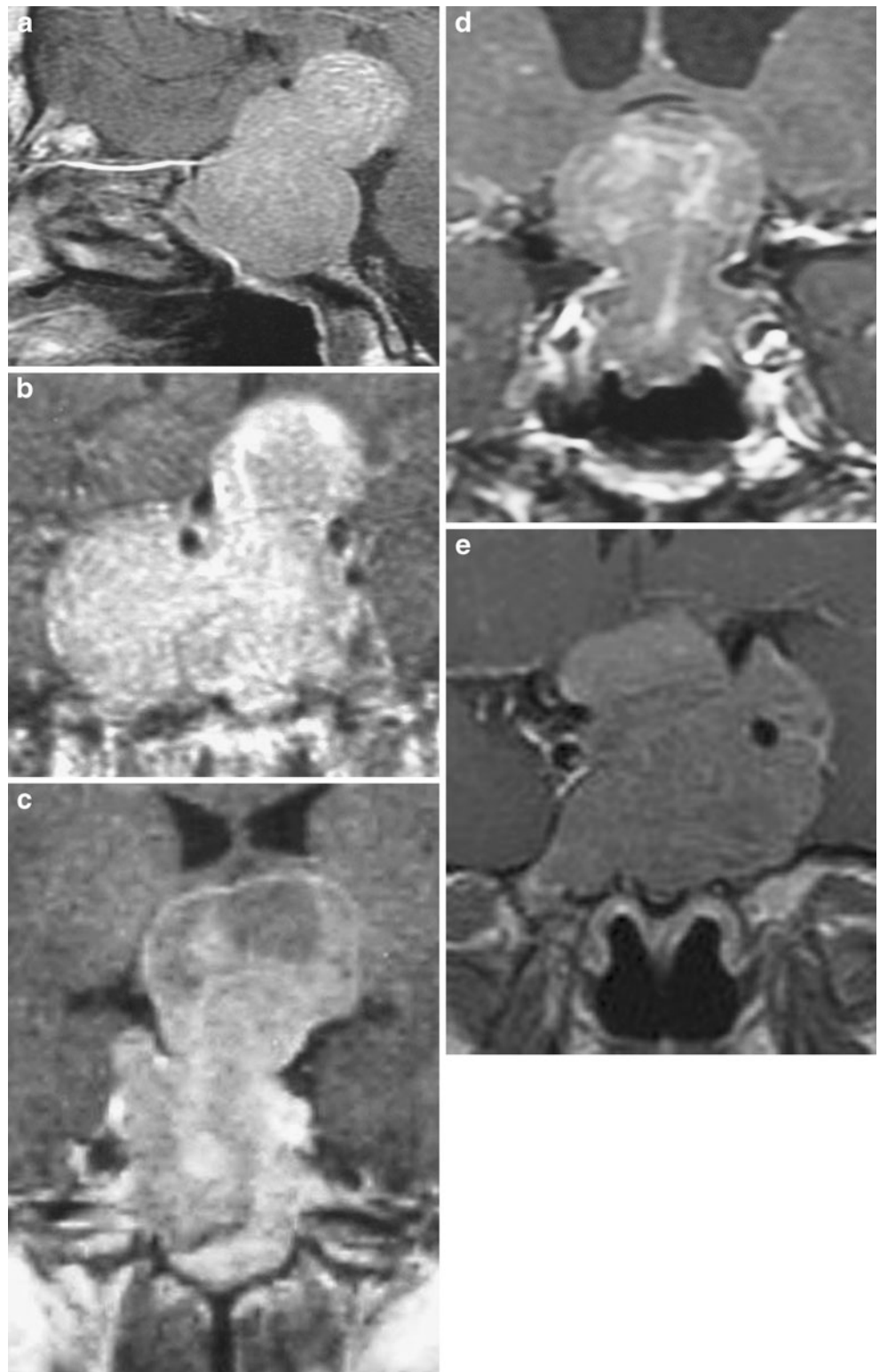
After the initial opening, two operating microscopes were brought into position (Fig. 1). The tumour was exposed on the cranial side, but every effort was made to avoid breaching the tumour capsule in order to minimize the amount of bleeding within the subarachnoid space. The cranial surgeon’s role was to deliver the tumour down towards the sphenoidal sinus, to dissect the tumour capsule from adjacent intradural structures, and to protect the latter against the transsphenoidal surgeon’s manipulations, which may at times extend well up rostrally. The tumour capsule was opened on the transsphenoidal side, followed by tumour debulking with suction and curettage. In all of our cases, the intrasellar and intradural tumour bulks were removed completely. Figure 2 illustrates tumours that were removed using this technique.

