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Pure endoscopic endonasal treatment of acromegaly; classification, remission rates, factors affecting remission, and complications

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Abstract

Aim: This study aims to evaluate the effectiveness of the pure endoscopic endonasal transsphenoidal (PEET) approach in treating acromegaly, focusing on remission criteria set by the 2002 and 2010 consensus guidelines. It also seeks to identify variables that affect remission and to analyze early postoperative IGF-1 levels 24 hours after surgery to determine their predictive value for remission.

Materials and Methods: The study retrospectively reviewed the medical records of 129 acromegaly patients who underwent the PEET (Pure Endoscopic Endonasal Transsphenoidal) surgical approach between November 2010 and March 2016 at Ankara Numune Training and Research Hospital. Out of these, 124 patients with complete follow-up and laboratory data were included in the analysis. The study evaluated a range of variables including patients' symptoms, pre- and postoperative GH and IGF-1 levels, imaging results, and remission statuses based on the 2002 and 2010 consensus guidelines. Inclusion criteria for the study required patients to have specific preoperative and postoperative data and a minimum follow-up duration of at least 6 months.

Results: The study found statistically significant differences between the remission rates based on the 2002 and 2010 consensus criteria for acromegaly, with a 73.4% remission rate under the 2002 criteria and a 65.3% remission rate under the 2010 criteria ($p=0.002$). Multivariate logistic regression analysis indicated that the atypical nature of the adenoma ($p=0.018$) and surgical intervention due to recurrence ($p=0.028$) were significant negative factors affecting cure rates. The study also identified that advanced stages in Hardy Wilson ($p=0.008$) and Knosp ($p<0.001$) classifications had a statistically significant negative impact on achieving a cure. No statistically significant predictive value was found for early postoperative IGF-1 levels in relation to cure ($p=0.612$).

Conclusion: PEET is currently the preferred treatment option for GH-secreting pituitary adenomas and has high remission rates.

Introduction

Although pituitary adenomas are benign tumors, they cause significant morbidity and mortality, especially in patients with acromegaly, due to elevated levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [1, 2]. The primary reason for this is that GH and IGF-1 lack a specific target organ and affect the functioning of multiple organs throughout the body. Patients with acromegaly may present with a multitude of symptoms such as gigantism, growth in hands and feet, soft tissue enlargement, coarsening of facial features, prognathism, excessive sweating, fatigue, weight gain, spondylosis, trapped neuropathies, paresthesias, joint pain, skin oiliness, snoring, and sleep apnea. However, analyses show that the main complaints of acromegaly patients upon hospital admission are usually headaches and/or vision impairment. In other words, these patients may remain asymptomatic until pressure symptoms develop. Patients are generally diagnosed in their fourth decade and may have secondary pathologies like hypertension (25%), cardiomegaly (15%), glucose intolerance, and insulin resistance, among others at time of diagnosis [3]. The mortality rate in untreated acromegaly patients has been reported to be 32%; high GH/IGF-1 levels are held responsible for this rate [4]. Indeed, when GH levels return to normal, the mortality rates for acromegaly patients are stated to be the same as the

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general population [5]. Therefore, the criteria for curing acromegaly primarily target biochemical remission and are defined based on serum GH and IGF-1 levels. The remission criteria, initially outlined in 2002, were further tightened and revised in 2010. According to the 2010 consensus guidelines, a cure is defined as a normal IGF-I level and a random GH level below 1.0 ng/mL, or a GH level below 0.4 ng/mL during an oral glucose tolerance test [6].

It is evident that acromegaly needs to be effectively treated, and the primary treatment is surgical, aimed at achieving a rapid and controlled reduction in GH/IGF-I levels [7, 8]. Currently, pure endoscopic transsphenoidal approach is the first-line, efficacious surgical method accepted for the treatment of acromegaly [3, 9, 10].

The objective of this study is to evaluate the remission criteria in acromegaly patients operated on using a pure endoscopic endonasal transsphenoidal (PEET) approach, according to the 2002 and 2010 consensus guidelines. Additionally, this study aims to investigate variables affecting remission and to analyze early postoperative IGF-1 levels at the 24th hour to search for a predictive value for remission.

