CLINICAL STUDY

Transsphenoidal surgery in acromegaly investigated by intraoperative high-field magnetic resonance imaging

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Abstract

Objective: The aim of the study was to evaluate the effect of intraoperative high-field (1.5 Tesla) magnetic resonance imaging (MRI) on the results of transsphenoidal surgery of GH-secreting pituitary macroadenomas.

Methods: Twenty-three acromegalic patients (mean tumor size, 25 ± 12 mm; untreated preoperative GH, 4.2–159 μg/l; IGF-I, 349–1111 μg/l) were investigated by intraoperative high-field MRI. If intraoperative imaging depicted an accessible tumor remnant, resection was continued.

Results: In five patients intraoperative MRI led to further tumor removal, two of these met the consensus criteria for endocrine remission after 3 months. In two patients basal GH and oral glucose tolerance test (OGTT) were <2 μg/l, only IGF-I was slightly elevated, and in one patient GH was <5 μg/l and OGTT was 2 μg/l with elevated IGF-I. Final intraoperative MRI showed no tumor remnants in 14 patients; eight of them met the consensus criteria for remission of acromegaly. In the patients with MRI showing incomplete removal (four suspect findings and five patients with intended partial removal) none was normalized.

Conclusion: With regard to the patients with a tumor configuration in whom complete tumor removal was considered (n = 18), intraoperative MRI increased the rate of endocrine normalization from 33 to 44% applying the consensus criteria, and improved endocrine outcome to ‘nearly normalization’ in another 17%. With regard to preoperative GH levels and tumor size, intraoperative MRI can help to achieve endocrine remission in patients who are normally considered not to be curable. However, taking GH as the tumor marker, even intraoperative high-field MRI was not able to detect tumor remnants in every case.

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Introduction

Transsphenoidal surgery in acromegaly leads to normalization of growth hormone (GH) excess in about 50% of the patients (1–6), based on the definition of normalization following the strict Giustina criteria (7, 8). In our series of 668 patients undergoing surgery for acromegaly, 57.3% of all patients undergoing primary transsphenoidal surgery (290 of 506) fulfilled these criteria (GH <1 μg/l, oral glucose tolerance test (OGTT) <1 μg/l, and normal insulin-like growth factor-I (IGF-I)). The best results were achieved in microadenomas (75.3%); however, when considering the macroadenomas, only 51.4% (182 of 354) had a normalized GH excess (9).

Among advanced technologies in transsphenoidal surgery, neuronavigation (10–13), endoscopy (14, 15), and especially intraoperative magnetic resonance imaging (MRI) (16–21) are remarkable adjuvant techniques that have been introduced into the operating room in recent years. Intraoperative imaging is used as immediate intraoperative quality control, allowing the extending of a resection in cases where tumor remnants are depicted (16–21). By applying a low-field magnetic resonance (MR) scanner in the operating room environment we were able to demonstrate that in a third of pituitary macroadenomas suprasellar tumor remnants could be detected during surgery by intraoperative MRI (17). This included tiny remnants of 3–4 mm and also larger adenoma remnants which were hidden from the surgeon’s eye in folds of the descending sella diaphragm. Low-field MRI, however, has the drawback of a reduced image quality, especially for the region of the cavernous sinus, compared with the image quality in routine neuroradiology. As a consequence, in 2002 we advanced our concept of surgery in the fringe field of a MR scanner and adapted a standard high-field 1.5 Tesla (T) MR scanner to the operating room environment (22). The aim of this study was to evaluate the effects of intraoperative high-field MRI
in transsphenoidal surgery of GH-producing macroadenomas.

**Subjects and methods**

**Patient population**

A total of 23 consecutive patients (thirteen female and ten male; age range, 30–69 years) with GH-secreting pituitary macroadenomas underwent transsphenoidal surgery between June 2002 and May 2004 in a prospective study with the setup described below. None of the patients had had pituitary surgery previously. Eight patients (nos 4, 5, 6, 10, 11, 12, 16 and 17) had received presurgical medical treatment with somatostatin analogues and in four patients (nos 4, 6, 11 and 16) it was continued after surgery. The mean tumor size was 25±12 mm, in the untreated patients preoperative GH levels ranged from 4.2 to 159 μg/l and IGF-I levels ranged from 349 to 1111 μg/l. Patient details are summarized in Tables 1 and 2. In five patients (nos 6, 8, 10, 11 and 16) preoperative imaging revealed an extensive tumor configuration with either a distinct asymmetrical suprasellar extension or a definite invasion of the cavernous sinus so that in these patients it was specified before surgery that only a subtotal resection was possible. The local ethical committee approved the intraoperative high-field MRI, and signed informed consent was provided in all cases.

