

# Initial Experience with Diffusion-weighted Imaging to Predict the Tumor Consistency and Surgical Success in Solid Growth Hormone Producing Pituitary Macroadenomas

## Abstract

**Background:** Tumor consistency is an important factor impeding transsphenoidal resection of some pituitary macroadenomas. Preoperative prediction of the tumor consistency may help neurosurgeons in preparing the patients for other therapeutic options after a subtotally resected growth hormone (GH)-producing macroadenoma. We present the preliminary results of our study about the application of the preoperative diffusion-weighted (DW) magnetic resonance imaging (MRI) to predict the consistency and resection rate of GH-producing pituitary macroadenomas. **Materials and Methods:** Sixteen primary patients with solid GH-producing pituitary macroadenomas were enrolled. Hormonal assays as well as standard and DW-MRI were obtained before surgery. All the patients were operated via an endoscopic transsphenoidal approach. The intraoperative tumor consistencies (suctionable versus nonsuctionable) were documented. The samples were stained for measurement of the collagen content (low, moderate, and high). Postoperative hormonal study and MRI were performed after 8 weeks to evaluate the resection ratio and the hormonal remission. **Results:** On DW images, the tumor diffusion was enhanced (free) in four, moderate in ten, and restricted in two patients. The tumor was suctionable in 14 cases; gross total resection and hormonal remission were achieved in 12/14 of these. All the 14 suctionable tumors had moderate to enhanced diffusion on DW imaging (DWI). The two patients with a nonsuctionable fibrous tumor had a restricted diffusion in DWI. These were the only ones to have high collagen content in the histopathologic study. **Conclusion:** DWI could help identify the fibrous nonsuctionable GH-producing adenomas from the others.

**Keywords:** *Acromegaly, diffusion weighted, hypophysis, pituitary adenoma, transsphenoid*

## Introduction

Pituitary adenoma accounts for 90% of intrasellar pathologies and 10–15% of all intracranial neoplasms and is usually a benign tumor.<sup>[1]</sup> The most common hormone secreting adenomas are prolactinomas, followed by growth hormone (GH) secreting and mixed GH and prolactin-producing adenomas, respectively.<sup>[2]</sup>

Transsphenoidal surgery is often the primary therapeutic option for acromegalic patients although it may not be curative for some of them. Several studies have been carried out so far to find the major determinants of treatment outcome in patients with GH-secreting pituitary adenoma. Tumor size, invasion into the surrounding structures, and the serum GH level before and just after the surgery are noted to influence the final outcome.<sup>[3]</sup>

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Tumor consistency is another important factor that impedes the safe and effective resection of these tumors, especially through a transsphenoidal approach.<sup>[4-6]</sup> Preoperative prediction of tumor consistency plays an important role in planning the treatment strategy; those patients supposed to have a hard tumor may need another transcranial operation and/or postoperative radiotherapy or radiosurgery.

Hereby, we present our experience with application of diffusion-weighted (DW) magnetic resonance imaging (MRI) for prediction of tumor consistency of GH-producing pituitary macroadenomas operated through an endoscopic transsphenoidal route.

## Materials and Methods

Sixteen primary patients with GH-producing pituitary macroadenomas were enrolled.

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Those with grossly hemorrhagic and/or macrocystic changes were excluded from the study. Preoperative levels of basal GH and insulin-like growth factor-1 (IGF-1) were measured for all of them. Using a 1.5-T whole body system (Magnetom Vision, Siemens Healthcare, Germany) MRI scanner equipped with high-performance gradients, the imaging was performed with identical sequencing parameters in all patients: 3 mm thick sections in coronal, axial, and sagittal planes consisted of the T1-weighted, fast spin-echo T2-weighted, and echo-planar DW-MR images and then postcontrast T-weighted images after administration of 0.1 mmol/kg gadolinium. Before contrast agent administration, breath hold DW imaging (DWI) was performed in the transverse plain with a single-shot spin-echo echo-planer sequence (TR/TE: 3500–4500/94–110, matrix size 128 mm × 96 mm, section thickness 5 mm, interslice gap 2 mm, field of view 240 mm<sup>2</sup>, one image acquisition with a b value of 0 and diffusion gradient encoding in three orthogonal directions at a b value of 1000 s/mm<sup>2</sup>). The apparent diffusion coefficient (ADC) maps were calculated automatically, and ADC values were measured using circumferential region of interest (8–50 mm<sup>2</sup>) in the central portion of the solid tumor.