Materials and Methods

Records of 129 acromegaly patients who underwent surgery using the PEET (Pure Endoscopic Endonasal Transsphenoidal) approach between November 2010 and March 2016 at Ankara Numune Training and Research Hospital were retrospectively reviewed. Five of these patients were found to have incomplete follow-up and missing lab tests and examinations in their records, and thus were excluded from the study. The remaining 124 patients were included in the study. Clinical information, laboratory tests, radiological imaging and surgical records of the patients were accessed through our hospital's information system.

The patients' complaints, neurological examinations, GH and IGF-1 levels, imaging studies, radiological classification of the adenoma, surgical process, complications, early and late postoperative follow-ups of GH and IGF-1 levels, OGTT (Oral Glucose Tolerance Test) suppression test results, radiological imaging outcomes, pathology results, medical treatments received for acromegaly, and their status in achieving the remission target were evaluated.

The remission statuses of the patients were evaluated according to the 2002 and 2010 consensus guidelines on acromegaly remission criteria. Factors such as the size of the adenoma, the pathological and immunohistochemical examination of the adenoma (typical-atypical), changes caused by the adenoma at the base of the sella turcica, and its suprasellar extension (classified by Hardy-Vezina and Modified Hardy scales), as well as its extension into the cavernous sinus (classified by Knosp's classification), and recurrence statuses were assessed for their impact on remission.

The inclusion criteria for the patients in the study were as follows:

- Before the PEET Surgery, clinical correlation with elevated basal GH levels (>5 ng/ml), insufficient suppression with an oral glucose tolerance test (OGTT), and elevated serum IGF-1 levels.
- Completion of preoperative and postoperative pituitary MRI scans, and the ability to access these images from our hospital's data system.
- Immunohistochemical staining conducted by the pathology department and a resulting diagnosis of a GH-secreting adenoma.
- Regular attendance by the patients in their outpatient follow-ups in the first, third, and sixth months, and the availability of lab tests (GH and IGF-1) and examinations (Pituitary MRI) conducted during these follow-ups from the hospital's data system.
- A minimum postoperative follow-up duration of at least 6 months for the patients.

This study was approved by T.C. Public Hospitals Institution Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (Approval number: 2016-1104).

Endocrine and biochemical analysis

Data were collected on adrenohypophyseal hormone levels in all cases. Evaluation of TSH, Free T3, Free T4, cortisol, LH, FSH, progesterone, estradiol, Total Testosterone, and prolactin hormone levels was carried out in the biochemistry laboratory of Ankara Numune Training and Research Hospital. Until March 2014, the measurements were performed using the Roche Cobas E601 (Mannheim, Germany) instrument with the ECLIA (Electro-chemiluminescence immunoassay) method, and after March 2014, with the Beckman Coulter DXI800 using the CLIA (Chemiluminescence Enzyme Immunoassay) method. Free Testosterone measurements were carried out using the Beckman Gamma Counter with the RIA method, and ACTH, GH, and IGF-1 measurements were done using the Siemens Immulite 200 with the ECLIA method. Additionally, complete blood counts, routine biochemistry, and hemostasis parameters were evaluated. Electrolyte levels were determined using the Hitachi Modular P-800 device with the ion-selective electrolyte method until March 2014, and after that date with the Beckman Coulter AV 5800 using the ion-selective electrolyte method. Anterior pituitary hormones were monitored in the early postoperative period. During the patients' postoperative hospital stay, electrolyte and urine osmolarity were monitored at least twice. For these follow-ups, reference ranges from the biochemistry and hormone laboratory of Ankara Numune Training and Research Hospital were considered.

