Endoscopic Endonasal Transsphenoidal Treatment for Acromegaly: 2010 Consensus Criteria for Remission and Predictors of Outcomes

Akromegalinin Endoskopik Endonazal Transsfenoidal Tedavisi: 2010 Kriterlerine Göre Remisyon Oranları ve Remisyonu Etkileyen Faktörler

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ABSTRACT
AIM: Acromegaly is a chronic disorder characterized by enhanced growth hormone (GH) secretion and elevated insulin-like growth factor–I (IGF-I) levels, usually caused by pituitary adenomas. In this retrospective study, we reviewed our experience with endoscopic endonasal transsphenoidal surgery (EETS) with in remission rates using the 2010 consensus criteria, predictors of remission and associated complications.

MATERIAL and METHODS: The authors retrospectively analyzed data from 56 acromegalic patients who underwent pure EETS. Tumors were classified according to size and suprasellar/parasellar extension. The criteria of remission were GH levels < 1 ng/mL randomly, < 0.4 ng/mL after oral glucose tolerance test and normal IGF–I levels for age and sex within the first 3 and 6 months after surgery.

RESULTS: Biochemical remission was achieved in 4 of 5 microadenomas (80%) and in 33 of 51 macroadenomas (64.7%). The total remission rate was 66.1% (37 of 56 adenomas). Age, gender and suprasellar extension did not affect the remission rate. However, cavernous sinus invasion, sphenoid sinus invasion and history of prior surgery were associated with lower rates of disease control.

CONCLUSION: EETS represents an effective and safe option for the treatment of patients with acromegaly. High disease control rates and a small number of complications are some of the most important points related to the technique.

KEYWORDS: Acromegaly, Endoscopic transsphenoidal surgery, Remission, Predictive factors

ÖZ

YÖNTEM ve GEREÇLER: Pür EETC ile tedavi edilmiş 56 GH salgılayan hipofiz adenomu tanılı hastalar retrospektif olarak incelendi. Adenomlar boyutlarına göre mikro/makroadenom olarak ve suprasellar/parasellar yönelimlerine göre sınıflandırıldı. Hastalığın remisyon kriterleri olarak, rastgele bakılan GH düzeyi < 1 ng/mL, oral glukoz tolerans testi sonrası GH düzeyi < 0,4 ng/mL ve cerrahi sonrası ilk 3-6 ay arasında bakılan IGF–I düzeyinin yaşa ve cinsiyete göre normal olması kabul edildi.

BULGULAR: 5 mikroadenomun 4’ünde (%80), 51 makroadenomun 33 (%64,7) ünde remisyon sağlandı. Hastaların tümü incelendiğinde, remisyon oranı 56 hastada 37 (%66,1) olarak bulundu. Yaşın, cinsiyetin ve suprasellar büyümenin remisyon oranına etkisinin olmadığı görüldü. Ancak daha önce cerrahi geçirmiş olmak, kavernöz sinus ve sfenoid sinus invazyonunun remisyon oranlarını azalttığı saptandı.

SONUC: EETC, akromegalinin tedavisinde etkili ve güvenli bir yöntemdir. Bu teknikle yüksek başarı ve düşük komplikasyon oranlarına ulaşmak mümkündür.

ANAHTAR SÖZCÜKLER: Akromegali, Endoskopik transsfenoidal cerrahi, Remisyon, Etkili faktörler
INTRODUCTION

Acromegaly is a chronic disease characterized by high levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I) primarily dependent upon a pituitary adenoma (24). Acromegaly is usually manifested by progressive bone and cartilage growth that leads to dysmorphic craniofacial features and extremity changes, as well as cardiovascular, metabolic, and respiratory complications. Elevated GH and IGF-I levels may cause various systemic complications such as hypertension, cardiomyopathy, diabetes, sleep apnea, and arthritis (8). Untreated acromegaly and high levels of GH/IGF-I are associated with increased mortality as observed in patients with 32% increased risk for all-cause mortality (26). Cardiovascular disease, respiratory complications and cancers are the main factors related to poor outcome in these patients (5, 12). Therefore, acromegalic patients have a significant reduction in their quality of life, but the standardized mortality ratio returns to that of the normal population if GH levels are normalized (8). According to 2010 consensus guidelines, remission is defined as a normal IGF-I level and random GH level less than 1.0 ng/mL or GH level less than 0.4 ng/mL during an oral glucose tolerance test (11).