From the DWI, the tumor signal intensity in comparison to the normal white matter of temporal lobe was documented, and the mean ADC value of the tumor was calculated by a neuroradiologist. All patients were operated via endoscopic endonasal transsphenoidal approach by the same surgeon, and the intraoperative consistency was classified as either suctionable (removable by gentle application of suction and/or curettage) or nonsuctionable. On histopathological analysis, a semi-quantitative evaluation of collagen content was performed using Gomori's trichrome staining and the collagen containing area in total tumor area was estimated as low (<10%), intermediate (10–50%), and high (>50%).

The postoperative hormonal assessment and MRI examinations were performed 8 weeks after the operation. Tumor size was measured in largest craniocaudal diameter before and after the surgery (if still present) and the resection ratio was calculated.

Statistical analysis was performed using the SPSS software (version 19.0 for Windows; SPSS, Inc., Chicago, IL, USA).

“Mann–Whitney U-test” and “Pearson Chi-square” tests were applied.

## Results

Sixteen cases of acromegaly (11 males and five females), without any history of prior surgery, radiotherapy, and medical treatment were enrolled in the study. The mean preoperative serum GH and IGF-1 levels were 30.11 ng/ml and 814.25 IU/ml. Two patients had an evidence of cavernous sinus invasion in their preoperative MRI.

The patients were classified according to the signal intensity of the tumor on the preoperative DW-MRI as free diffusion (bright signal, high ADC), moderate diffusion, and restricted diffusion (dark signal, low ADC) groups. Table 1 presents the hormonal, intraoperative, and histopathologic findings of each group.

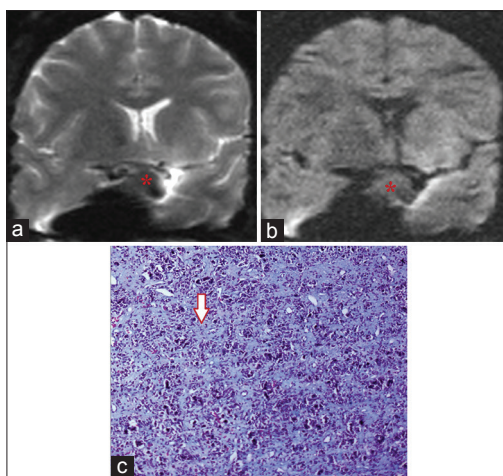
As shown in the table, all of the four cases with free diffusion tumors in DW images had low collagen content and had a gross total resection at operation. From the ten cases with moderate diffusion tumor in their DWI, four had intermediate collagen content, and the other six had low collagen levels. Although all the ten were judged to be suctionable during surgery, two could not be totally removed due to infiltration of the cavernous sinus by the tumor. The two cases with restricted diffusion tumors in DWI were found to have high collagen containing tumors and a firm consistency during the operation. Both tumors were subtotally resected by piece meal removal with 55% and 75% resection ratios. Postoperative hormonal evaluation showed failure of surgical treatment in achieving hormonal remission in these two patients. Histopathologic study revealed a high collagen content of the both tumors [Figure 1].