The diagnosis of acromegaly was made clinically and biochemically after lack of suppression of serum GH levels below 1.0 μg/l during OGTT, as well as elevated IGF-I levels. Preoperative as well as follow-up examination after 7 days and 3 months included endocrine dynamic testing, as well as ophthalmological examination according to a standard protocol (see below). MRI was performed pre-, intra- and 3 months postoperatively. In neuropathological examination, immunohistochemical analysis was available in all patients. Furthermore, in all patients surgical complications, such as cerebrospinal fluid fistulas and meningitis, were documented.

**Operating room setup**

A 1.5 T Magnetom Sonata Maestro Class scanner (Siemens AG Medical Solutions, Erlangen, Germany) was installed in an operating room with radiofrequency shielding (22). This was a high-field MR scanner with a superconductive 1.5 T magnet with a length of 160 cm and an inner bore diameter of 60 cm equipped with a gradient system with a field strength of up to 40 mT/m (effective 69 mT/m) and a slew rate of up to 200 T/m per s (346 T/m per s effective). A rotatable surgical table (Trumpf, Saalfeld, Germany) was adapted to the scanner to allow for a special surgical MR tabletop. This surgical table could be locked into various positions. The principal surgical position was at 160°, with the patient’s head at the 5 G line (<4 m distance to the center of the scanner). As soon as the rotating mechanism was locked, the height of the table and the angle of tilt as well as the lateral tilt could be modified. The table movements were controlled remotely. Only the rotation about the table axis to turn the table into the axis of the scanner was performed manually for safety reasons, MR-compatible ventilation (Servo 900C; Siemens AG Medical Solutions, Erlangen, Germany) and MR-compatible monitoring (Invivo Research, Orlando, FL, USA).

**Table 1** Tumor configuration and endocrine data in patients with resectable adenomas where first intraoperative MRI did not reveal any tumor remnant (n = 10).

<table>
<thead>
<tr>
<th>Patient numbers</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Suprasellar extension</th>
<th>Maximum diameter (mm)</th>
<th>Preoperative GH (μg/l)</th>
<th>7 days postoperative GH (μg/l)</th>
<th>3 months postoperative GH (μg/l)</th>
<th>Endocrinology OGTT (μg/l) Preoperative IGF-I (μg/l) 7 days postoperative IGF-I (μg/l) 3 months postoperative IGF-I (μg/l)</th>
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†Patients were treated with somatostatin analogues before surgery (preoperative endocrine data are hormone levels under medication just prior to surgery); M, male; F, female; is, intrasellar; s1, suprasellar extension without visual compromise; s2, suprasellar extension with visual compromise; sphe, tumor extension to the sphenoid sinus; OGTT, nadir GH level during an OGTT; *normalized sex- and age-adjusted IGF-I level; shaded values, endocrine remission meeting consensus criteria.
Table 2  Tumor configuration, consequences of intraoperative imaging, and endocrine data in patients where first intraoperative MRI was at least suspicious for a tumor remnant \((n = 13)\). In patient nos 6, 8, 10, 11 and 16 only partial resection was intended due to an unresectable tumor configuration in preoperative MRI.

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†Patients were treated with somatostatin analogues before surgery (preoperative endocrine data are hormone levels under medication just prior to surgery); M, male; F, female; is, intrasellar; s1, suprasellar extension without visual compromise; s2, suprasellar extension with visual compromise; sphe, tumor extension to the sphenoid sinus, ps, parasellar tumor extension (cavernous sinus invasion); ic, incomplete resection; s, suspicious for remnant; c, complete resection; OGGT, nadir GH level during an OGGT; *normalized sex- and age-adjusted IGF-I level; shaded values, endocrine remission meeting consensus criteria; n.a., not available; ‡continued treatment with somatostatin analogues; §postoperative radiotherapy and continued treatment with somatostatin analogues.
were available for control of anesthesia and for wireless 2.4 GHz data transfer from the RF cabin. The perfusors and infusion pumps were shielded for MR compatibility (MRI-Caddy; MIPM, Mammendorf, Germany). The NC4 multivision microscope (Zeiss, Oberkochen, Germany) was installed at the left side of the head outside the 5 G line.