It stands to reason that an effective treatment of acromegaly is necessary. Treatment options for acromegaly include surgery, medical therapy, and radiotherapy. Surgery is the first choice of treatment for GH-secreting adenomas due to rapid control of GH/IGF-I levels and lower costs (13, 14). Conventionally, transsphenoidal microsurgery has been considered the best surgical approach for most pituitary adenomas such as GH secreting adenomas (12, 13, 30). Nowadays, the endoscopic transsphenoidal approach has become an initial option for resection of all pituitary adenomas because of having a lot of advantages such as better illumination, improved visualization, less nasal trauma, increased patient comfort, using angle scopes to reach the parasellar region, and achieving better results on tumor removal (4, 13, 30). In published literatures, biochemical remission rates following surgical intervention for acromegaly range from 34 to 83% (12, 17, 18, 23, 27, 30, 37). Most of these studies show that, microadenomas tend to be more responsive to surgical treatment than macroadenomas, although tumor size has not been consistently reported to be predictor of biochemical remission. The factors reported to be associated with increased likelihood of biochemical remission include lower Knosp score, preoperative GH level, and preoperative IGF-I level (17). But, there is limited published literature with new criteria for acromegaly on outcomes and factors affecting the remission rates. Patients for which biochemical remission is not achieved with initial resection are left with few options; reoperation, medical therapy and radiosurgery are costly and variably effective options.

In this study we describe our experience with pure endoscopic transsphenoidal approach in 56 patients with GH-secreting pituitary adenomas. Our aim was to analyze the predictors of biochemical remission rates of GH-secreting pituitary adenomas after endoscopic resection by using the more stringent 2010 consensus guidelines to assess disease remission in acromegaly.

PATIENTS and METHODS

Patient Demographics

Data were collected by retrospective review of medical records of all patients treated by EETS at Ankara Numune Education and Research Hospital, Department of Neurosurgery, Ankara, Turkey, between June 2009 and September 2013. Among the 60 acromegalic patients operated by EETS within this time period, 4 patients who did not have adequate GH and IGF-I data and therefore could not be evaluated for remission were excluded from the analysis. Fifty-six patients with sufficient data with regard to postoperative GH and IGF-I values, which were assessed more than 6 months postoperatively for evaluation of remission, were included in this study.

Of the 56 patients who were included in this retrospective study, 39 were female and 17 were male, and the mean age was 42.3 years (range, 23-65). Sixteen patients had recurrent or relapsing adenomas, 14 of them had previously been operated in other clinics.

The mean follow-up was 18 months.

Radiological Analysis

The size and the extension of the tumor as well as the degree of resection were assessed by pre- and post-operative T1 or T2-weighted magnetic resonance (MR) images of patients. Postoperative imaging was performed 3 and 6 months after surgery. Tumor sizes were classified as microadenomas (<1 cm in greatest diameter) or macroadenomas (≥1 cm in greatest diameter) on coronal images.

The suprasellar extension of the tumors was classified according to Modified Hardy’s classification (35). Grade 0 means that the tumor remains intrasellar. Grade A means that the tumor is expanding into the suprasellar cistern. Grade B means that the anterior recess of the third ventricle is obliterated. Grade C means that the floor of third ventricle is grossly displaced.

The suprasellar extension and spheno sinus invasion by the tumors were classified according to Hardy–Wilson classification (Hardy classification, modified by Wilson) (35) (Table I). The degree of suprasellar and parasellar extension was graded as Stages A–E, and the degree of sellar floor erosion as Grades I–IV.

Cavernous sinus invasion by the tumors was classified according to Knosp classification. Knosp classification is based upon parasellar extension of the tumor in the coronal section of MRI scans with internal carotid artery (ICA) serving as the radiological landmark (19). It consists of five grades. Grade 0 means that the adenoma does not encroach into the cavernous sinus space or cross the medial aspect of intra- and supra-cavernous ICA. Grade I means that the tumor crossed the medial tangent but does not extend beyond
Table I: Hardy Classification Modified by Wilson (Hardy–Wilson)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
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<tbody>
<tr>
<td>0: no suprasellar extension</td>
<td>I: sella normal; tumor&lt;10 mm</td>
</tr>
<tr>
<td>A: extension to suprasellar cistern</td>
<td>II: sella enlarged; tumor ≥10 mm</td>
</tr>
<tr>
<td>B: recesses of third ventricle obliterated</td>
<td>III: local perforation of sellar floor</td>
</tr>
<tr>
<td>C: third ventricle grossly displaced</td>
<td>IV: diffuse sellar floor destruction</td>
</tr>
<tr>
<td>D: intracranial</td>
<td></td>
</tr>
<tr>
<td>E: into/beneath cavernous sinus</td>
<td></td>
</tr>
</tbody>
</table>

the intercarotid line. Grade II means that the tumor crossed beyond the intercarotid line but does not cross beyond the lateral tangent of intra- and supra-cavernous ICA. Grade III means that the tumor has crossed beyond the lateral tangent of intra- and supra-cavernous ICA. Grade IV means that there was total encasement of the intra-cavernous ICA by the tumor.

