



Adjunctive Benefit of High-Field 3 Tesla MRI Guidance in Endoscopic Transsphenoidal Resection of Pituitary Adenoma

Kartik Manoj Multani¹ Anandh Balasubramaniam¹ Boyina Jagadeshwar Rajesh¹ Krishna Kumar¹
Nitin Manohar² Anjani Kumar³

¹ Department of Neurosurgery, Yashoda Hospital, Secunderabad, Telangana, India

² Department of Anesthesia, Yashoda Hospital, Secunderabad, Telangana, India

³ Department of Radiodiagnosis, Yashoda Hospital, Secunderabad, Telangana, India

Address for correspondence Anandh Balasubramaniam, MCh, Department of Neurosurgery, Yashoda Superspeciality Hospital, Secunderabad, Telangana 500003, India (e-mail: anandhbala@gmail.com).

Indian J Neurosurg 2023;12:51–58.

Abstract

Introduction Pituitary adenomas (PAs) although benign, are difficult to resect intracranial tumors and their residues are associated with morbidity and reduced quality of life. Thus, gross total resection (GTR) is the goal for all PAs. Role of various modalities for better intraoperative visualization and thus improve resection of adenoma have been tested and each have their pros and cons. The aim of this paper is to analyze adjunctive benefit of high-field 3 Tesla intraoperative magnetic resonance imaging (iMRI) in PAs resection by endoscopic transnasal transsphenoidal surgery (eTSS).

Materials and Methods A total of 50 patients who underwent iMRI-guided eTSS were included. MRI findings in preoperative, intraoperative, and 3 months postoperative stage were compared. Adjunctive value of iMRI in improving resection rates of adenoma, postoperative endocrinological outcomes, need for adjuvant radiotherapy, and postoperative cerebrospinal fluid leak rates was assessed.

Results High-field 3 Tesla iMRI helped us to detect residues in 24 (48%) patients and iMRI-guided second look surgery increased our GTR rates from initial 52 to 80% and also helped us to identify and achieve 100% GTR in intrasellar residues and parasellar residues that were medial to medial carotid tangential line. With better resection rates, need for adjuvant radiotherapy was also reduced and only 2% received adjuvant radiotherapy. Average increase in surgical time with the use of iMRI was 38.78 minutes without any side effects pertaining to prolonged surgery.

Conclusion High-field iMRI is a useful adjunct in assessment and improvement in extent of resection of PA by endoscopic transsphenoidal surgery. Also, it was found beneficial in preserving normal anatomical gland and, thus, reducing the need for postoperative adjuvant hormonal and radiation therapy.

Keywords

- ▶ pituitary adenoma
- ▶ endoscopic transsphenoidal surgery
- ▶ intraoperative MRI
- ▶ intraoperative adjuncts
- ▶ intraoperative imaging

article published online
April 29, 2021

DOI <https://doi.org/10.1055/s-0042-1743267>.
ISSN 2277-954X.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Pituitary adenomas (PAs) represent 10 to 15% of all central nervous system (CNS) tumors and are the cause of ~25% of all surgical resections in CNS tumors.^{1,2} In published large series, the radical tumor removal was achieved in 28 to 70% of all nonfunctioning pituitary adenoma (NFPAs)^{3,4} and chemical remission was seen in 40 to 56% after surgery in functioning pituitary adenoma (FPAs)⁵ the data described are suggestive of significant postoperative residue after surgery in pituitary tumors. The left behind residue is strongly associated with complications like postoperative hemorrhage, need for adjuvant radiotherapy or hormonal therapy, significant higher risk of adenoma regrowth, and possibly reduced life expectancy⁶⁻⁸ thus, gross total resection (GTR) is recommended for both NFPAs and FPAs.

With improvement in neurosurgeon's armamentarium, there has been a dramatic shift in choice of surgical approach to lesions of pituitary from open transcranial surgery to microscopic transsphenoidal surgery. Introduction of endoscopes in brain surgery by Sir Walter dandy was the landmark neoteric event that has revolutionized the field of neurosurgery.⁹ With their self-sustained illumination and ability to give angled and panoramic view, endoscopes in transsphenoidal surgery have come a long way from being used as an adjunct to microscopes to their present status of standalone instrument in complete endoscopic removal of tumor by transsphenoidal approach.¹⁰ At present, endoscopic transsphenoidal surgery (eTSS) is the standard of care for all pituitary resections unless otherwise contraindicated.

