Use of High-Field Intraoperative Magnetic Resonance Imaging During Endoscopic Transsphenoidal Surgery for Functioning Pituitary Microadenomas and Small Adenomas Located in the Intrasellar Region

Takafumi TANEI,1 Tetsuya NAGATANI,2 Norimoto NAKAHARA,1 Tadashi WATANABE,3 Tomoki NISHIHATA,4 Matthew L. NIELSEN,5 Shigenori TAKEBAYASHI,1 Masaki HIRANO,1 and Toshihiko WAKABAYASHI2

Departments of 1Neurosurgery and 4Radiology, Nagoya Central Hospital, Nagoya, Aichi; 2Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi; 3Department of Neurosurgery, Nagoya Daini Red Cross Hospital, Nagoya, Aichi; 5Imaging & Therapy Systems Division, Siemens Japan K.K., Tokyo

Abstract

The usefulness of 1.5-T high-field intraoperative magnetic resonance (iMR) imaging during transsphenoidal surgery for functioning pituitary adenomas was retrospectively evaluated based on long-term endocrine remission from the records of 14 patients who underwent transsphenoidal surgery with iMR imaging for functioning pituitary microadenomas and small adenomas located in the intrasellar region. The maximum tumor diameter was 9.3 ± 2.6 mm. Patients were diagnosed with acromegaly (n = 7), prolactinoma (n = 4), and Cushing’s disease (n = 3). If iMR imaging detected tumor remnants after resection, the resection cavity was reexamined and further resection was performed. Postoperative endocrine follow-up period was mean 33.7 ± 13.3 months. Tumor remnants were detected after the first resection in seven patients. Further resection was performed in five of these patients, and three achieved long-term endocrine remission. As a result, the overall long-term endocrine remission rate was 78.5% (11/14), instead of the 57.1% (8/14) that would be expected if iMR imaging had not been performed. Long-term endocrine remission had a tendency to be associated with the absence of tumor remnants on the final iMR images, but this was not significant (p = 0.09). Long-term endocrine remission was associated with presence of tumor remnants in the cavernous sinus on the final iMR images (p = 0.03). High-field iMR imaging is useful for depicting tumor remnants after resection, and increased the long-term endocrine remission rate for patients with functioning pituitary microadenomas and small adenomas.

Key words: functioning pituitary adenoma, high-field intraoperative magnetic resonance imaging, intrasellar region

Introduction

In recent years, advanced technologies such as neuronavigation and endoscopy have been used as adjuvant techniques in transsphenoidal surgery.1,7,16,18) The endoscopic approach improves visualization and overcomes certain drawbacks of microsurgical approaches. However, even when applying endoscopic techniques, a small part of pituitary adenomas can be overlooked. Intraoperative magnetic resonance (iMR) imaging combined with a neuronavigation system can provide real-time navigation images and enable image-guided surgery, allowing the surgeon to correct morphological and structural deformations that occur during tumor resection. In addition, visualizing tumor remnants using iMR imaging allows an objective judgment of whether to perform further tumor resection. As a result, the use of iMR imaging increases the rate of complete tumor removal and thus prevents further unnecessary exploration.2,10,11,24,29–31,33) High-field (1.5 tesla) iMR imaging offers superior image quality to low-field (0.12–0.2 tesla) iMR imaging, and can de-
tect intra- or para-sellar tumor remnants in addition to suprasellar tumor remnants.\(^{10,24,30}\) This may be advantageous in the treatment of patients with functioning microadenomas or small pituitary adenomas located in the intrasellar region. Although functioning microadenomas or small adenomas have high endocrine remission rates after transsphenoidal surgery, not all patients achieve endocrine remission.\(^{6,9,13,22}\) Our first hypothesis is that further resections of intrasellar remnant tumors depicted by high-field iMR imaging will increase long-term endocrine remission rate.