Radiological analysis

All patients underwent preoperative paranazal sinus computed tomography (CT) scans (Toshiba Activion 16 multislice CT, Toshiba Aquilion 64 multislice CT, Toshiba Alexion 16 multislice CT; Tokyo, Japan). For diagnostic and evaluative purposes preoperatively and for early postoperative imaging, gadolinium-enhanced pituitary magnetic resonance imaging (MRI) studies were carried out (GE 1.5

T Signa Excite MR, GE Optima 450W 1.5 T MR, GE Optima 360 Advance 1.5 T MR New York, USA). The test results of the patients included in the study were evaluated based on their dimensions: microadenoma (n<1cm), macroadenoma (n>1cm), and giant adenoma (n>4cm). They were also assessed using Modified Hardy, Hardy-Wilson, and Knosp classifications. Based on these classifications, the surgical process, postoperative GH and IGF-1 follow-up, and cure rates according to the 2010 and 2002 consensus remission criteria were evaluated and compared.

Surgical technique and follow-up

All patients underwent surgery using a pure endoscopic endonasal transsphenoidal approach, performed by the same surgeon. The choice between a mononostril or binostril approach was made based on the size of the adenoma, suprasellar and cavernous invasion, and preoperative evaluations conducted through paranasal sinus CT and pituitary MRI scans.

2002 and 2010 remission criteria

According to the remission criteria for acromegaly published in 2002, patients can be considered to be in complete remission if their random GH (Growth Hormone) levels are <2.5ng/ml, their suppressed GH levels with an OGTT (Oral Glucose Tolerance Test) are <1 ng/ml, and their IGF-I (Insulin-like Growth Factor-I) levels are within normal limits. In 2010, new consensus remission criteria were introduced, stating that patients with acromegaly will be considered in remission if their random GH levels are <1ng/ml, their IGF-I levels are within age- and sex-adjusted normal limits, and their GH levels with OGTT suppression are <0.4ng/ml [6, 8, 11, 12, 13].

Statistical analysis

The retrospective analysis of patients was carried out using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) software. The normality of the distribution of continuous numerical variables was examined using the Kolmogorov-Smirnov test. The significance of differences in means between groups was investigated using Student's t-test, while the significance of differences in medians was examined using the Mann-Whitney U test. Nominal variables were evaluated using Pearson's Chi-Square test or Fisher's exact test. The statistical significance of the difference in pre- and post-operative IGF levels within groups was evaluated using the Wilcoxon Signed-Rank test.

The significance of the difference in the prevalence of cure or non-cure outcomes according to the 2010 and 2002 cure criteria was assessed using McNemar's test. The level of agreement between the two sets of criteria was evaluated by calculating the Kappa coefficient. The statistical significance of the change in IGF levels before and after surgery as an indicator for distinguishing between the group cured and not cured according to the 2010 criteria was examined by calculating the area under the ROC curve and the 95% confidence interval.

Factors most determinant in distinguishing between the group cured and not cured according to the 2010 criteria were identified through Multiple Logistic Regression analysis. All variables identified as having a p-value of less than 0.10 in univariate statistical analyses were included as candidate risk factors in the multiple logistic regression model. Odds ratios for each variable, 95% confidence intervals, and Wald statistics were calculated. Results were considered statistically significant if p<0.05.

Results

Of the 124 patients included in the study, 36.3% (n=45) were male with an average age of 44.10 (ranging from 22-78). Preoperative hormonal values for the patients were an average GH of 16.64 (0.2-120.0) ng/mL and an average IGF-1 of 850.24 (32.0-3000.0) ng/mL. 23.4% (n=29) of the patients had recurrent cases. At the time of presentation, 16.9% (n=21) were on somatostatin analog therapy. Based on the examination results, adenomas were classified as follows: 7.3% (n=9) were microadenomas, and 92.7% (n=115) were macroadenomas.

Postoperative imaging evaluations showed that 73.4% (n=91) underwent total resection, while 26.6% (n=33) underwent subtotal resection. Of the 33 patients who had a subtotal resection, 72.7% (n=24) were at Knosp grades 3 and 4, 66.6% (n=22) were at Hardy-Wilson stages 3 and 4, and 45.4% (n=15) had recurrent cases.

For patients who underwent subtotal resection, somatostatin analog therapy was initiated postoperatively in 22

Table 1. Frequency distribution of cases according to 2002 and 2010 criteria.