In FPAs, postoperative chemical remission can act as a marker of gross total excision; whereas one has to rely on imaging modalities to assess extent of resection (EOR) in surgery for NFPAs, which makes it a difficult process to get accustomed to. Role of various modalities for intraoperative imaging of pituitary tumors has been tested namely intraoperative fluoroscopy, transcranial ultrasonography, and intraoperative contrast-enhanced computed tomography. All these modalities have shown suboptimal results when compared with intraoperative magnetic resonance imaging (iMRI) in various comparative studies. The aim of this article is to evaluate efficacy of high-field 3 Tesla iMRI in improving EOR of PAs.

Materials and Methods

Prospective observational study was conducted from August 2017 to May 2020 at Yashoda Hospital, Hyderabad. All patients with age above 18 years undergoing iMRI-guided transnasal endoscopic transsphenoidal resection of PA were included in this study irrespective of their sex, demographic data, and socioeconomic status and patients with PAs who underwent surgery from transcranial route or patients who underwent surgery from transsphenoidal route but iMRI was not done were excluded from this study.

All iMRI were conducted using a 3 Tesla machine (MAGNETOM SKYRA, Siemens medical system, Erlangen,

Germany), installed in a "NEAR BY OT TYPE" configuration. At the end of surgery, the expected EOR of surgeon with expected location of residues was recorded and patient was mobilized into and out of iMRI suite as per institution protocols.¹¹ A team of dedicated neuroanesthetists and neurosurgeons observed the patient throughout and strict asepsis was maintained.

Plain followed by dynamic post contrast iMRI was performed using siemens 3T Skyra MRI scanner after resection of PA. High-resolution noncontrast sagittal and coronal T1, T2 and T1 FS image followed by postcontrast sagittal and coronal T1 FS image were acquired for pituitary region. In few patients where intraoperative damage to major neurovascular structure was seen, a diffusion-weighted imaging sequence was also performed to rule out infarcts.

The intraoperative imaging findings were compared with preoperative imaging and EOR, presence and location of residues with their size, and proximity to important structures were noted. All patients with residues seen at iMRI were classified into two groups based on surgeons' impression recorded at end of surgery. "Surprise Residue group" included the cases in which surgeon expected GTR at end of surgery and iMRI was done with the goal to confirm GTR and "Expected Residue Group" included the cases where surgeon expected subtotal resection (STR) at the end of surgery and iMRI was done with residue seeking goal, that is, to improve our EOR by visualizing relation of critical structures to the residue and thus by identifying resectable residues. Further resection was continued if residue was considered accessible and surgery was discontinued if residue was deemed nonaccessible or nonresectable. A postoperative 3 months MRI was obtained in all patients to determine final resection status.

For our ease, we classified resection status into four groups: *primary GTR* (GTR confirmed in first-look iMRI), *secondary GTR* (GTR achieved after second-look surgery and confirmed on postoperative MRI), *overall GTR* (sum of primary and secondary GTR), and *STR* (residue was detected in iMRI but not resected further).

The data on demography, clinical presentation, preoperative and intraoperative imaging findings, 3 months postoperative imaging findings with adjuvant therapy received were noted and analyzed with SPSS version 24 (IBM Inc, New York). All *p*-value <0.05 was considered statistically significant.

Results

Demography and Tumor Characteristics

A total of 50 patients underwent iMRI-guided eTSS in study period. Mean age of the patients harboring PAs was 45 years (range: 25–65 years, standard deviation [SD]: 11.2); 54% of the total cases were male and 46% were females. Thirty-five patients had nonfunctioning adenoma and 15 had functioning adenoma, of which 4 were growth hormone (GH) secreting, 2 were thyrotropin secreting, 4 were ACTH secreting adenomas, 5 were prolactinomas, 4 were on

Table 1 Characteristics and distribution of 50 patients with pituitary adenoma undergoing 3T iMRI-guided endoscopic transnasal transsphenoidal surgery

Characteristics	Number (n)	%
Age		
Mean	45 y	
Range	25–65 y	
Sex		
Male	27	54
Female	23	46
Adenoma classification (based on tumor secretion)		
NFPAs	35	70
FPAs	15	30
• GH secreting	4	8
• TSH secreting	2	4
• ACTH secreting	4	8
• PRL secreting	5	10

Abbreviations: ACTH, adrenocorticotropic hormone; FPA, functioning pituitary adenoma; GH, growth hormone; iMRI, intraoperative magnetic resonance imaging; NFPAs, nonfunctioning pituitary adenomas; PRL, prolactin; TSH, thyroid stimulating hormone.

medical treatment with apoplexy and clinical worsening, and 1 was invasive prolactinoma. So, surgery was preferred choice of treatment. Overall, 46 were macroadenomas and 4 were microadenomas (► **Table 1**).