**Endocrine Analysis**

Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits (hGH—IRMA CT; RADIM, Roma, Italy). The sensitivity of the assay was 0.04 ng/ml. The calibrator was calibrated against the WHO 80/505 International Standard preparation (1 ng hGH = 2 µIU). The reference ranges of GH were 0–16 ng/ml for women and 0–8 ng/ml for men. Serum IGF-I was measured by a solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite IGF-I, Siemens Medical Solutions Diagnostics, UK), using the IMMULITE 1000 System. In our laboratory, the reference ranges of IGF-I in patients aged 21–25, 26–30, 31–35, 36–50, 51–60, 61–70, and >70 years were 116–358, 117–329,115–307, 94–284, 81–238, 69–212, and 55–188 ng/ml, respectively. The analytical sensitivity of the assay was 20 ng/ml. Calibration was up to 1600 ng/ml (WHO NIBSC 1st IRR 87/518). The within-run coefficients of variation were 6.1, 6.9, and 5.8% for the low, medium, and high points of the standard curve, respectively. The within-run coefficients of variation were 3.1, 4.3 and 3.5% for the low, medium, and high points of the standard curve, respectively. The total coefficients of variation were 6.1, 6.9, and 5.8% for the low, medium, and high points of the standard curve, respectively.

**Surgical Technique**

All patients were operated using the pure endoscopic en-donasal transsphenoidal approach. For larger adenomas, a binosistral and extended approach was preferred. Macroadenomas growing to the parasellar area were operated by using angled scopes (30º and 45º) for gross total excision. After the removal of the tumor, multilayer skull base reconstruction by using autologous grafts and fibrin sealant was done, if necessary.

**Statistical Analysis**

Data were analyzed using commercially available software (SPSS version 18). Univariate comparison of continuous variables with a normal distribution was assessed using 2-sample t tests, and continuous variables not meeting the normality assumption were assessed using the Mann–Whitney U test. All categorical data were assessed by v2 test or Fisher exact test, as appropriate. Remission rates were compared between degrees of invasiveness, tumor size, tumor growth direction, sex, age and preoperative hormone level. When p values were ≤ 0.05, the differences were considered statistically significant.

**RESULTS**

Between June 2009 and September 2013, 415 patients underwent endoscopic transsphenoidal surgery for the treatment of skull base lesions at Ankara Numune Education and Research Hospital, Department of Neurosurgery, Ankara, Turkey. Pituitary adenomas were the most common lesions treated, representing 335 of the 415 cases. In the group of functioning pituitary adenomas, the most common subtype was GH-secreting adenomas.

During the study period, 60 GH-secreting pituitary adenomas were treated by pure EEHT by the senior author (A.E.Y.). Fifty-six patients, who had sufficient data regarding postoperative GH and IGF-I values, which were assessed more than 6 months postoperatively and used for evaluation of remission, were included in this study. Seventeen of the patients were male and 39 were female. The mean age of the 56 patients was 42.3 years (range from 23 to 65 years).

All pituitary adenomas were anatomically analyzed based on MR imaging findings. Five patients had microadenomas (8.9%) and 51 patients had macroadenomas (91.1%). Hormonal remission was achieved by surgical treatment in 4 out of 5 microadenomas (80%), 33 out of 51 macroadenomas (64.7%), and totally 37 out of 56 adenomas (66.1%). Out of 19 patients (33.9%) that could not be cured by surgery alone, 2 had total resection and 17 patients did not. Hormonal control
was achieved in 16 of 19 patients with medical treatment. Radiosurgery was performed in 3 patients.

In adenomas, that were classified according to Modified Hardy's classification, which is based upon only suprasellar extension of the tumor, no significant difference in remission ratios was observed between the grades (p>0.05) (Table II).

The suprasellar/parasellar extension and sphenoid sinus invasion of the tumors were classified according to Hardy–Wilson classification. Although the stage values, showing suprasellar extension, have no effect on the remission rates, the success rate of surgery reduced by a statistically significant level in Stage E which indicates cavernous sinus invasion and in grade 3 and 4 which show sphenoid sinus invasion (p≤0.05) (Table III).