The subsequent skull base defect was repaired with abdominal fat graft. Again, the cranial surgeon served to prevent against over-enthusiastic packing by the transsphenoidal surgeon. The rest of wound closure was performed in the standard manner. A subgaleal suction



**Fig. 1** The setting in the operating room, with two microscopes positioned to allow the simultaneous participation of the transcranial and transsphenoidal surgeons

**Fig. 2** Pre-operative contrasted T1-weighted MRI studies illustrating tumours which were removed using the combined technique. The patient numbers correspond to those in Table 1. **a** Patient 4, **b** patient 5, **c** patient 9, **d** patient 11, **e** patient 12



drain was inserted on the cranial side, and the nasal passages were packed for one to two days. No lumbar drain was used. All patients received post-operative care in the intensive care unit. Except for those patients who had previous irradiation therapy, all were offered post-operative fractionated external irradiation as adjuvant treatment.

## Results

### Patient characteristics

There were four (33.3%) men and eight (67.7%) women, with a mean age of 47.6 years (range: 32–79) (Table 1).

**Table 1** Patient characteristics and operative procedures

Patient no.	Sex/age (years)/	Symptoms	Tumor size (cm) <sup>a</sup>	Tumor grade <sup>b</sup>	Cranial approach	Transsphenoidal approach	Extent of removal	Operation time (mins)
1	F/54	BTH	3.0×3.2×4.5	III C	AIH	Sublabial	GTR	420
2	F/45	HA	2.9×2.5×4.4	III E	Subfrontal	Sublabial	STR	360
3	M/41	HA	2.8×2.3×2.3	III D	Subfrontal	Sublabial	GTR	400
4	M/62	BTH	3.0×4.1×5.2	III D	AIH	Sublabial	GTR	380
5	F/62	Acromegalic features, BTH	3.3×2.6×3.6	III E	AIH	Sublabial	STR	460
6	M/47	HA	3.0×3.5×5.5	IIIE	AIH	Sublabial	STR	370
7	F/32	BTH	3.0×3.7×3.1	III E	AIH	Transnasal	STR	380
8	F/65	BTH	3.2×2.2×2.9	III E	AIH	Sublabial	STR	350
9	F/58	BTH	3.3×2.2×5.0	IV C	AIH	Sublabial	GTR	450
10	F/52	BTH	3.6×4.4×4.6	IV E	AIH	Sublabial	STR	210
11	M/79	Confusion	2.0×1.8×2.8	III C	AIH	Transnasal	GTR	300
12	F/34	BTH	3.7×3.6×5.3	IV E	AIH	Sublabial	STR	360

AIH anterior interhemispheric, BTH bitemporal hemianopia, GTR gross total removal, HA headache, RT external radiotherapy, STR subtotal removal

<sup>a</sup> Width × length × height

<sup>b</sup> Modified Hardy's grading staging

Eleven patients had non-functioning PAs and one had a growth-hormone-secreting tumour. The mean tumour height was 4.1 cm (range: 2.3–5.5). Nine were grade III tumours and three were grade IV tumours. The numbers of stage C, D and E tumours were three, two and seven, respectively. Three cases were recurrent tumours with previous transsphenoidal surgery and radiotherapy performed. The predominant presenting symptoms were visual field loss in eight, headache in three, and mental confusion in one patients.