Resection Results

At first look, iMRI primary GTR was confirmed in 52% (26/50) patients and residues were detected in 48% (24/50) patients. Surgery was continued and secondary GTR was achieved in 28% (14/50), while residues were deemed unresectable in 20% (10/50) patients.

Among 24 detected residues, 45.83% (11/24) were expected at end of surgery, while 54.16% (13/24) were surprise residues in which operating surgeon expected a GTR before iMRI.

Thus, iMRI helped us to achieve statistically significant increase in GTR rate from 52 (26/50) to 80% (40/50) (p -value < 0.05; ► **Fig. 1**).

Location of Adenoma Residues

Residual adenoma locations were classified as intrasellar (IS), parasellar (PS) including both intracavernous and intradural residues, suprasellar (SS), and combined intrasellar and suprasellar (IS + SS).

In our series, a total of 48% (24/50) residues were detected, of which 11 were PS residues, 8 were IS residues, 3 were SS, and 2 were combined IS + SS residues.

Resection Results Based on Location of Residue

All eight patients with IS residues alone underwent second look surgery and at 3 months postoperative MRI secondary

Resection statistics

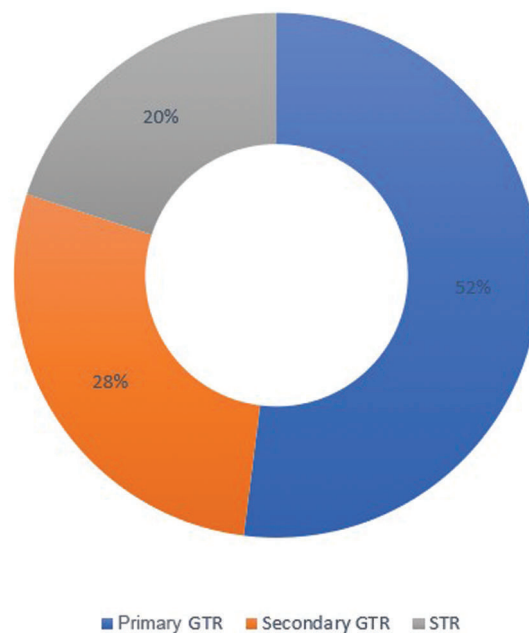


Fig. 1 Resection results. GTR, gross total resection; STR, subtotal resection.

GTR was achieved. Of two IS + SS residue, surgery was continued in one and STR was accepted in one adenoma due to difficulty to access SS component. In SS residue group of three patients, one patient underwent second look surgery and secondary GTR was achieved and STR was accepted in two patients. In PS residue group of 11 patients, secondary GTR was achieved in four patients in which residue was medial to medial tangential carotid line as per Knosp's description and STR was accepted in seven patients where residue was either located lateral to lateral tangential line or was encasing carotid artery or intradural residues in anterior and middle cranial fossa and thus deemed unresectable by eTSS.

Thus, iMRI-guided second look surgery helped us to achieve 100% GTR in IS residues (8/8), 50% (2/1) GTR in IS + SS, 33.33% (1/3) GTR in SS, and 36.33% (4/11) GTR in PS residue group (► **Figs. 2,3,4,5**).

Postoperative Adjuvant Radiation Therapy

Of 10 patients with STR as final resection status, we had three postoperative mortalities: (1) Patient with giant GH secreting adenoma died at postoperative day 8 due to sudden cardiac arrest as a sequelae to constructive cardiomyopathy, (2) patient was taken for eTSS with a preoperative suspicion of chordoma that in postoperative histopathological examination turned out to be invasive prolactinoma and patient died due to profuse cerebrospinal fluid (CSF) rhinorrhea and meningitis post bromocriptine therapy, (3) patient died due to diencephalic and brain stem infarcts because of intraoperative damage to posterior cerebral