There is only one previous report of high-field iMR imaging in transsphenoidal surgery for functioning pituitary adenomas.\(^{10}\) Therefore, the reliability of high-field iMR imaging, especially of the intra- and para-sellar regions, is still unclear. Tumor remnants prevent endocrine remission or cause recurrence, and remission status after surgery can therefore be used as an indicator of the reliability of iMR imaging.\(^{35}\) Our second hypothesis is that long-term endocrine status will be associated with the presence or absence of tumor remnants on iMR imaging at the end of transsphenoidal surgery.

Tumor invasion of the cavernous sinus (CS) is correlated with poor endocrine outcome after surgery.\(^{6,9,13,22,30}\) However, postoperative changes make it difficult to interpret postoperative MR imaging in the intrasellar and CS region,\(^{35}\) and it is therefore difficult to judge whether or not remnant tumors are present. Our third hypothesis is that long-term endocrine status will be associated with the presence or absence of tumor remnants in the CS on the iMR imaging at the end of transsphenoidal surgery.

The present study was intended to evaluate our three hypotheses.

**Patients and Methods**

I. **Patient population**

A total of 67 patients with pituitary adenomas underwent endoscopic transsphenoidal surgery using high-field iMR imaging at the Department of Neurosurgery of Nagoya Central Hospital between September 2006 and June 2012. Thirty-nine of these patients had nonfunctioning pituitary adenomas and 28 had functioning pituitary adenomas. We reviewed the records of all 28 patients with functioning pituitary adenomas. Microadenoma was defined as a pituitary tumor with a maximum diameter \(< 1\) cm, or a small adenoma, defined as a pituitary tumor located only in the intrasellar region. Of the 28 patients with functioning pituitary adenomas, 14 (2 men and 12 women; age, mean \(\pm\) standard deviation [SD] 37.4 \(\pm\) 11.8 years) were classified with microadenomas \((n = 7)\) or small adenomas \((n = 7)\) and were included in the present analysis. The maximum tumor diameter was 9.3 \(\pm\) 2.6 mm \((\text{mean} \pm \text{SD})\). All patients presented with clinical symptoms due to hormone hypersecretion and had pituitary tumor on MR imaging. Preoperative diagnosis was made by endocrinologists, and was acromegaly in 7 patients, prolactinoma in 4, and Cushing’s disease in 3. Preoperative MR imaging revealed that two patients had tiny tumor invasion of the CS, nine patients had tumor attached to the CS without invasion, and three patients had no attachment of tumor to the CS. Patient details are summarized in Table 1.

II. **Endocrine assessments**

Postoperative endocrine assessments were performed on the first postoperative day and every 3 months thereafter. All follow-up examinations were performed at on-site visits. We analyzed the assessments that were obtained on the first postoperative day, 3 months postoperatively, and the latest follow-up time point. The endocrine follow-up period was 13–54 months \((\text{mean} \pm \text{SD} 33.7 \pm 13.3 \text{ months})\). Endocrine remission was determined at 3 months postoperatively, and was defined as improvement of preoperative clinical symptoms and normalization of endocrine levels. Endocrine remission of acromegaly was defined as basal plasma growth hormone \(< 1.0 \text{ ng/ml}\) and normalization of age-related insulin-like growth factor-1. Endocrine remission of prolactinoma was defined as basal plasma prolactin (PRL) \(< 20 \text{ ng/ml}\). Endocrine remission of Cushing’s disease was defined as normalization of basal plasma adrenocorticotropic hormone and either dependency on glucocorticoid substitutions or morning plasma cortisol between 6 and 26 \(\mu\)g/dl without hormone replacement.\(^{15}\) Patients who did not meet these criteria at 3 months postoperatively were considered to have persistent active disease. Patients who did meet these criteria at 3 months postoperatively were considered to be in remission. Patients who maintained this status until the latest follow-up time point were considered to be in long-term remission. Endocrine recurrence was defined as remission at 3 months postoperatively but reappearance of clinical symptoms and secondary increase in plasma hormone levels above the normal range during follow-up.