	2010			p-value	κ coefficent
	Cure	Not cure	Total		
2002				**0.002**†	0.812‡
Cure	81(65.3%)	10 (8.1%) 3	91 (73.4%)		
Not cure	0 (0.0%)	3 (26.6%)	33 (26.6%)		
Total	81 (65.3%)	43 (34.7%)	124 (100.0%)		

κ: Kappa, † McNemar test, ‡ p<0.001.

Table 2. The effects of demographic and clinical characteristics of patients on cure according to 2010 criteria.

Variables	Cure (n=81)	Not Cure (n=43)	p-value
Age (years)	45.6±11.9	41.4±12.4	0.068†
Gender			0.307‡
Male	32 (39.5%)	13 (30.2%)	
Female	49 (60.5%)	30 (69.8%)	
Atypical	16 (19.8%)	17 (39.5%)	**0.018**‡
Dimension			0.718¶
Micro	5 (6.2%)	4 (9.3%)	
Macro	76 (93.8%)	39 (90.7%)	
Pre-op IGF	729 (180-1933)	890 (253-3054)	0.065$
Pre-op GH	7.0 (0.2 - 94.0)	10.1 (1.2-120.0)	0.214$
History of recurrence	14 (17.3%)	15 (34.9%)	0.028‡

†Student's t test, ‡ Pearson's Chi-Square test, ¶ Fisher's exact probability test, $ Mann Whitney U test.

Table 3. Examination of the factors that can be the most determinant in distinguishing the cured group and the non-cured group according to the 2010 criteria, according to the multivariate logistic regression analysis.

	Odds Ratio	%95 Confidence Interval		Wald	p- value
		Lower Limit	Upper Limit		
Age	0.992	0.954	1.031	0.180	0.671
Atypical	1.392	0.494	3.922	0.392	0.531
Hardy Wilson stage	0.873	0.594	1.284	0.478	0.489
Grade	0.734	0.403	1.337	1.022	0.312
Knosp	2.456	1.485	4.060	12.263	**<0.001**
History of recurrence	2.036	0.717	5.784	1.781	0.182
Pre-op IGF	1.001	1.001	1.002	1.621	0.203

cases, while 11 continued with their preoperative treatments. Among these patients, two met the criteria for remission under somatostatin therapy at their 6-month follow-up (medical cure). However, due to the use of subtotal resection and the lack of remission achieved through surgical treatment, they were not considered as cured in our study.

In 5 patients, no reduction in serum IGF-1 and GH levels was observed at the sixth month following surgery. For this reason, stereotactic radiosurgery (SRS) was administered to these patients.

65.3% (n=81) of patients received only surgical treatment. 16.9% (n=21) were on somatostatin analog therapy at the time of presentation. Medical treatment had been initiated in 18 of these patients due to recurrence, and in 3 for preoperative preparation. Somatostatin analog therapy was discontinued in 9 of these patients postoperatively. Of the 33 patients who underwent subtotal resection, 11 continued their ongoing medical treatment, while somatostatin was initiated postoperatively in 22.

Upon evaluation of pathology reports, it was found that all patients had GH-secreting adenomas. However, 26.6% (n=33) showed high mitotic activity, increased p53 immunoreactivity, and a Ki-67 proliferative index above 3% (Atypical Adenomas).

According to the 2002 and 2010 consensus cure criteria, our remission rates were 73.4% (n=91) for the 2002 evaluation and 65.3% (n=81) for the 2010 evaluation. The lower number of acromegaly patients considered in remission according to the 2010 criteria was found to be statistically significant (p=0.002) (Table 1). The agreement between the 2002 and 2010 criteria was determined to be statistically highly concordant (Kappa=0.812 and p<0.001).

Upon examination through "multivariate logistic regression" analysis according to the 2010 criteria, the atypical nature of the adenoma (p=0.018) and the surgery being conducted due to recurrence (p=0.028) were found to be statistically significant and negative variables affecting cure rates (Table 2). Among all risk factors, it was observed that the Knosp stage had a statistically significant independent impact on the absence of a cure (Odds ratio=2.456; 95% Confidence Interval: 1.485-4.060 and p<0.001) (Table 3).