**Intraoperative MRI**

In transsphenoidal surgery that did not require head fixation, imaging was performed using a standard U-shaped large flexible coil that was adapted and draped to the head. The whole transsphenoidal procedure was identical to that performed in regular operating rooms. It was accomplished as a pernasal approach, paraseptal-submucosal or direct transsphenoidal with endoscope assistance. Selective adenectomy was performed in all patients. Except for a MR-compatible nasal speculum, which was inserted just prior to intraoperative imaging, regular operating microinstruments were used during transsphenoidal surgery at the 5 G line. In all patients the sella floor was covered with muscle fascia, which was obtained during the same surgical session from the right thigh; for security reasons fully MR-compatible instruments were used to obtain the fascia. In case of intraoperative cerebrospinal fluid leakage a transitory lumbar drainage was administered. In direct pernasal surgery no nasal package was necessary.

The timing of intraoperative imaging was decided by the neurosurgeon; intraoperative imaging was either performed when the surgeon had the impression of complete tumor removal or, in the case of incomplete removal, when the surgeon thought that no further removal at this stage of surgery was possible by the transsphenoidal approach. All operations were performed by the first author (R.F). Just prior to intraoperative imaging, the opened sella floor was covered with a piece of bone wax for better delineation of the sella outlines in the intraoperative images. The surgical site was then covered with a drape and the table was rotated 160° into the scanner. The time between the decision for intraoperative MRI and the actual start of imaging was about 2 min.

After the patient was moved into the center of the scanner certain circuits were switched off, including the fluorescent lamps and the operating microscope. Imaging then started with a localizer sequence (field of view (FOV), 280 mm; repetition time (TR), 20 ms; echo time (TE), 50 ms; scan time, 9 s), T2-weighted half Fourier single shot turbo spin echo (HASTE) sequences (slice thickness, 5 mm; FOV, 230 mm; TR, 1000 ms; TE, 89 ms; scan time, 25 s at five acquisitions) in coronal and sagittal orientation were measured next to give a quick overview. Afterwards, T1-weighted coronal and sagittal spin echo sequences were applied (slice thickness, 3 mm; FOV, 270 mm; TR, 450 ms; TE, 12 ms; scan time, 4 min 57 s at four acquisitions). Additionally, high-resolution T2-weighted turbo-spin echo sequences with an in-plane resolution of 0.6 × 0.4 mm were measured (slice thickness, 3 mm; FOV, 230 mm; TR, 4000 ms; TE, 97 ms; scan time, 6 min 6 s at three acquisitions).

In cases where intraoperative imaging depicted some remaining tumor that seemed to be accessible for further resection, surgery was continued. After further resection, a repeated intraoperative MRI was performed prior to closure. The identical imaging protocol was applied for preoperative as well as postoperative imaging after 3 months.

**Endocrine assessment**

All patients underwent a standard protocol for dynamic endocrine testing that included basal serum measurement of free thyroxine, thyrotropin, prolactin, luteinizing hormone, follicle-stimulating hormone, and testosterone or estradiol. The pituitary–adrenal axis was assessed by a short adrenocorticotropic stimulation test. For endocrine assessment of acromegaly mean basal GH, nadir GH values following OGTT, and IGF-I were measured. GH was measured using a two-site chemiluminescent immunometric assay (Immulite 2000 HGH; DPC, Los Angeles, CA, USA). This assay has an intra- and interassay variation of 3.4 and 5.5% respectively, in assay midrange. Serum IGF-I was measured using a solid-phase enzyme-labeled chemiluminescent immunometric assay (Immulite 2000 IGF-I; DPC). This assay has an intra- and interassay variation of 3.0 and 8.1% respectively, in assay midrange. Normal ranges according to age and sex were provided by the manufacturer.