III. **Operating room setup**

The high-field strength (1.5 tesla) MR imager (Magnetom Symphony; Siemens Healthcare, Erlangen, Germany) consisted of a superconductive magnet \((\text{length} 160 \text{ cm}, \text{inner bore diameter} 60 \text{ cm})\), gradient system maximum field strength 30 mT/m,
Table 1 Patient characteristics, intraoperative magnetic resonance (iMR) imaging findings, and endocrine outcomes

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Function</th>
<th>Follow up (mos)</th>
<th>Tumor characteristics</th>
<th>Tumor remnants on 1st iMR imaging</th>
<th>Further resection performed</th>
<th>Tumor remnants on final iMR imaging</th>
<th>Remission at 3 mos</th>
<th>Long-term remission</th>
<th>Plasma hormone levels*</th>
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*Plasma hormone levels above the upper normal limit. bMorning plasma cortisol level without hormone replacement. cMorning plasma cortisol level with hormone replacement. dPlasma growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels with octreotide acetate. eUnits are ng/ml for prolactin (PRL), GH, and IGF-1, or μg/dl for adrenocorticotropic hormone (ACTH) and cortisol. Acro: acromegaly, CS: cavernous sinus, Cushing: Cushing disease, F: female, M: male, preop.: preoperative, postop.: postoperative, PRLoma: prolactinoma.
and effective slew rate 125 T/m/sec) and was located in an operating room with radiofrequency shielding. The operating table was positioned parallel to the scanner during surgery so that the patient’s head was outside the 5-gauss line. When imaging was necessary, the table was manually rotated by 180 degrees about a vertical axis to align it with the scanner bore. The head-holder had a bivalve shape, consisting of two parts, and contained an 8-channel receiver array. The upper part of the head-holder was sterilized with plasma and placed above the operating field for MR imaging, but was removed during surgery. Rapid automatic image registration was realized with a reference array attached to the upper part of the head-holder. The array contained 14 MR imaging-visible fiducial markers and four infrared reflector spheres that were continuously tracked by a ceiling-mounted infrared camera. Navigation was accomplished with an error <0.6 mm.

IV. Preoperative MR imaging

Before surgery, the patient’s head was fixed in the head holder with five metallic pins, and MR imaging with three sequences was performed. Fat suppression MR images were taken using fat saturation pulses, and the pulse sequence was called ‘FatSat’ (FS). A pulse sequence with a reduced frequency of fat saturation pulses was called ‘Quick FatSat’ (Q-FS). First, T2-weighted images were acquired in the sagittal and coronal planes using two-dimensional turbo spin echo with the FS pulse sequence. Images were acquired in stacks of 17 slices that were centered on the pituitary gland and covered 30 mm along the slice axis (1.6 mm slice thickness). Next, contrast-enhanced T1-weighted images were acquired in the coronal plane using the Q-FS pulse sequence with three-dimensional (3D) fast low angle shot (FLASH) in a 107-mm-thick slab centered on the pituitary gland (0.7 mm slice thickness). This T1-weighted Q-FS 3D FLASH sequence is called volumetric interpolated brain examination (VIBE).17,32

Finally, T1-weighted 3D FLASH images of the entire head and fiducial markers were acquired to be used as reference images for registration with the navigation system. The contrast-enhanced VIBE and T1-weighted 3D FLASH images were sent to the navigation system.

V. iMR imaging

Transsphenoidal surgery was performed by endonasal endoscopy using rigid endoscopes that visualized the surgical site on a monitor without a microscope. The whole transsphenoidal procedure was same as the regular operating technique. The adenoma was removed using curettes, grasping forceps, and suction devices. The first iMR imaging was performed when the surgeon judged that most or all of the tumor had been excised. Bone wax was placed inside the resection cavity to prevent the blood from pooling and to improve interpretation of the intraoperative images. The surgical site was covered with a sterile drape and the surgical table rotated 180 degrees into the center of the scanner. iMR images were obtained using two types of pulse sequences, T2-weighted turbo spin echo and contrast-enhanced VIBE, in the same manner as the preoperative MR imaging. If this first iMR imaging depicted tumor remnants, new contrast-enhanced VIBE images were sent to the navigation system, the resection cavity was reexamined, and further resection was performed. In the case of intraoperative cerebrospinal fluid leakage, the intrasellar region was packed with abdominal fat that was obtained from the right lower abdomen and covered with fibrin glue. Final iMR imaging was performed after all surgical procedures were completed. The final iMR image was used to determine the presence or absence of tumor remnants, and the presence or absence of tumor remnants in the CS.