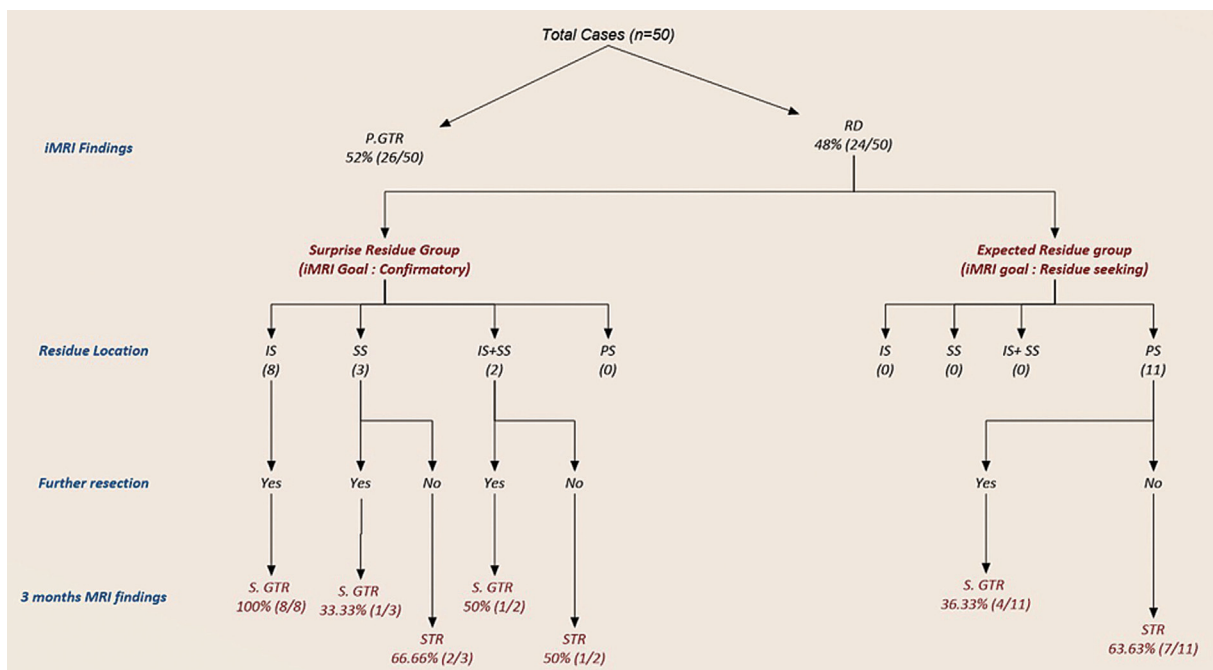


Fig. 2 Flowchart with schematic depiction of impact of 3T intraoperative magnetic resonance imaging in endoscopic transnasal transsphenoidal surgery. PGTR, primary gross total resection; RD, residues detected; SGTR, secondary gross total resection; STR, subtotal resection.