Single-variable statistical analyses were used to investigate whether the radiological classification of adenomas had a significant impact on achieving a cure; it was found that advanced stages in Hardy-Wilson (p=0.008) (Figure 1) and Knosp (Figure 2) classifications had a statistically significant negative effect on achieving a cure (p<0.001).

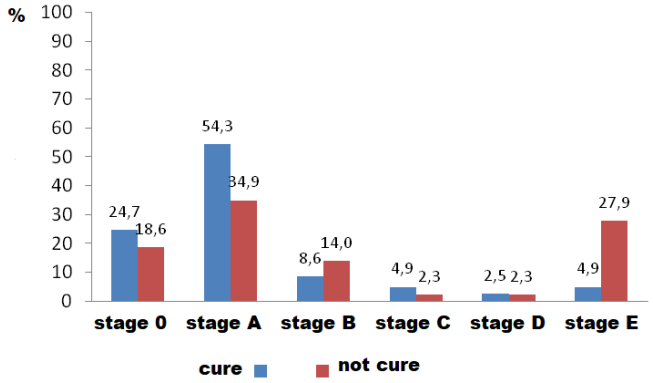

Figure 1. Distribution of acromegaly patients in remission according to the 2010 cure criteria by Hardy Wilson stage classification.

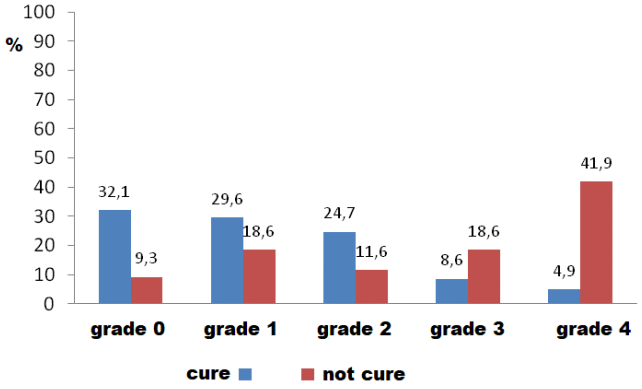

Figure 2. Distribution of acromegaly patients in remission according to the 2010 cure criteria by Knosp stage classification.

In our study, we searched for a significant value that could serve as an indicator for cure between preoperative IGF-1 levels and early postoperative IGF-1 levels in patients who achieved a cure. The patients' pre- and post-operative IGF-1 levels were analyzed with the ROC curve, but no

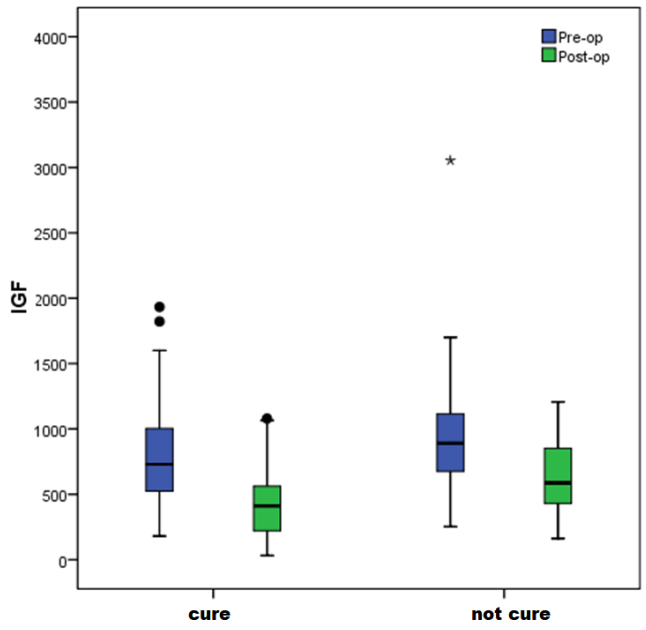

Figure 3. Effect of the change between preoperative and early postoperative IGF-1 values in predicting remission in acromegaly patients.

statistically significant value was obtained (p=0.612) (Figure 3).