We merged the two groups of free diffusion and moderate diffusion into one single group for statistical analysis. We compared the resection rate between the two groups (those with free diffusion and moderate diffusion versus those with restricted diffusion) using “Mann–Whitney U-test” that revealed a statistically significant difference between the two groups (96% vs. 65% respectively,  $P = 0.007$ ). There was also a statistically significant difference

**Table 1: Hormonal, intraoperative and histopathologic findings of the patients according to the signal intensity of the tumor on diffusion weighted imaging**

DWI finding	Number of patients	Mean ADC values	Mean preoperative GH (ng/ml)/ IGF-1 (IU/ml)*	Mean postoperative GH (ng/ml)/ IGF-1 (IU/ml)	Intraoperative Tumor consistency	Collagen content	Average resection ratio
Free diffusion	4	$0.924 \times 10^{-3} \text{ mm}^2/\text{s}$	30/882	1.2/179	All suctionable	Low in all	100%
Moderate diffusion	10	$0.752 \times 10^{-3} \text{ mm}^2/\text{s}$	31.7/780	1.6/360	All suctionable	Low in 6, Intermediate in 4	94.5%
Restricted diffusion	2	$0.640 \times 10^{-3} \text{ mm}^2/\text{s}$	22.4/850	11.9/759	Both non-suctionable	High in both	65%

\*ADC – Apparent diffusion coefficient; GH – Growth hormone; IGF-1 – Insulin-like growth factor-1



**Figure 1:** Growth hormone producing pituitary macroadenoma in a 43-year-old woman. Tumor consistency was judged as hard at surgery. Coronal apparent diffusion coefficient map and diffusion-weighted imaging (a and b) images show hypointense signal from the tumor (red star) compared with normal brain tissue. The photomicrograph (c) shows abundant fibrous stroma (collagen is depicted in blue color: arrow) with scant cellularity

between the number of suctionable tumors among the two above-mentioned groups (Chi-square test,  $P = 0.008$ ).

## Discussion

The transsphenoidal approach is well-recognized as the surgical approach of choice for removal of the majority of pituitary tumors. However, the success of this approach depends on many parameters. Tumor consistency is one of the most important factors that determines the extent and safety of tumor resection through transsphenoid approach.<sup>[7]</sup>

Some previous studies have found no correlation between the signal intensity of the tumor in T1- and T2-weighted MR images and the tumor consistency,<sup>[8-10]</sup> while the other authors have showed decreased T2-weighted signal intensity to be more prevalent among highly fibrous tumors.<sup>[7,11,12]</sup>

Usefulness of DW imaging in prediction of the tumor consistency and resection rate of nonfunctional pituitary adenomas have been reported in some studies with significant controversy. While Suzuki *et al.*<sup>[13]</sup> and Mahmoud *et al.*<sup>[14]</sup> found no relationship between DWI signal intensity and ADC values and the tumor consistency, Mohamed and Abouhashem<sup>[15]</sup> and Pierallini *et al.*<sup>[5]</sup> found that higher ADC values are predictive of harder consistencies. All of these studies have been done on the patients with nonfunctional pituitary adenomas, in whom the radicality of tumor removal is less critical than those dealing with clinical consequences of a hormone-secreting pituitary adenoma. Boxerman *et al.*<sup>[9]</sup> evaluated the usefulness of MR imaging features for prediction of successful transsphenoidal surgery in 28 patients and reported that adenomas with macrocystic and macrohemorrhagic features and solid tumors with increased diffusivity are more likely to be successfully managed with transsphenoidal approach, whereas those

with solid consistency and restricted diffusion were more likely to fail. Since the most challenging part of the tumor for surgical resection is the solid part, in this study, we focused just on the solid GH-secreting pituitary adenomas.

In our study, the two patients with fibrous tumors impossible to be totally removed through a transsphenoidal route were the only ones to have restricted diffusion in DW imaging. Therefore, we recommend finding of a tumor with restricted diffusion (low ADC) on DWI as an alarm sign for the existence of a firm, fibrous macroadenoma, and the potential failure of transsphenoidal surgery in achieving a hormonal remission.

## Conclusion

The results of our initial experience with application of DWI for GH-producing pituitary macroadenomas suggest that it may have a promising role in the preoperative prediction of tumor consistency and help to determine the ultimate success of transsphenoidal surgery for hormonal control of the disease.

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## Conflicts of interest

There are no conflicts of interest.

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