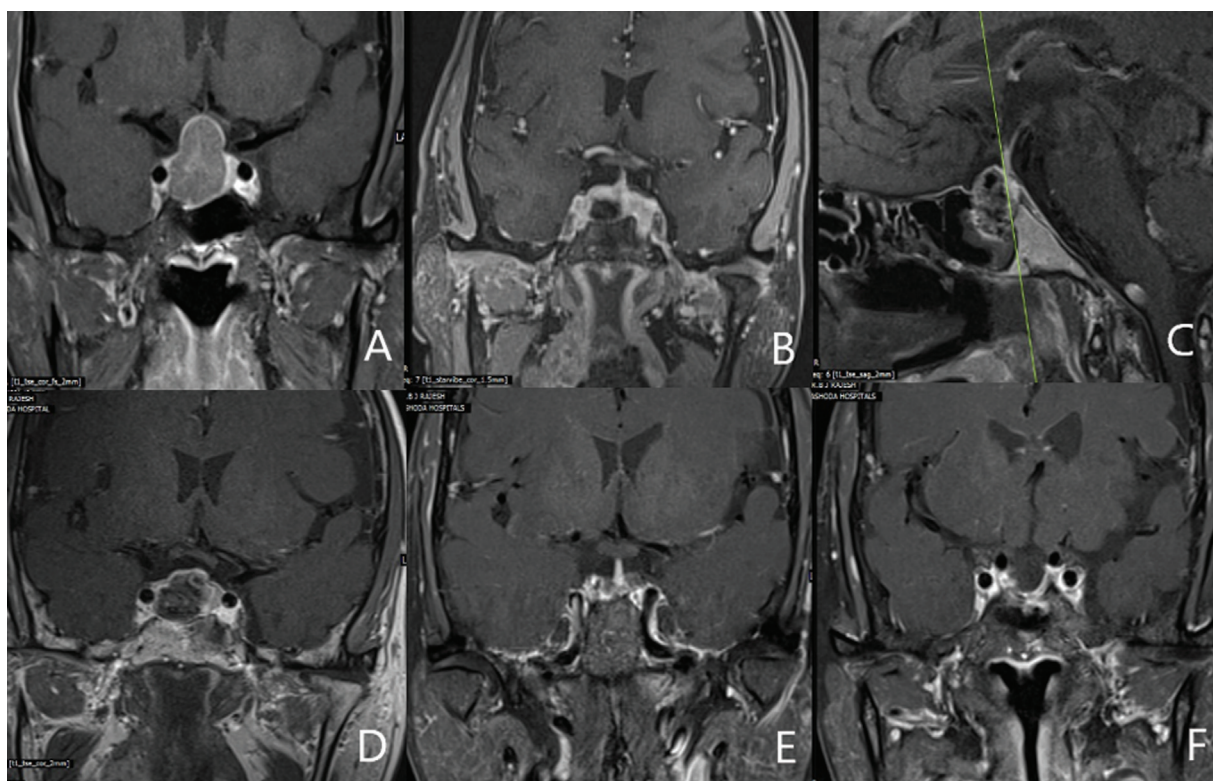


Fig. 3 (A) Preoperative magnetic resonance imaging (MRI) showing WILSON GRADE B macroadenoma. (B, C) Intraoperative magnetic resonance imaging (iMRI) showing surprise posterosuperior intrasellar residue. (D) iMRI showing preserved normal enhancing gland adjacent to left cavernous sinus. (E, F) 3 months postoperative MRI confirming secondary gross total resection.

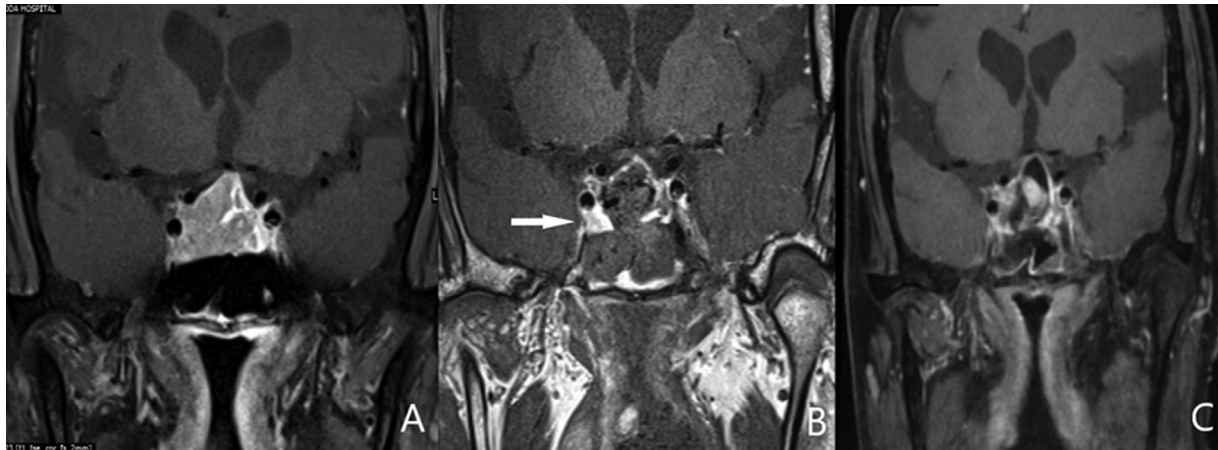


Fig. 4 (A) Preoperative magnetic resonance imaging (MRI) showing macroadenoma with right cavernous invasion. (B) Intraoperative MRI showing intracavernous residue medial to medial tangential line. (white arrow) (C) Postoperative MRI confirms secondary gross total resection.

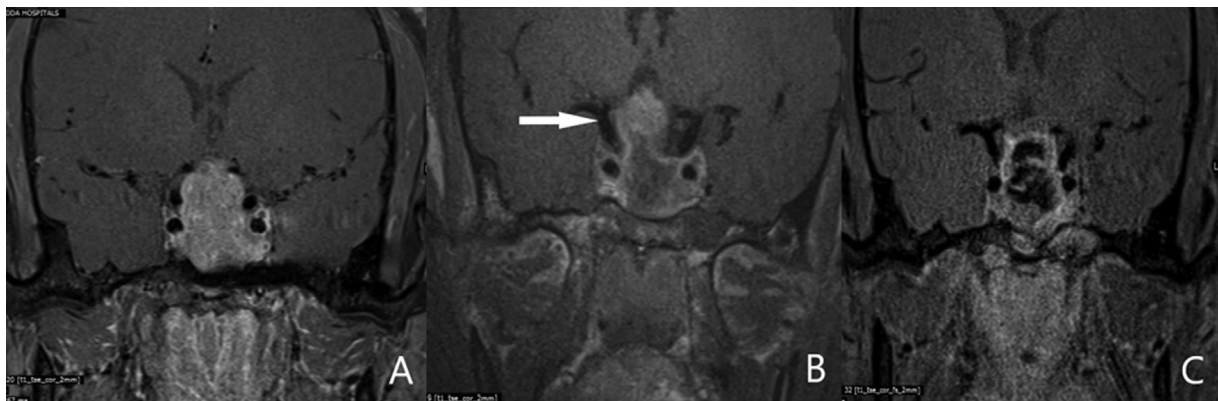


Fig. 5 (A) Preoperative magnetic resonance imaging (MRI) showing macroadenoma with suprasellar extension. (B) Intraoperative MRI showing surprise isolated suprasellar residue. (white arrow) (C) Postoperative MRI after second look surgery showing gross total resection with normal enhancing capsule.