#### Operative procedures and complications

The transcranial approach was anterior interhemispheric in ten patients and subfrontal in two patients (Table 2). The transsphenoidal approach was sublabial transseptal in ten patients and transnasal in two patients. The mean operation time was 370 min (range: 210–460).

There was no operative mortality. One patient died 28 months after surgery due to an unrelated cause. One patient (8.3%) had post-operative CSF leakage, which was successfully treated with lumbar drainage. One patient (8.3%) developed deep vein thrombosis without pulmonary complication, and was successfully managed with an inferior vena caval filter and anticoagulation. No patient suffered from meningitis, hydrocephalus or new onset of cranial nerve palsy.

Of all eight patients who presented with visual field loss, five (62.5%) achieved full visual field recovery, and three (37.5%) had partial improvement. None experienced worsening of vision. All four patients who presented with

headache and confusion had symptomatic improvement after surgery. Four patients developed diabetes insipidus (DI) after surgery—two were transient (16.7%) and two permanent (16.7%). Panhypopituitarism occurred in one patient. Three other patients had new onset of isolated anterior pituitary deficiencies. All patients had KPS of 70 or above upon the last follow-up.

#### Tumour control

Based on the first post-operative MRI, GTR was achieved in five (41.7%, all stage C or D lesions), and STR in seven patients (58.3%, all stage E lesions). Three patients received previous external radiotherapy and were not offered further irradiation. Of the remaining nine patients, seven received post-operative fractionated external irradiation and two declined it. The mean follow-up period was 53.1 months (range: 14.1–92.1). Upon the last follow-up, all five patients who had GTR remained tumour-free, whilst all patients with STR had stable residual diseases. The one patient with acromegaly had STR and continued to receive bromocriptine for biochemical control.

#### Discussion

Large and giant PAs are difficult to remove safely. The operative mortality rates have been reported to be as high as 25% for transcranial resection and 14% for transsphenoidal resections [31]. Advancement in neurosurgical techniques has led to an improvement in outcome. Sinha et al. [28]



**Table 2** Patients' post-operative outcome

Patient no.	Visual function	New permanent hormonal deficit	Surgical complication	Post-op RT	Tumour status	KPS	FU duration (months)	Remarks
1	Normal	DI, ↓ACTH	None	Yes	Tumour-free	90	109	None
2	Normal	None	None	No	Stable residue	90	104	Recurrence after previous transsphenoidal removal and RT
3	Normal	None	None	No	Tumour-free	90	105	Recurrence after previous transsphenoidal removal and RT
4	Normal	DI	None	Yes	Tumour-free	80	28	Died 28 months later from unrelated cause
5	Residual left HeAn	Panhypopituitarism	None	Yes	Stable residue	90	93	Biochemical remission with bromocriptine
6	Normal	None	CSF leakage	Yes	Stable residue	90	65	None
7	Normal	None	None	No	Stable residue	100	63	Patient refused RT
8	Improved BTH	None	None	No	Stable residue	80	55	Recurrence after previous transsphenoidal removal and RT
9	Normal	↓TSH	Deep vein thrombosis	Yes	Tumour-free	100	54	Deep vein thrombosis treated with caval filter.
10	Residual left HeAn	↓ACTH	None	Yes	Stable residue	100	24	None
11	Normal	None	None	No	Tumour-free	70	24	Patient refused RT
12	Normal	None	None	Yes	Stable residue	100	26	None

*ACTH* adrenocorticotropic hormone, *BTH* bitemporal hemianopia, *CSF* cerebrospinal fluid, *DI* diabetes insipidus, *FU* follow-up since surgery, *HeAn* hemianopia, *KPS* Karnofsky Performance Score, *RT* external radiotherapy, *TSH* thyrotropic stimulating hormone

reported the surgical outcomes of 250 patients with giant PAs. Near-total (>90%) tumour removal was achieved in 74% and improvement of vision in 53% of patients. The mortality and morbidity rates were 4.4% and 14%, respectively. Xue-Fei et al. [35] treated 54 patients with large PAs using a variety of surgical approaches and achieved complete tumour removal in 21% of cases. The peri-operative mortality rate was 7.9%. In another series of 111 patients, Mortini et al. [21] reported a mortality rate of 2.7%. The incidences of 'major' complications (e.g. cranial nerves, hypothalamic and vascular injuries, CSF leakages and tumour haemorrhages), and 'minor' complications (e.g. endocrinological) were 18% and 26%, respectively. Using the same categorization, the incidences of 'major' and 'minor' complications in our present series were comparable at 8.3% and 25%, respectively. The extent of removal in our series, however, was comparatively lower, which was probably due to our conservative approach towards tumours within the cavernous sinuses.