VI. Statistical analysis

The associations between the final iMR imaging finding (tumor remnants or no tumor remnants) and endocrine outcome (remission or no remission), and between the final iMR imaging finding (tumor remnants in the CS or no tumor remnants in the CS) and endocrine outcome (remission or no remission), were analyzed by Fisher’s exact test using JMP® software (SAS Institute Inc., Cary, North Carolina, USA). Probability values <0.05 were considered statistically significant.

Results

Long-term endocrine remission was achieved by 11 of the 14 patients. Figure 1 gives an overview of the results and consequences of iMR imaging in all 14 cases. The first iMR image after resection showed no tumor remnants in 7 patients. No further resection was performed, and all seven patients achieved long-term endocrine remission (Fig. 1). In the other seven patients, the first iMR image after resection indicated some tumor remnants. Further resection was performed in five patients, and remnant tumor tissues were found. Further resection was not performed in the other two patients because the remnant tumor had invaded the CS (Case 14; Fig. 2) or had strongly adhered to the normal pituitary gland (Case 13). Three of the five patients who received further resection went on to achieve long-term endo-
High-Field iMR Imaging for Functioning Pituitary Adenomas

Fig. 1 Overview of the results and consequences of high-field intraoperative magnetic resonance (iMR) imaging used in transsphenoidal surgery for functioning pituitary microadenomas and small adenomas located in the intrasellar region of 14 patients. After each resection, iMR images were examined for tumor remnants. If evidence of tumor remnants was present, further resection was considered. Patients were classified as “Remission” or “No remission” according to their endocrine status at final follow-up. False negative indicates no remnant tumor identified on the final iMR image but patient did not achieve endocrine remission. False positive indicates remnant tumor identified on the final iMR image but patient achieved endocrine remission.

One of these cases is illustrated in Fig. 3. Tiny tumor remnants were depicted on contrast-enhanced VIBE images, and the presence of remnant tumor tissue was confirmed by endoscopy (Fig. 4). Two of the five patients who received further resection did not go on to achieve endocrine remission. In one patient (Case 5) further partial resection was performed, but the remnant tumor invading the CS portion was not resected. In the other patient (Case 1), complete tumor removal was confirmed by endoscopy and final iMR imaging, and the patient was in endocrine remission at 3 months postoperatively. However, plasma PRL level was elevated at 16 months postoperatively, so this case was classified as recurrent. In this case, the final iMR imaging finding (no tumor remnants) gave a false negative according to the long-term endocrine remission status. As a result, the overall long-term endocrine remission rate was 78.6% (11/14), instead of the 57.1% (8/14) that would be expected if iMR imaging had not been performed. Further resections of the remnant tumors depicted by the iMR imaging therefore led to a 21.4% (3/14) increase in the long-term endocrine remission rate.

Eleven patients were classified as having no tumor remnants on the final iMR image, and 10 of these achieved long-term endocrine remission. Three patients were classified as having some tumor remnants on the final iMR image. In two of these cases, the remnant tumor was located in the CS, and although plasma hormone levels had decreased slightly at the first postoperative day, they subsequently increased and the patients did not achieve endocrine remission. In the other patient (Case 13), the remnant tumor could not be completely removed because the tumor was fibrous and strongly adhered to the normal pituitary gland. However, this patient achieved long-term endocrine remission. In this patient, the final iMR imaging finding (tumor remnants) gave a false positive according to the long-term endocrine remission status. Long-term endocrine remission tended to be associated with the absence of tumor remnant findings on the final iMR image, but this did not reach the level of statistical significance (Fisher’s exact test, \( p = 0.09 \)). The patients with false negative and false positive find-
ings both had prolactinoma, both were taking cabergoline preoperatively, and the tumors consisted mainly of fibrous components on endoscopic examination.