artery while resecting prepontine extension of lesion. Out of remaining seven patients, six patients are on regular follow-up with stable disease and only one (2%) of fifty patient showed regrowing residue at 1-year follow-up scan and received adjuvant radiotherapy (→ **Table 2**).

Endocrinological Outcomes and Intraoperative Identification of Normal Gland

Overall, 26 patients presented with preoperative abnormal endocrine profile, of which 11 presented with hormone undersecretion and 15 presented with hormone oversecretion (including both microadenoma and macroadenoma).

Table 2 Need for postoperative adjuvant RT in STR cohort

Characteristics	Number (n)	%
Final STR status	10	20
Mortality	3	6
Stable disease	6	12
ON adjuvant STR	1	2

Abbreviations: RT, radiotherapy; STR, subtotal resection.

Among preoperative undersecretion cohort of eleven patients, two patients had hypothyroidism, two had combined hypothyroidism and hypocortisolism, five had mildly elevated prolactin and stalk section like picture, and two had panhypopituitarism. After iMRI-guided resection, six patients had transient deficiencies of thyroid and cortisol for which they were treated with short course hormonal replacements and only two patients with preoperative panhypopituitarism remained same in postoperative phase and are on continuous hormonal replacement therapy.

In preoperative oversecretion cohort of 15 patients (types of adenomas described in → **Table 1**), chemical remission was achieved in 14 patients, while one patient with GH secreting adenoma continued to have excess insulin-like growth factor 1 in postoperative phase (died on postoperative day 8). Three patients developed postoperative transient hormonal deficiencies for which they received short course replacement therapies.

In remaining 24 patients with normal preoperative endocrinological profile, 9 patients developed postoperative deficiencies. Of which five patients had transient postoperative hormonal dysfunctions in one or other axes,

Table 3 Endocrinological outcomes and identification of normal gland at iMRI

Characteristics	Number (n)	%
Preoperative hormonal profile		
Normal profile	24	
Undersecretion profile	11	
Oversecretion profile	15	
Postoperative hormonal profile		
(A) Normal secretion cohort		
Transient deficit (one or other axes)	5	
Permanent deficit		
Hypocortisolemia	3	
Hypothyroidism	1	
(B) Undersecretion cohort		
Transient deficit	6	
Permanent deficit (panhypopituitarism)	2	
(C) Oversecretion cohort		
Transient deficit	3	
Permanent deficit	Nil	
(D) Overall cohort		
Transient deficit	14	28
Permanent deficit	6	12
Normal gland identification at iMRI	38	76

Abbreviation: iMRI, intraoperative magnetic resonance imaging.

while 3 developed permanent hypocortisolemia and 1 developed permanent hypothyroidism, while remaining 15 patients continued to have normal hypothalamic-pituitary-axis function.

So, in our series, preoperative hormonal deficiencies were seen in 22% (11/50) patients. After iMRI-guided eTSS, transient hormonal deficiencies were seen in 28% (14/50) patients, while permanent pituitary hypofunction was seen in 12% (6/50) of which 4% (2/50) patients were panhypopituitarism, 6% (3/50) had isolated hypocortisolism, and 2% (1/50) had postoperative isolated hypothyroidism. At iMRI, normal pituitary gland was identified in 76% (38/50) patients (► **Table 3**; ► **Fig. 6**).

Perioperative CSF Leak

A total of 26% patients (13/50) had intraoperative CSF leak due to inadvertent arachnoid tear. Twenty-two percent (11/50) patients developed leak before iMRI and their final resection status was STR in 4% (2/50) and primary GTR in 18% (9/50). Only 4% (2/50) developed leak during second look surgery while chasing residue seen in iMRI.

Timeline Assessment

The average time to shift patient to MRI suite and shifting back to operating room was 17.21 minutes (range: 15–

25 minutes; SD ± 3.31). The average time for image acquisition was 21.56 minutes (range: 18–34 minutes; SD ± 5.13). Thus, the average increase in overall surgical time was 38.78 minutes (range: 33–55 minutes; SD ± 7.01).