However in the Knosp classification, which is based on cavernous sinus invasion, remission rates decrease significantly while invasion levels, i.e. grade, increase (p≤0.05) (Table IV).

In our series, 16 patients underwent repeat operation for acromegaly utilizing EETS when biochemical remission was not achieved after the first operation and medical therapy. Fourteen of them underwent initial operation by different surgeons, 10 patients were operated via microscopic or endoscopic transsphenoidal approach and 4 patients were operated transcranially. Only 2 patients were operated our department via EETS by senior author. All of these 16 patients were reoperated via a pure EETS, hormonal remission was achieved in 7 of them (43.7%), and medical therapy was stopped.

According to our study, age, sex and preoperative hormone levels did not affect the remission rates (p>0.05).

**COMPLICATIONS**

Postoperatively, there were 4 patients with other hormone deficits. Three patients developed panhypopituitarism, 1 patient developed hypothyroidism and adrenal insufficiency. One patient developed permanent diabetes insipidus (DI) and 2 patients developed transient DI. Transient cranial nerve (CN) III palsy developed in 1 patient. There were 2 patients (3.8%) with CSF leaks and reoperation was done. One patient was reoperated because of hemorrhage into the sella after surgery.

**DISCUSSION**

Surgery is the first choice of treatment for acromegaly. The main aim in the treatment of acromegaly is the total resection of the tumor if possible, prevention of its recurrence and to restore the normal GH/IGF-1 levels with the long-term aim of avoiding increased morbidity and mortality associated with uncontrolled serum GH and IGF-1 levels (22, 26, 28, 34).

Transsphenoidal surgery for treatment of acromegaly has been used since the initial work of Cushing (6). The development and the popularization of endoscopic transsphenoidal pituitary surgery have been associated with better tumor resection results, which are often related to better visualization and improvement in the resection of suprasellar and parasellar components of the adenoma (9, 14). The success of endoscopic transsphenoidal surgery in the treatment of acromegaly has been reported by different authors (12, 17,

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**Table II: Distribution of Patients According to the Modified Hardy Classification**

<table>
<thead>
<tr>
<th>Modified Hardy</th>
<th>Number of Patients</th>
<th>Cure</th>
<th>Non Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>A</td>
<td>31</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Grade 0 and A were compared with Grade B and C according to T Test Analysis: p>0.05.

**Table III: Distribution of patients according to the Hardy Wilson Classification**

<table>
<thead>
<tr>
<th>Hardy-Wilson</th>
<th>Number of Patients</th>
<th>Cure</th>
<th>Non Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>A</td>
<td>30</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Stage 0, A and B were compared with Stage C, D and E according to t test analysis: p≤0.05. Grade 1 and 2 were compared with grade 3 and 4 according to t test analysis: p≤0.05.

**Table IV: Distribution of Patients According to the Knosp Classification**

<table>
<thead>
<tr>
<th>Knosp</th>
<th>Number of Patients</th>
<th>Cure</th>
<th>Non Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Grade 0, 1 and 2 were compared with grade 3 and 4 according to t test analysis: p≤0.05.
In this study, we present hormonal remission results, outcomes, and predictive factors of endocrinological remission in acromagalic patients after pure endoscopic transsphenoidal pituitary surgery.

The definition of biochemical remission of acromegaly has changed noticeably over the past 2 decades. In the 1980s, postoperative GH levels < 5 ng/ml were considered as criteria of biochemical remission of disease (1). However, mortality rates remained high, and in 2000 the new and stringent consensus criteria for the treatment of acromegaly were presented (2, 10, 25). According to this consensus, the random GH should be < 2.5 ng/ml, GH had to be suppressed to < 1 ng/ml during OGTT, and IGF-I had to be within normal limits in order to consider acromegaly in complete remission (10, 21, 25). With the recent development of highly sensitive and specific GH assays, the new and more stringent consensus criteria were presented in 2010, and this recent consensus described “remission” as random GH < 1 ng/ml and IGF-I levels within an age- and sex-adjusted normal range, or nadir GH levels < 0.4 ng/ml with OGTT [18]. In the present study, we used more stringent 2010 consensus criteria to describe the endocrinological remission of acromegalic patients. There are many of endoscopic and microscopic transsphenoidal surgery series published using 2000 criteria for remission of acromegaly, and remission rates ranged from 42% to 70% (3, 10, 12, 20, 27, 29, 31). In our series we had a hormonal remission rate of 74.6% according to the 2000 consensus criteria. The 2010 criteria are more stringent than 2000 criteria and it is more difficult to achieve a hormonal remission according to the new criteria. There are limited numbers of studies in literature according to the new criteria, and hormonal remission rates were reported between 46%-70% (12, 15, 16, 29). In our series, hormonal remission was achieved in 66.1% of patients.