Twelve patients were classified as having no tumor remnants in the CS on the final iMR image. Of these 12 patients, 11 achieved long-term endocrine remission. Neither of the two cases that were classified as having tumor remnants in the CS on the final iMR image achieved long-term endocrine remission. The final iMR imaging finding of tumor remnants in the CS was associated with a failure to achieve long-term endocrine remission (Fisher’s exact test, \( p = 0.03 \)).

There were no adverse events related to high-field iMR imaging, and no accidents caused by the ferromagnetic instruments. Postoperative endocrine evaluations did not reveal new endocrine deterioration of pituitary hormones. Intraoperative cerebrospinal fluid leakages were identified in eight patients. Postoperative cerebrospinal fluid leakage was not identified in any patients. Postoperatively, nine patients had diabetes insipidus and two patients had syndrome of inappropriate secretion of antidiuretic hormone. All of these complications were transient and improved within 2 weeks of surgery. There were no permanent complications or deaths during the follow-up period.

Discussion

The results of this retrospective review support our three hypotheses. Further resection of remnant tumors depicted by iMR imaging increased the long-
term endocrine remission rate from 57.1% to 78.6%, and long-term endocrine remission tended to be associated with absence of tumor remnants on the final iMR images, and was associated with tumor remnants in the CS on the final iMR images. Even tiny remnant tumors were associated with a failure to achieve long-term endocrine remission.

iMR imaging and its neurosurgical applications were first described in 1997. Since this time, iMR imaging has been frequently applied, particularly in craniotomies. The first uses of iMR imaging in transsphenoidal surgery for pituitary adenomas were reported around 2000, and iMR imaging is now well known to be an effective and safe modality for transsphenoidal surgery of pituitary adenomas. Detection and visualization of tumor remnants by iMR imaging contributes to an increased rate of complete tumor removal, and prevents unnecessary exploration and injury around normal tissues. iMR imaging can reliably detect the presence of tiny remnant tumors in the CS. Interpretation of the iMR imaging findings of tumor remnants in the intra- and para-sellar regions to be highly reliable, because all five patients who underwent further resections had the presence of remnant tumor tissues confirmed by endoscopy, and no patient with tumor remnants in the CS achieved long-term endocrine remission. Pseudocapsulectomy was tried to remove the tumor en bloc in many cases of microadenomas, but the procedure was not completed in some cases, resulting in remnant tumor tissues. Remnant tumor tissues were prone to remain at the bottom of the sella turcica, which is a blind angle for endoscopy. The association between long-term endocrine remission status and the absence of tumor remnants on the final iMR images did not reach the level of statistical significance; however, we believe that this finding is because of the small number of patients.

