Akromegalide Prognostik Faktörlerde Güncelleme

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12. Hipofiz Sempozyumu
4-5 Kasım 2016, Ankara

Sunum planı

- Akromegalide mortalite, morbidite
- Cep telefonu ile keypad uygulamasının yüklenmesi
- Akromegali tedavi algoritminde başlıklar
- Prognozu belirleyen faktörler

Akromegalide Morbidite

- Tümörün kitle etkisi
  - Hipopitüitarizm
  - Başağrısı
  - Görme kaybı
- Hipersomatotropinomaya bağlı yan etkiler
  - Diyabetes mellitus
  - Hipertansiyon
  - Kardiyomiyopati
  - İnme
  - Kolon ca
  - Tiroid ca
  - Artrit
  - Dismorfik görünüm
  - Uyku apnesi

Akromegalide Mortalite

- En eski derleme (Evans HM 1966)
  - 50 yaşına kadar mortalite oranı % 50
  - 60 yaşına kadar mortalite oranı % 89

Akromegalide Mortalite

- Dekkers OM, 2008

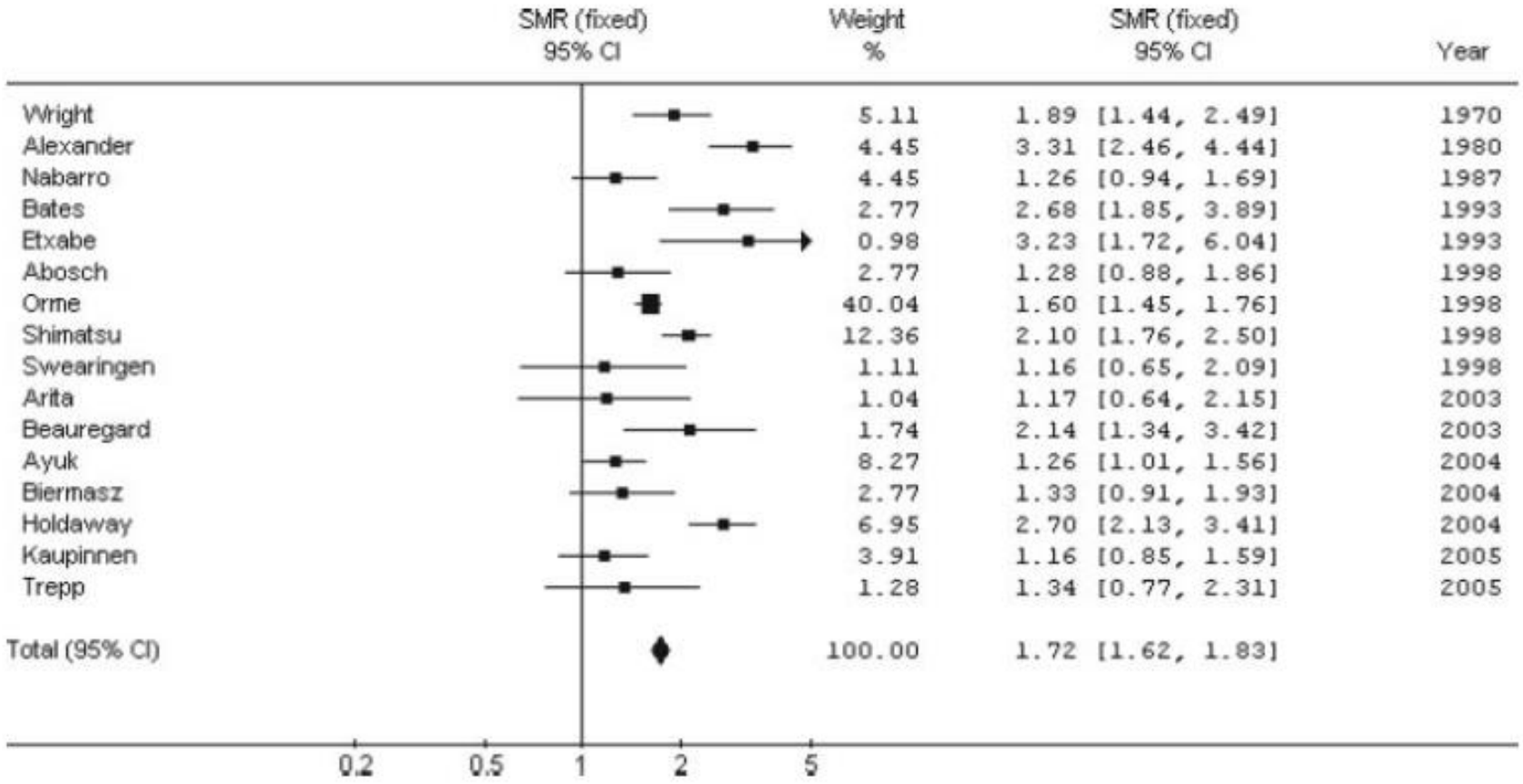
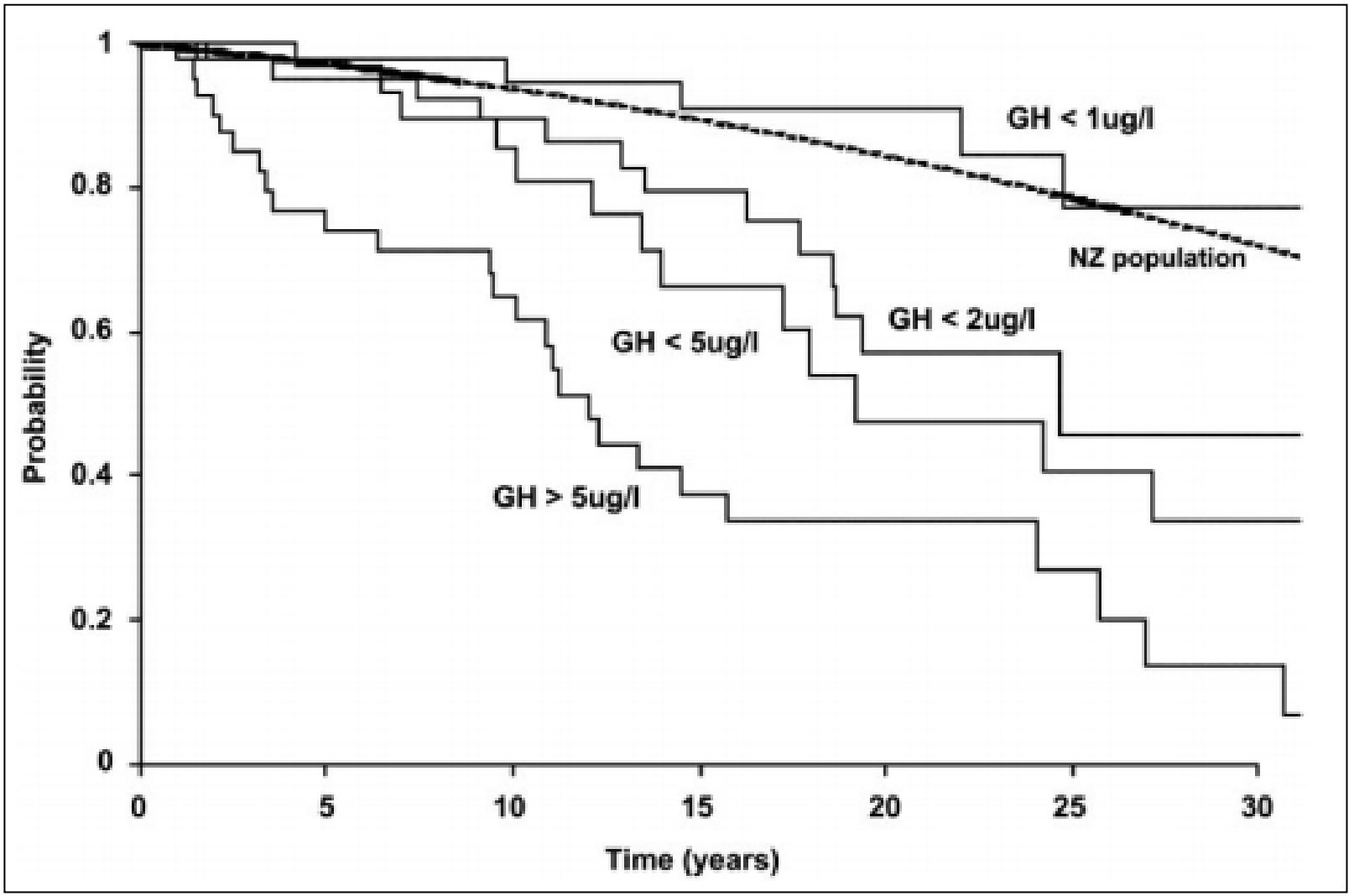


FIG 2. Metaanalysis of SMRs in acromegaly.