**Results**

We did not observe any adverse events related to intraoperative high-field MRI; there were no accidents caused by the ferromagnetic instruments. The surgical workflow was interrupted by imaging for about only 15 min. Postoperative endocrinological evaluation did not reveal a deterioration of the thyroid, adrenocorticoïd, or gonadotropin axis in any patient. We did not observe any other complications, such as wound infections, postoperative meningitis, visual disturbance, or postoperative cerebrospinal fluid leakage in this series.

Neuropathological examination documented pituitary adenomas in all cases. In all patients immunohistological evaluation confirmed GH expression; in 11 patients the GH expression was a major part of a plurithormonal secretion (nos 1, 2, 3, 8, 9, 11, 12, 13, 19, 22 and 23). In two of these (nos 1 and 22) preoperative serum prolactin levels were elevated (538 and 1480 mU/l; norm < 500 mU/l).

Intraoperative imaging quality compared well with preoperative standard image quality obtained with
high-field MR scanners. There were no artifacts caused by the surgical site impeding image interpretation. In contrast to our previous experience with intraoperative low-field MRI, where only the suprasellar tumor extension could be reliably evaluated, intraoperative high-field MRI even allowed the identification of the intrasellar extent of tumor removal, as well as evaluation of an invasion of the cavernous sinus. Application of a piece of bone wax at the position of the removed sella floor and irrigation with saline, which remained in the intrasellar cavity during imaging, prevented problems with image interpretation such as blood mimicking tumor remnants. The identical pre- and intraoperative image slice position allowed a good comparison of pre- and intraoperative images in a side-by-side display. Hence fibrin glue applied for hemostasis could be identified and differentiated from tumor remnants.

Furthermore, the use of porcelain-coated drills prevented extensive drilling artifacts which would otherwise obscure image interpretation. Since T2-weighted imaging proved to be superior in the identification of tumor remnants and additional T1-weighted imaging did not provide any further information T1-weighted imaging was omitted from the intraoperative imaging protocol in most of the patients. HASTE imaging gave a quick overview after some 20 s, so that in the case of a larger remnant surgery could have been continued without further detailed time-consuming imaging. This shortcut was applied in one of the five patients with extended resection (no. 14).

Figure 1 gives an overview of the results and consequences of intraoperative MRI in the 23 acromegalic patients. In ten patients first intraoperative MRI had shown no tumor remnants (Table 1). Among these patients 60% (six of ten) were in remission after 3 months according to the consensus criteria. In none of the other four patients did imaging after 3 months reveal a suspicious tumor remnant. Examples for complete tumor removal and endocrine normalization from 33.3% (six of 18) to 44.4% (eight of 18) using the consensus criteria, and improved endocrine outcome in another 16.7% (three of 18).

In the group of patients in whom the first intraoperative imaging depicted some remaining tumor (n = 13; Table 2), resection was extended in five patients (38.5%). Among the other eight patients, in five a subtotal resection was intended primarily (nos 6, 8, 10, 11 and 16) due to their tumor configuration (Fig. 4). In two patients (nos 4 and 7) an invasion of the cavernous sinus that became apparent during surgery prevented further resection, and in another patient (no. 1) the remnant that was depicted by intraoperative MRI was fixed in a suprasellar fold so that it could not be further removed (Fig. 5).

Considering only the 18 patients with intended complete tumor removal, intraoperative imaging revealed definite tumor remnants or at least suspicious findings in eight patients (44.4%), leading to an extended resection in five (27.8%; five of 18). This increased the rate of complete tumor removal and endocrine normalization from 33.3% (six of 18) to 44.4% (eight of 18)

Among the five patients undergoing further resection there was one patient (no. 20) in whom the resection was extended twice (Fig. 6). Final intraoperative scanning had shown no further remnant in four and a suspicious finding in one patient (no. 3), depicting an invasion into the cavernous sinus, where the tumor was not further accessible. The endocrine follow-up in two of them (nos 14 and 20) revealed that they had met the consensus criteria for endocrine remission in the postoperative control after 3 months (Fig. 6). In two patients (nos 5 and 9) the GH excess was nearly normalized: basal serum GH levels and GH levels after OGTT were <2 μg/l, only the IGF-I level was slightly elevated. Repeated imaging at 3 months did not show any remnant (Fig. 7). In a fifth patient undergoing extended resection (no. 3) no postoperative control after 3 months was available because the patient went back to his home country. Endocrine evaluation after 1 week had shown improved endocrine results with a serum GH level <5 μg/l, an OGTT of 2 μg/l, and an elevated IGF-I level.