Tumor size predicted remission, and microadenomas had higher hormonal remission rates than macroadenomas in our series reported in numerous earlier publications (15, 17, 29). In our current study, remission was achieved in 80% of microadenomas and in 64.7% of macroadenomas. Tumor size is not the most important predictive factor for remission. According to the previous large published series, tumor growth direction is very important. In this current study, we classified the patients according to suprasellar extension alone with Modified Hardy Classification. In the grade 0 and A groups there were 44 patients and 29 have achieved remission (65.9%). In the grade B and C groups there were 12 patients and 8 have achieved remission (66.6%). This findings show that suprasellar extension alone does not affect the endoscopic transsphenoidal surgery success.

We also classified patients according to the suprasellar/parasellar extension and sphenoid sinus invasion with the Hardy–Wilson classification. In this classification, stage shows supra- and parasellar extensions, and grade shows sphenoid sinus invasion. In stage 0 and group A, there were 35 patients and 28 have achieved remission (80%). In stage B, C and D, there were 11 patients and 8 have achieved remission (72.7%). Stage E group (i.e. cavernous sinus invasion) had 10 patients and only 1 patient has achieved remission (10%). In grade 1 and 2 groups, there were 31 patients and 28 have achieved remission (90.3%). In group 3, 9 of 19 patients have achieved remission (47.3%). In group 4, none of 6 patients have achieved remission (0%). These findings show that suprasellar extension does not affect the success of endoscopic transsphenoidal surgery, but invasive adenomas with cavernous and sphenoid sinus invasions affect the success rates. Although the surgical access to sphenoid sinus invasion is relatively easy, it affects the surgical success negatively. We believe that this is related to high degree of invasiveness of adenomas.

The other classification is Knosp classification, which is based upon the cavernous sinus invasion. In grade 0 and 1 groups, there were 22 patients and 20 have achieved remission (90.9%). In grade 2 and 3 groups, there were 23 patients and 16 of them have achieved remission (69.5%). In grade 4 group, only 1 of 11 patients has achieved remission (9%). These findings show that Knosp grade is important for hormonal remission as described in previous studies (12, 16, 17, 29).

There are profoundly successful results in utilizing endoscopic technique due to better illumination, direct entrance into the sella, and use of an angled endoscope, especially in Knosp grade 2 and 3 adenomas. The endoscopic technique is clearly superior to all other techniques in the treatment of adenomas with cavernous sinus invasion. Nevertheless, Knosp grade 4 adenomas could be treated by advanced endoscopic techniques, because of their certainly invasion (4).

For patients in whom biochemical remission is not achieved after the initial operation, physicians have few options such as medical management, radiosurgery and likelihood of repeat surgical intervention attempts. Repeat endoscopic transsphenoidal surgery is an effective and safe option for uncontrolled acromegalic patients, and has similar remission rates compared to medical therapy and radiosurgery (36). In our series, 16 patients underwent repeat operation for acromegaly by EETS after biochemical remission was not achieved following the first operation and medical therapy. Ten patients were operated via microscopic or endoscopic transsphenoidal approach and 4 patients were operated via transcranial approach by other authors. Only 2 patients were operated in our department via pure EETS by a senior author. All of these 16 patients were reoperated via pure EETS, and hormonal remission was achieved in 7 of them (43.7%), and medical therapy was stopped. After reoperation, only 1 patient had different hormonal deficits, and no morbidity and mortality was observed. Reoperation for acromegaly is a safe, effective and cost-effective treatment option. In our opinion, reoperation via endoscopic transsphenoidal approach is the first-line treatment option for recurrent acromegaly if possible.

According to our present study, age, sex and preoperative GH/IGF-1 levels do not affect the remission rates.
CONCLUSION

EETS is currently the first-line treatment option for GH-secreting pituitary adenomas with higher remission rates. The aim of this study was to discuss the remission rates of this important disease according to the new 2010 consensus criteria and to determine the predictive factors. In our opinion, excessive cavernous sinus invasion (Knosp grade 3-4), sphenoid sinus invasion (Hardy-Wilson stage E), failure of first surgery and surgeon experience are the most important factors that affect the surgery success. Consequently, surgery performed by an experienced surgeon using the most effective method is very important to achieve optimal results in the treatment of acromegaly, which has a negative impact on human life.

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