Factors Influencing Mortality in Acromegaly



Holdaway IM, JCEM 89:667, 2004

Acromegaly: An Endocrine Society Clinical Practice Guideline

4.0 Surgery

Indications

4.1 We recommend transsphenoidal surgery as the primary therapy in most patients. (1|⊕⊕⊕◯)

Katznelson L, JCEM 99:3933, 2014

Akromegalide cerrahi tedavi sonuçları

- Kalıcı küratif sonuç elde edilmesi
- Küratif sonuç sonrası yıllar içinde rekürrens
- Aktif hastalığın devam etmesi

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5.0 Medical therapy

5.1 We recommend medical therapy in a patient with persistent disease following surgery. (1|⊕⊕⊕⊕)

Katznelson L, JCEM 99:3933, 2014

Akromegalide medikal tedavi sonuçları

- Aktif hastalık, tedavilerle hastalığın kontrol altına alınması
- Aktif hastalık, tedavilerle kontrol altına alınamaması
- Spontan rezolüsyon ile küratif sonuç

Akromegalide sonuç

- Kalıcı küratif sonuç elde edilmesi
- Küratif sonuç sonrası yıllar içinde rekürrens
- Aktif hastalık, tedavilerle hastalığın kontrol altına alınması
- Spontan rezolüsyon ile küratif sonuç
- Aktif hastalık, tedavilerle kontrol altına alınamaması