Comparing the results of intraoperative imaging and the estimation of the surgeon about the extent of resection revealed a discrepancy in six patients (26.1% = six of 23). In five patients intraoperative MRI had shown some remaining tumor where the surgeon did not suspect any remnant, so surgery was continued (see above). In
another patient (no. 2) the surgeon was not sure whether
the tumor had been completely removed but intraopera-
tive MRI confirmed complete removal, as did postoperative
endocrine evaluation. In four patients an invasion of the
cavernous sinus (focal invasion in patient no. 3 and gen-
eral invasion in patients nos 4, 7 and 10) was suspected by
intraoperative inspection, as well as by intraoperative
MRI. In five patients clear tumor remnants were antici-
pated by the surgeon and visualized by intraoperative
MRI (nos 1, 6, 8, 11 and 16). Among them only in one
patient (no. 1) was complete removal intended because
of the tumor configuration visualized in preoperative
imaging; however, during surgery a firm remnant was
stuck in a suprasellar fold, fixed under the optic chiasm
close to the anterior cerebral artery that was not further
accessible.

There were no false positive findings of intraoperative
MRI compared with endocrine remission criteria, i.e. in
none of the patients where intraoperative MRI had
depicted a tumor remnant were remission criteria
met. In all cases where intraoperative MRI was suspi-
cious for some parasellar remnant (n = 4), postopera-
tive imaging after 3 months confirmed the infiltration
of the cavernous sinus. In all cases where intraopera-
tive imaging had depicted complete removal and no
full endocrine remission was achieved (n = 6; false
negative six of 23 = 26.1%), postoperative imaging
after 3 months also did not shown any definitive
tumor remnant.

**Discussion**

Persisting acromegaly after transsphenoidal surgery
depends on parameters such as GH levels, IGF-I levels,
tumor size, and invasiveness. The higher the GH
excess, the larger the tumor, the more invasive con-
figuration then normalization is less probable (9). Medi-
cal treatment of acromegaly is becoming more
common, some authors even argue that resectable ade-
nomas should no longer be operated on and be treated
primarily by somatostatin analogues, or propagate
medical pretreatment as an alternative for the acrome-
galic patients (23–28). In an ongoing study, the signifi-
cance of debulking macroadenomas in medically
pretreated patients is under investigation (personal
communication, D Kleinberg).

In cases of biochemical cure, follow-up MRI may not
even be required if endocrine parameters are controlled,
since no tumor remnant will be visible (29). On the
other hand, persistent postoperative GH excess can be
accompanied by a larger visible either resectable or
unresectable tumor remnant. It is also possible that
despite elevated GH levels a tumor remnant cannot
be visualized by postoperative MRI. In all these scen-
arios the question of re-operation arises. Re-operations
are reasonable when tumor remnants that seem to be
resectable are visualized. Normally, these tumor rem-
nants are documented in MRI routine controls 2–3
months after surgery. This time-span is necessary to
obtain artifact-free control MRIs. Second surgeries
may only offer a rate of normalization of GH excess
between 20 and 30% (9, 30, 31).

There have been various attempts to apply intrao-
perative imaging in the neurosurgical operating room
for immediate intraoperative quality control. However,
first attempts for evaluating the effects of transsphenoi-
dal surgery starting in the 1980s, with the application
of ultrasound (32, 33) and computed tomography (34),
were not encouraging because of the restricted quality

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**Figure 2** A 38-year-old female patient (no. 21) with an intra- and
suprasellar GH-producing pituitary adenoma. Intraoperative MRI
depicts complete resection confirming the intraoperative esti-
mation of the surgeon. Remission of acromegaly was proved by
postoperative endocrine evaluation after 3 months. (a and b)
Coronal T2-weighted, (c and d) sagittal T2-weighted images, (a
and c) pre- and (b and d) intraoperative. Note the compressed
normal pituitary gland in (a).