The transsphenoidal approach is the treatment of choice for the majority of PAs. But for tumours that arise in or extend into the suprasellar region, transsphenoidal surgery is generally contraindicated when there is a normal-sized sella turcica, normal pituitary function, or adherence of the

tumour to major intracranial structures [6, 12, 14, 18]. A tumour that is fibrous in consistency or has an hour-glass configuration may also be difficult to remove completely with a single transsphenoidal procedure [20]. Lumbar subarachnoid saline or air injection may be used to facilitate the descent of the suprasellar tumour bulk into the sella, but the method is effective only in a subgroup of patients [29, 37]. In a prospective study, Honegger et al. [11] demonstrated that the vertical intracranial extension, and an irregular or multilobular configuration, were significant and independent predictors for incomplete resection. To address this, the two-staged transsphenoidal approach has been advocated, in which, after the removal of the intrasellar tumour component, the suprasellar residual tumour was given time to descend and then removed by a second-stage transsphenoidal procedure [1, 26, 31]. The disadvantages of this approach include the need for two operations and the potential risks of tumour swelling and haemorrhages after the first-stage surgery.

The introduction of endoscopic transsphenoidal surgery has revolutionized the treatment of sellar tumours [4]. It has been shown to be safe and effective, and is now an arguably standard therapy for the majority of PAs. But despite the vastly improved illumination and visualization provided by

the use of endoscopes, a giant or invasive PA is amenable to a single-stage removal by a limited number of experts only [30]. Wang et al. [33] reported an 80% total resection rate in a series of 64 patients without mortality or tumour recurrence. Similarly, Sanai et al. [27] reported a GTR rate of close to 50%, with no incidence of CSF leakage, new panhypopituitarism or worsening of vision. Nakao et al. [23] treated 43 patients using the endoscopic endonasal approach and an intracapsular resection technique. Gross total removal was achieved in close to 50% of cases and there was no major complication. While the indications for endoscopic pituitary surgery are expanding, its use and limits for the treatment of huge PAs are yet to be defined. The extended endoscopic transsphenoidal approach, in particular, is a technically demanding technique. It requires specialized and advanced training, and may not be readily acquired by surgeons without the necessary case volume [4].

For many, the transcranial approach continues to play a role in the management of PAs inaccessible from the transsphenoidal route alone [36]. When compared with the transsphenoidal approach, there is a trend towards greater visual improvement, but the benefit may be offset by a greater risk of post-operative pituitary dysfunction [22]. The disadvantages of the transcranial approach include the amount of brain retraction required and the limited visualization of the intrasellar area [15]. In our experience, a transcranial resection of vascular tumours may also be associated with significant bleeding within the intradural space. This may further obscure the surgical view, and potentially increase the risks of brain swelling and hydrocephalus. One of the advantages of our simultaneous combined approach is that tumour bleeding would occur predominantly on the transsphenoidal side. The transcranial surgeon only serves to deliver the tumour bulk towards the sella, and to protect the intradural structures.