Complications

Postoperatively, two patients developed rhinorrhea. Both patients had macroadenomas, and one was a recurrent case. The patients were managed with lumbar drainage. No second surgical procedure was performed.

In one patient whose visual acuity worsened after surgery, a hematoma was detected in the surgical area upon examination. Emergency surgery was performed on the patient, the hematoma was excised, and hemostasis was achieved. The patient's visual acuity improved in the early postoperative period after the second surgery.

During the operation on one of the recurrent cases, a pseudo-aneurysm ruptured. Emergency angiography was performed on the patient, and a stent was placed at the ruptured site in the cavernous segment of the internal carotid artery (ICA). The patient had no neurological deficits during early and long-term postoperative follow-ups.

Discussion

In many studies, remission rates for acromegaly following endoscopic and microscopic transsphenoidal surgery have been evaluated according to the 2002 cure criteria and have been reported to range between 42% and 70% [5, 14, 15, 16]. In our study, this rate is 73.4% (n=91) based on the 2002 criteria and 65.3% (n=81) based on the 2010 criteria. The remission rates we have obtained are consistent with the data in the literature.

Variables that are stated in the literature to have significant impacts on acromegaly remission have also been analyzed in our study [5, 13, 14, 15, 16]. Contrary to what is indicated in the literature, our study found that preoperative GH and IGF-1 levels, adenoma size, suprasellar extension of the adenoma, and early postoperative IGF-1 levels had no effect on remission. However, negative effects on remission were observed for advanced-stage cavernous sinus invasions (Knosp) and sphenoid sinus invasions (Hardy-Wilson). The result is not surprising for advanced-stage Knosp adenomas, as total resection would be challenging. However, it is unexpected that a tumor exhibiting sphenoid sinus invasion at an advanced Hardy Wilson stage would be more easily excised, making it an unexpected outcome.

Publications exist that indicate microadenomas have higher rates of meeting remission criteria compared to macroadenomas [15, 16, 17]. In our study, remission rates were similar for macroadenomas at 92.7% (n=115) and microadenomas at 7.3% (n=9), leading to the conclusion that tumor size does not affect remission. However, the small number of microadenomas in our study could call into question the validity of this statistical data. Even though it's difficult to detect acromegaly at the microadenoma level, volume measurement studies could re-evaluate the impact of tumor size on remission.

Studies exist that emphasize the significant effect of suprasellar extension on the cure rate of acromegaly [17, 18]. However, in our study, the distribution of adenomas based on Modified Hardy classification according to suprasellar extension was not found to be significant on remission. This data could be interpreted in the following way: the fact that all the cases in our study were performed by an experienced surgeon, that a pure endoscopic transsphenoidal surgical approach was applied, and that this method allows easy access to the suprasellar region may have rendered the Modified Hardy classification ineffective on remission.

As mentioned in other studies, parasellar extension and cavernous sinus invasion have also been found to have a negative impact on remission in our study [5, 14, 16]. Unlike other studies, we observed that as the grade increased in the Knosp Classification, the decrease in remission rates became more attenuated.

Although there are publications stating that recurrence cases achieve the same remission rates as primary cases [14, 16, 18], in our study, recurrence has been identified as a negative factor for remission.

Limitations

The limitations of our study include its retrospective nature, the fact that recurrent patients had their initial surgeries at other centers, the lack of volumetric measurements for evaluating total-subtotal excision, and the low number of patients with microadenomas. However, these shortcomings have been taken into account when interpreting the statistical analyses.

Conclusion

PEETS (Pure Endoscopic Endonasal Transsphenoidal Surgery) is currently the preferred treatment option for GH-secreting pituitary adenomas and has high remission rates. Our study sheds light on the future by showing that

significant remission rates can be achieved with PEETS according to the 2002 and 2010 remission criteria. We believe that even if the remission criteria change, remission rates with PEETS will continue to be consistent with the literature values. Of course, this thesis needs to be supported by future data.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical approval

This study was approved by T.C. Public Hospitals Institution Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (Approval number: 2016-1104).

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