**Figure 3** A 30-year-old male patient (no. 22) with an adenoma with
sphenoidal extension. Intraoperative MRI depicts complete
removal. Postoperative endocrine evaluation confirms remission
of acromegaly. Sagittal T2-weighted images (a) pre- and
(b) intraoperative.
Figure 4 A 42-year-old female patient (no. 11) with an invasive pituitary adenoma extending into the right cavernous sinus. Intraoperative imaging confirms partial removal (removed intrasellar tumor parts, white arrow). Coronal T2-weighted images (a) pre-, (b) intraoperative and (c) 3 months postoperative.

Figure 5 A 52-year-old female patient (no. 1) in whom complete removal was intended due to (a) preoperative imaging; however, (b) some firm tumor parts were stuck in a suprasellar fold (white arrow), that were not further accessible, visualized by HASTE and (c) as well as high-resolution T2-weighted imaging. All views, sagittal scans.

Figure 6 A 40-year-old male patient (no. 20) with (a and e) an intra- and suprasellar GH-producing macroadenoma in which (b and f) first intraoperative MRI revealed some tumor remnant (white arrows) that was further removed. (c and g) Repeated intraoperative imaging confirmed further but incomplete removal (white arrows depicting still remaining tumor), so that the resection was extended again. (d and h) Imaging at the end of surgery could then confirm complete removal. Postoperative endocrine follow-up showed remission of acromegaly. (a–d) Coronal and (e–h) sagittal T2-weighted images.

Figure 7 A 57-year-old female patient (no. 5) with (a) a large macroadenoma with compression of the optic chiasm. (b) First intraoperative imaging revealed some remaining tumor, which was removed, confirmed by (c) repeated intraoperative imaging. (d) Postoperative imaging after 3 months did not show any definite tumor remnant. Endocrine testing resulted in normalized GH level and an OGTT <2 μg/l with a slight elevated IGF-I level. All views coronal T1-weighted images.
of the intraoperative images. The development of low-field MR scanners led to a renaissance of the idea of intraoperative imaging in transsphenoidal surgery for resection control. Soon after their introduction, these scanners were integrated in an operating room environment, starting in 1995 in Boston with a 0.5 T MR scanner that was developed for surgical use (35).

As our current study has shown, pituitary adenoma remnants can already be detected intraoperatively. It is much easier and more convenient for the patient and the surgeon to continue surgery and complete tumor resection. A prerequisite to detect tiny tumor remnants — especially considering the parasellar structures — is a high intraoperative imaging quality. This high quality can be achieved with high-field MRI. High-field MRI has a clear advantage in image quality compared with the intraoperative low- and mid-field MR systems (0.12–0.5 T). Suprasellar tumor removal can also be reliably evaluated with the low-field machines, as previously demonstrated (16–20). However, intraoperative image quality is crucial for the evaluation of the intra- and parasellar structures, where the high-field setup has definitive advantages over the low- and mid-field setups.

We did not investigate the separate effects of the application of endoscope assistance, which was routinely used in all patients in this series. Despite the application of an endoscope which may identify small tumor remnants, even in invaginations of the descending diaphragm, by applying a meticulous technique, intraoperative MRI was able to identify overlooked tumor remnants and to outline their localization so that they could be further removed. In contrast to the direct inspection by the endoscope, intraoperative MRI also allows the evaluation of hidden structures which are not accessible for a direct inspection. The identification of tumor remnants was particularly facilitated by the possibility of comparing pre- and intraoperative images that were acquired at the same slice position.

Why does the surgeon overlook tumor remnants? With continuous tumor removal within the intrasellar space the suprasellar capsule, i.e. the sella diaphragm, descends and invaginates into the large sella, resulting in folds of the capsule obscuring the view. Within these folds and preformed small cavities tumor parts can be overlooked. An insufficiently wide opening of the bony sella floor during transsphenoidal approach to the adenoma may aggravate these problems. In a recent paper (17), we demonstrated that, in pituitary tumors with a suprasellar extension, a third of the patients still had tumor remnants which could be detected by intraoperative low-field MRI. With continued surgery the rate of complete removal could be increased. However, with intraoperative low-field MRI only the suprasellar space could be reliably evaluated.