Loyo et al. [19] first described the combined supra-sellar and infra-sellar approach in 1984 for the resection of very large PAs, and advocated it as superior to either the transsphenoidal or the intracranial approach alone. Case reports on the use of the ‘above and below’ approach for a large craniopharyngioma [16], and a PA with lateral ventricle extension have been described [10]. To our knowledge, there are two reported case series on the combined approach for large-to-giant PAs. Alleyne et al. [2] reported a GTR rate of 40% in a cohort of ten patients. More than half of those who presented with pre-operative visual field loss experienced complete recovery. Permanent DI occurred in 20% of patients. In D’Ambrosio et al.’s series [7], GTR was achieved in six out of 11 patients (55%). Seven patients (64%) experienced visual improvement post-operatively and no major complication occurred. Panhypopituitarism was observed in four and persistent DI in two patients. The authors of these two series focused

mainly on early operative outcomes but not tumour control. Our present study yielded similar early outcomes. In addition, we were also able to demonstrate satisfactory medium-term tumour control. Admittedly, the use of up-front fractionated external irradiation, instead of radiosurgery, in our series warrants careful scrutiny in view of the former’s potential side-effects. This is a limitation of our treatment paradigm that needs to be improved.

Conceptually, we consider this technique to be a posterior extension of that of craniofacial resection for anterior skull base tumours, in that lesions which occupy two adjoining skull base compartments are best approached simultaneously from both compartments for maximal tumour removal and safety [15]. Although pathologically very different, these two disease groups may exhibit similar morphological features, such as close adherence to intracranial structures, irregular configurations and extensive skull base destruction. Technically, we favour the anterior inter-hemispheric route for the transcranial phase because it provides a better view of the parasellar region bilaterally. The subfrontal or pterional route, on the other hand, requires some head-turning, which may potentially disorientate the transsphenoidal surgeon.

One of the main goals of surgery for huge PAs is optic nerve/chiasm decompression, for which the combined approach appears to be a safe and effective method. The main advantages of our technique include the need for only one procedure, the protection offered by the transcranial surgeon, and the avoidance of complications potentially caused by any residual suprasellar tumour bulk. The main disadvantages include the involvement of two operative fields, the doubling of staff and instruments required, the long operating time, and the potential complications of a craniotomy. The need for two operating microscopes, however, may be obviated by the use of endoscopes for the transsphenoidal phase of the procedure. More recently, an alternative ‘above and below’ approach has been described by several authorities for the treatment of PAs with significant third ventricular extensions. It uses a simultaneous endoscopic transsphenoidal-transventricular technique and therefore obviates the need for a craniotomy [10, 24, 25].

In terms of tumour control, stage C (grossly displaced third ventricle) and D (intracranial parasellar extension) are potentially amenable to total removal with our technique; stage E (extradural parasellar extension) lesions may require a more extensive extradural approach. However, being a retrospective case series, this report may suffer from case selection bias, suboptimal data collection, and the lack of a control cohort for outcome analysis. The optimal treatment of large-to-giant PAs is likely to require a more tailored approach, based on individual patients’ conditions and the surgeons’ experiences and abilities. A multi-

modality management strategy should be adopted to take full advantages of the benefits provided by surgery and radiotherapy [8]. The use of intra-operative MRI may also significantly improve resection rate and safety [3]. Our combined approach represents only one of the many surgical strategies that can be used in dealing with these challenging PAs, particularly when expertise in endoscopic surgery is unavailable.

## Conclusion

Large and giant PAs are challenging lesions. Although many experienced surgeons would be able to remove these tumours endoscopically through the transsphenoidal route alone, the necessary expertise is not easy to acquire. The present study demonstrates that the simultaneous transcranial transsphenoidal approach is a safe and feasible alternative. It requires teamwork and more readily available technical skills from the transcranial and transsphenoidal surgeons. Its use, however, should be limited to a carefully selected group of patients, and tailored to individual users' expertise and experiences.

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**Conflicts of interest** None.

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## Comment

In managing a huge and multilobed tumour, the surgeon accepts that the now generally adopted transsphenoidal approach is going to run the risk of leaving benign tumour in the suprasellar space and, of course, invading the cavernous sinus and that residual will cause problems with swelling and haemorrhage in a few. The question is how to manage them.

I can accept the occasional need to link cranial and transsphenoidal surgery, but my problem is why there is a need to do them both together, exactly at the same time. Why not do the transsphenoidal and go on, if absolutely necessary, at the same sitting. The transsphenoidal is so quick, and all I could see is the cranial part getting in the way.

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