Discussion

As the need for GTRs in PA to improve postoperative quality of life (QOL) and reduce complications is very well documented in the published literature till date^{6–8} every neurosurgical center in the world is working toward improving its armamentarium to improve resection rates of PAs.

In various large series involving non-iMRI-guided transsphenoidal endoscopic resection of PA, average GTR rate of 79%¹² was reported with GTR range between 44 and 88%,¹³ while on analysis of studies that involved iMRI-guided eTSS for PAs, average initial GTR rate at iMRI was only 51% that was increased to 73% at 3 months postoperative MRI with the help of iMRI-guided resection.¹⁴ This data was in line with our series, where in overall cohort we had an initial GTR rates of 52% at iMRI that was improved to 80% at 3 months postoperative MRI.

The use of iMRI to guide resections of PAs has been a subject of forever debate among neurosurgeons as multiple studies have suggested that the use of iMRI biases the surgeon to perform a safer and less aggressive resections in pre-iMRI phase of surgery compared with surgeons who operate without iMRI guidance as suggested by significantly lesser resection rates at iMRI in various studies.^{15,16} Also, Powell in his experience suggested that iMRI shows only predictable remnants and does not help in improving GTR rates.¹⁷ With our experience of first 50 resections, we strongly disagree with this idea.

The majority of surprise residues in our series were located in IS space either alone ($n=8$) or in combination with SS residue in continuity ($n=2$) that were missed even on endoscopic inspection of resection cavity. Standalone rigid endoscopes, although are instrument of choice for PA resection but may fall prey to their straight trajectorial view, inability to “look behind” the normal gland, inability to grossly differentiate normal gland from tumor, and inability to inspect suprasellar space meticulously. In these scenarios, high-field 3T iMRI may serve as boon to detect surprise residues and further improve the resections and thus QOL of patient. Other isolated residues were seen in SS space ($n=3$), although they came to us as surprise, but majority were deemed unresectable due to difficult access. So, in surprise residue group, iMRI proved to be a very useful adjunct to identify residues in IS and SS space that would have been missed by endoscopes alone and helped us in improving GTR rate of this cohort by guiding us to resect 100% of IS residues, 33.33% of SS residue, and 50% of combined IS + SS residue. These findings are in consistency with findings of study by Serra et al,¹⁴ wherein they found that iMRI helped in detection of IS residue in 39% cases and the resultant second look surgery led to achieving GTR in 90% cases with IS residues.