Of course the number of investigated patients with GH-producing pituitary macroadenomas in this study is too low to draw definite conclusions. However, intraoperative high-field MRI allowed an increase in the number of patients with a favorable endocrine outcome. The true value of intraoperative MRI in influencing outcome in acromegalic patients can, however, only be determined by randomized studies. Unfortunately, this will be difficult to accomplish, since the centers having access to intraoperative high-field MRI and experience in treating acromegalic patients are few, as well as the fact that patients seeking treatment in specialized departments want to be operated with intraoperative imaging control and are not willing to be operated without, if such a technology is available. In this series, all five patients with visible and resectable tumor remnants underwent further resection which led to removal of the depicted remnants documented by intraoperative, as well as by the 3-month postoperative control in four of them; in one there was a suspicious intraoperative finding with invasion of the cavernous sinus. Of the four patients in whom repeated imaging had not shown any further remnant, all had a normalization of the GH levels, while two had only slightly elevated IGF-I levels, and two of them met the strict Giustina criteria (7, 8).

Intraoperative MRI in transsphenoidal surgery is a safe and reliable technique. The application of this technology increases the operation time only to a minimal extent, offering the chance for improved cure rates. We did not observe any false positive findings, i.e. if intraoperative imaging depicts a tumor remnant then acromegaly is not cured. On the other hand, the rate of false negatives of intraoperative imaging was six out of 23 (26%). This is not a problem of intraoperative imaging quality alone, since in all of these six patients imaging 3 months after surgery also did not reveal a definite tumor remnant. Acromegaly was not in full remission probably due to tiny remnants which may be especially located in the cavernous sinus, and are below the detection level of current imaging technology. First attempts to visualize the structures of the cavernous sinus with 3T magnets have been published (36). Whether imaging with higher field strength will help to identify the small remnants that escape the current imaging diagnostics and are responsible for the persisting GH excess needs to be clarified in the future.

Arguments for intraoperative MRI are as follows. Intraoperative imaging is an immediate intraoperative quality control, since the surgical result is obvious immediately after surgery. There is no psychological stress for the patient and no longer waiting time, which is normally 3 months, to have an artifact-free MRI. In the case of persisting GH excess, immediate planning for further management is possible, starting with medical treatment and/or radiotherapy. So in invasive tumors focused radiotherapy with linear accelerators (LINAC) (Novalis® shaped beam surgery) or gamma knife is possible immediately after surgery. The sooner GH normalization can be achieved the less are the financial costs, supporting the concept of the intraoperative MRI. On the other hand, this sophisticated form of intraoperative visualization, reflecting surgical quality
control, is quite cost intensive (37). Efforts must be undertaken to make intraoperative visualization more popular, to increase interest in the market and the industry. Furthermore, alternative effective visualization techniques like ultrasound and computed tomography must be developed further for the needs and challenges of transsphenoidal surgery. However, the suggestion of performing an additional craniotomy just for imaging purposes to monitor transsphenoidal surgery by ultrasound (38) is certainly no alternative for intraoperative MRI. Up to now, intraoperative MRI seems to be the only imaging modality that allows a reliable evaluation of pituitary adenoma removal. Other methods such as intraoperative GH measurement (39) can be of some use. Documenting still elevated GH levels during surgery encourages the surgeon to continue to search for a tumor remnant. However, this method gives no hint as to where to localize the tumor remnant but this is possible with intraoperative MRI.

Conclusion

With regard to the patients with a tumor extension and configuration in whom complete tumor removal was considered (n = 18), intraoperative MRI increased the rate of complete tumor removal and endocrine normalization from 33 to 44% applying the consensus criteria, and improved endocrine outcome to ‘nearly normalization’ in another 17% if it is assumed that the tumor remnants which were removed due to intraoperative MRI would have otherwise prevented remission of acromegaly because of their continued GH secretion. With regard to preoperative GH levels and tumor size, intraoperative MRI can help to achieve endocrine remission in patients normally considered not to be curable. However, taking GH as tumor marker, even intraoperative high-field MRI is not able to detect tumor remnants in every case.

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References