Morphologically complete tumor resection is a prerequisite for patients with functioning adenomas to achieve long-term endocrine remission. Tumor remnants prevent endocrine remission or induce endocrine recurrence. Anatomical localization of the tumor is one of important factors for endocrine outcomes. Tumor invasion of the CS is correlated with poor endocrine outcome after surgery. Complete tumor removal was not achieved in either of our two patients who had tiny tumor remnants in the CS on the final iMR images, and the presence of tumor remnants in the CS was significantly associated with failure to achieve long-term endocrine remission. These findings suggest that high-field iMR imaging can reliably detect the presence of tiny tumor remnants in the CS. Interpretation of the intra- and para-sellar regions on postoperative MR images is difficult due to postoperative changes. In determining whether or not remnant tumors are present, high-field iMR imaging may have an advantage over postoperative MR imaging because it is not confounded by such postoperative changes. Early confirmation of the presence of remnant tumors allows the implementation of early supplementary treatments such as gamma knife surgery and medical therapy. If the tumor invades the CS, complete tumor removal is difficult to achieve by the standard transsphenoidal approach and long-term endocrine remission is unlikely. Therefore, although high-field iMR imaging can depict tiny remnant tumors in the CS, removing these tumors requires other techniques. Another technique to increase long-term endocrine remission rate may be intraoperative measurement of plasma hormone level, as if the plasma hormone level did not sufficiently decline, additional searching for tumor resulted in higher rate of complete tumor resection and remission.
One of the advantages of high-field iMR imaging is the higher image quality compared to low-field iMR imaging, meaning that tiny tumor remnants can be detected not only in the suprasellar region, but also in the intrasellar region and the CS.20,24,30 Therefore, high-field iMR imaging has the advantage of being able to depict tiny tumor remnants in patients with microadenomas or small adenomas located in the intrasellar region. In this study, contrast-enhanced VIBE images were very useful for depicting tiny tumor remnants. VIBE sequence was originally developed for abdominal imaging,28 but several studies have reported the usefulness for brain imaging.17,32 By reducing the frequency of fat saturation pulses, the VIBE sequence has a shorter acquisition time than conventional T2-weighted pulse sequences with FS. Therefore, high-resolution T2-weighted Q-FS images can be acquired by obtaining thin slices without lengthening acquisition time. High (sub-millimeter) resolution MR images can detect tiny tumor remnants after tumor resection,24 Tumor remnants are depicted more clearly by using contrast medium; the pituitary adenomas are depicted as less enhanced lesions compared to normal pituitary gland. T1-weighted FS imaging can detect pituitary adenomas preoperatively, but intraoperative image quality is degraded due to artifacts induced by contamination from blood, saline, and air. Of our five patients who underwent further resections, remnant tumors were depicted on contrast-enhanced VIBE images and detected by endoscopy, whereas the remnants were not found on the intraoperative T2-weighted FS images. We observed one false negative case (no remnant tumor identified on iMR imaging but did not achieve endocrine remission) and one false positive case (remnant tumor identified on iMR imaging but endocrine remission achieved). Both patients had prolactinomas and were taking cabergoline preoperatively, and the tumors were mainly fibrous components. Dopamine agonists such as bromocriptine, cabergoline, and quinagolide are the most effective pharmacological tools to normalize plasma PRL levels with prolactinomas.20 Although the impact of long-term dopamine agonist therapy on subsequent surgical treatment is controversial, with some reports of similar or better surgical outcomes following surgery after pretreatment with dopamine agonist therapy,14,26 including one study suggesting that the surgical remission rate is lower following dopamine agonist therapy.21 Patients exposed to dopamine agonists were more likely to have tumor fibrosis, and fibrous tumors had lower probability of going into endocrine remission than non-fibrous tumors, suggesting that fibrosis may interfere with a complete hormonal cure.21 Therefore, fibrous tumors may be one of the factors contributing to the false positive or negative findings on iMR imaging, and may be a risk factor for long-term endocrine remission.

High-field iMR imaging is a useful supporting technique for endoscopic transsphenoidal surgery of functioning pituitary microadenomas and small adenomas located in the intrasellar region, and increased the overall long-term endocrine remission rates from 57% to 79%. In addition, visualization of tumor remnants by iMR imaging may prevent unnecessary exploration and injury to normal tissues. The present study is limited because of the small number of patients. Further studies of larger cohorts are needed to confirm the usefulness of high-field iMR imaging during endoscopic transsphenoidal surgery of functioning pituitary adenomas.

Conflicts of Interest Disclosure

No financial support was received for this research. The findings presented herein have not been previously published. T. Tanei, T. Nagatani, N. Nakahara, T. Watanabe, S. Takebayashi, M. Hirano, and T. Wakabayashi have registered online Self-reported COI Disclosure Statement Forms through the website for The Japan Neurosurgical Society members.

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Address reprint requests to: Takafumi Tanei, MD, PhD, Department of Neurosurgery, Nagoya Central Hospital, 3–7–7 Taiko, Nakamura-ku, Nagoya 453-0801, Japan.
e-mail: ns gtakasyun@msn.com