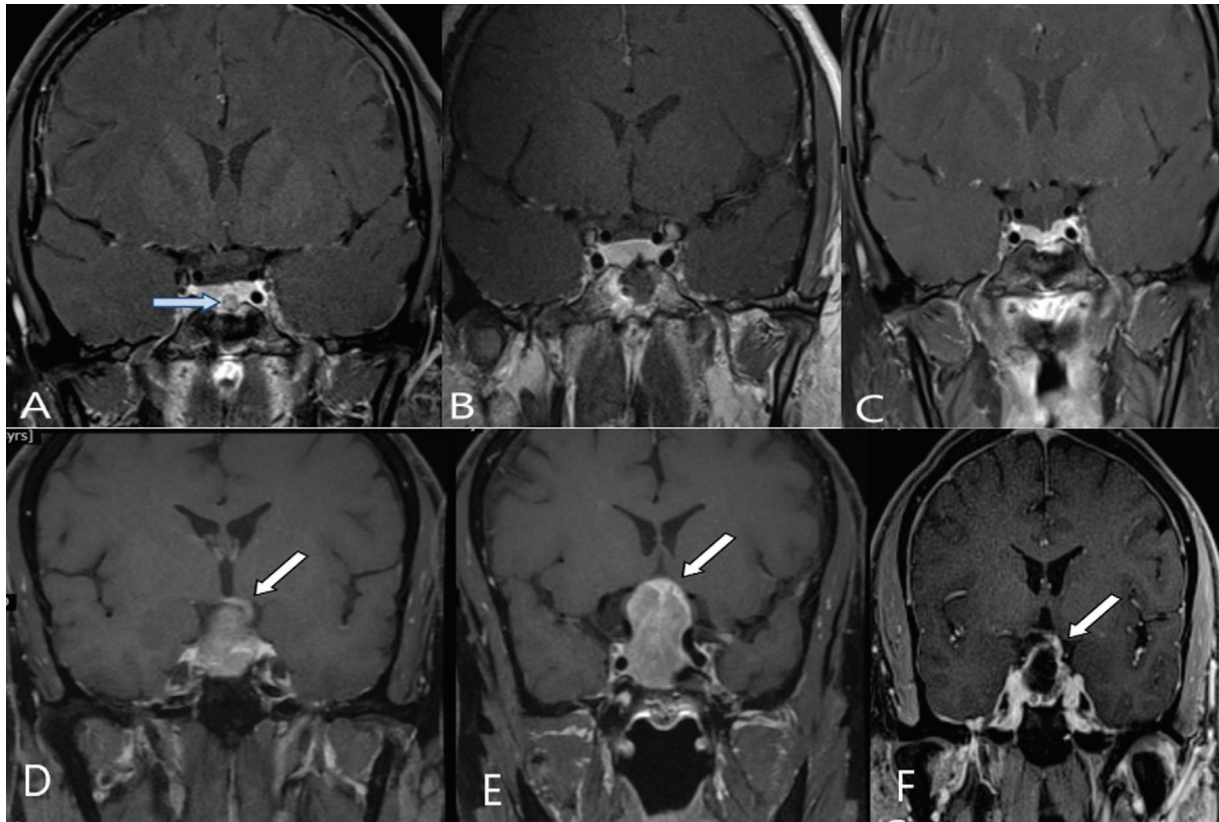


Fig. 6 (A) Preoperative magnetic resonance imaging (MRI) showing microadenoma (blue arrow). (B) Intraoperative (iMRI) showing primary gross total resection (GTR). (C) 3 months follow-up scan showing normal glandular anatomy. (D) Preoperative MRI showing enhancing stalk above macroadenoma. (white arrow) (E) Preoperative MRI showing macroadenoma with enhancing gland draped over left superolateral surface of adenoma. (white arrow) (F) iMRI showing GTR with preserved enhancing normal gland. (white arrow)

Among expected residue group, iMRI visualized 11 PS residues of which 4 were chased further and GTR was achieved. 3T MRI because of its high resolution helped us in better visualization of not only SS and IS region but PS region also and, thus, it helped in guiding us to further resect those four cavernous residues that were medial to medial carotid tangential line, thus achieving GTR in these cases that would otherwise have been missed. So, iMRI helped us to improve our GTR rates in this cohort by guiding our resection and thus helped us in achieving 36.33% (4/11) GTR in PS residues.

In our study, as GTR rates increased from 52 to 80%, thus reducing number of patients with residual disease significantly. Only 2 of 30 (6.66%) from intended STR group required adjuvant RT due to significant residual tumor left behind. Similar findings were seen in study by Berkmann et al,¹⁸ in which they observed that none of the patients in intended GTR iMRI group required adjuvant RT, whereas three patients in control group with non-iMRI-guided resection required further treatment with gamma knife radiotherapy.

Postoperative hypopituitarism is a known complication after eTSS with reported rates as high as 30% in old series.^{19,20} This is mainly because of normal gland resection due to its misidentification as tumor under endoscopic vision. iMRI serves as a useful adjunct to differentiate noncontrast enhancing gland from contrast enhancing tumor. Berkmann et al¹⁸ observed new onset hypopituitarism of any one of the

axes in 29% patients in iMRI-guided resection group versus 45% in control group operated without iMRI guidance. In our study, transient hormonal deficiencies were seen in 28% (14/50) patients and only 12% (6/50) required long-term replacement therapy (vs. 29% in other series). Thus, iMRI helped us in preserving normal pituitary functions in majority of patients with better identification of normal gland in 76% patients of our series

Multiple studies have demonstrated that increase cost of acquisition, delayed returns of investment, and increase in overall surgical time are major drawbacks of iMRI. At our center, we use a “nearby OT type” configuration, otherwise known as “Shared OR-MR configuration” that allows routine clinical work in between intraoperative runs, thus increasing the use of gantry and in turn results in a better cost-effectiveness. In our study, the overall increase in surgical time with iMRI use was 38.78 minutes, which was similar to average increase in time of 34.8 minutes reported in various studies^{16,21–24} and there were no untoward complications attributable to increased surgical time due to iMRI.

Conclusion

High-field intraoperative MRI is a useful adjunct in identifying not only SS but IS and PS residue and thus improving the EOR significantly in eTSS for PA, which in turn reduces overall treatment burden of patient and

improves QOL by reducing need for postoperative hormonal and adjuvant therapy. Most stupendous role of iMRI was its ability to detect and guide GTR of surprise IS residues and PS residues medial to carotids which would have been missed otherwise on standalone endoscopic inspection of resection cavity. With our initial experience we conclude that 3T iMRI should be used with eTSS to achieve a better and safe resection of PAs.

Funding

None.

Conflict of Interest

None declared.

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