Cep telefonu ile Keypad uygulaması

- Apple Store veya Google Play den **«Poll Everywhere »** adlı uygulama indirilecek.
- Uygulama açılacak, katılımcı bölümüne **«I'm participating»** girilecek.
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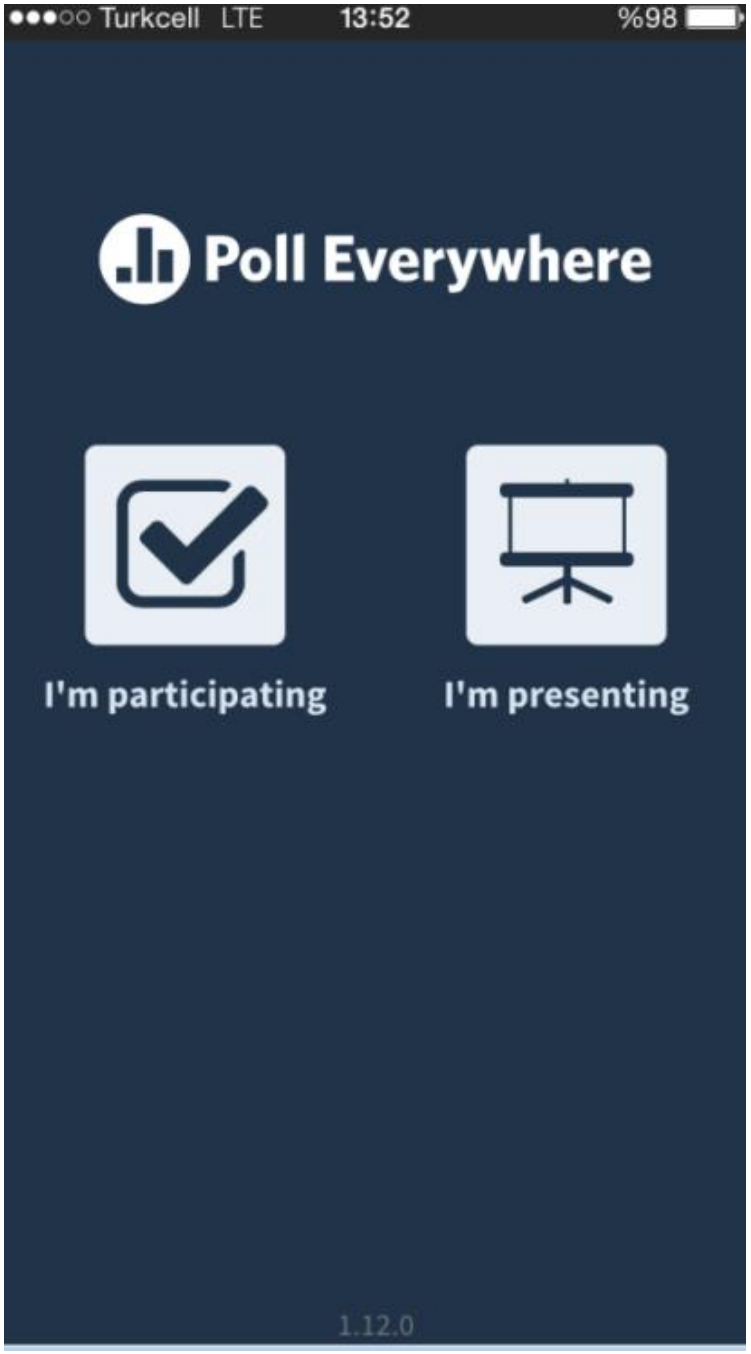
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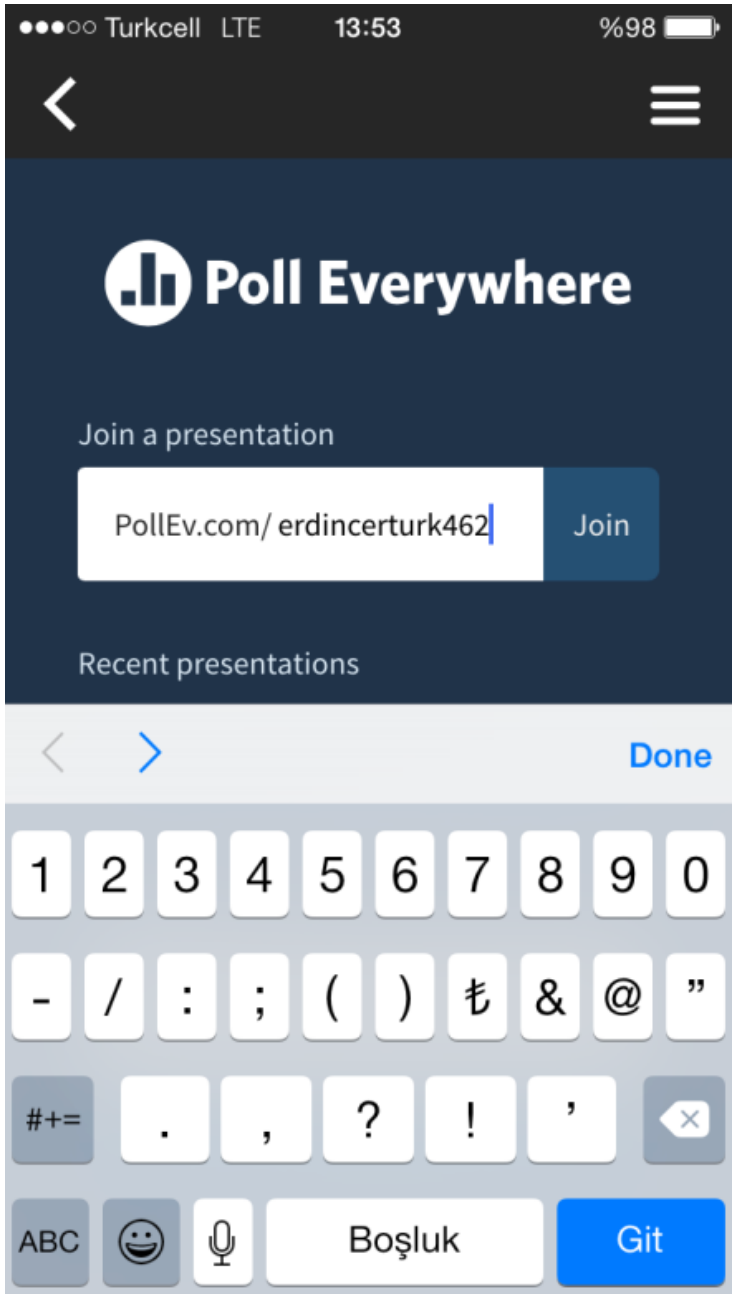

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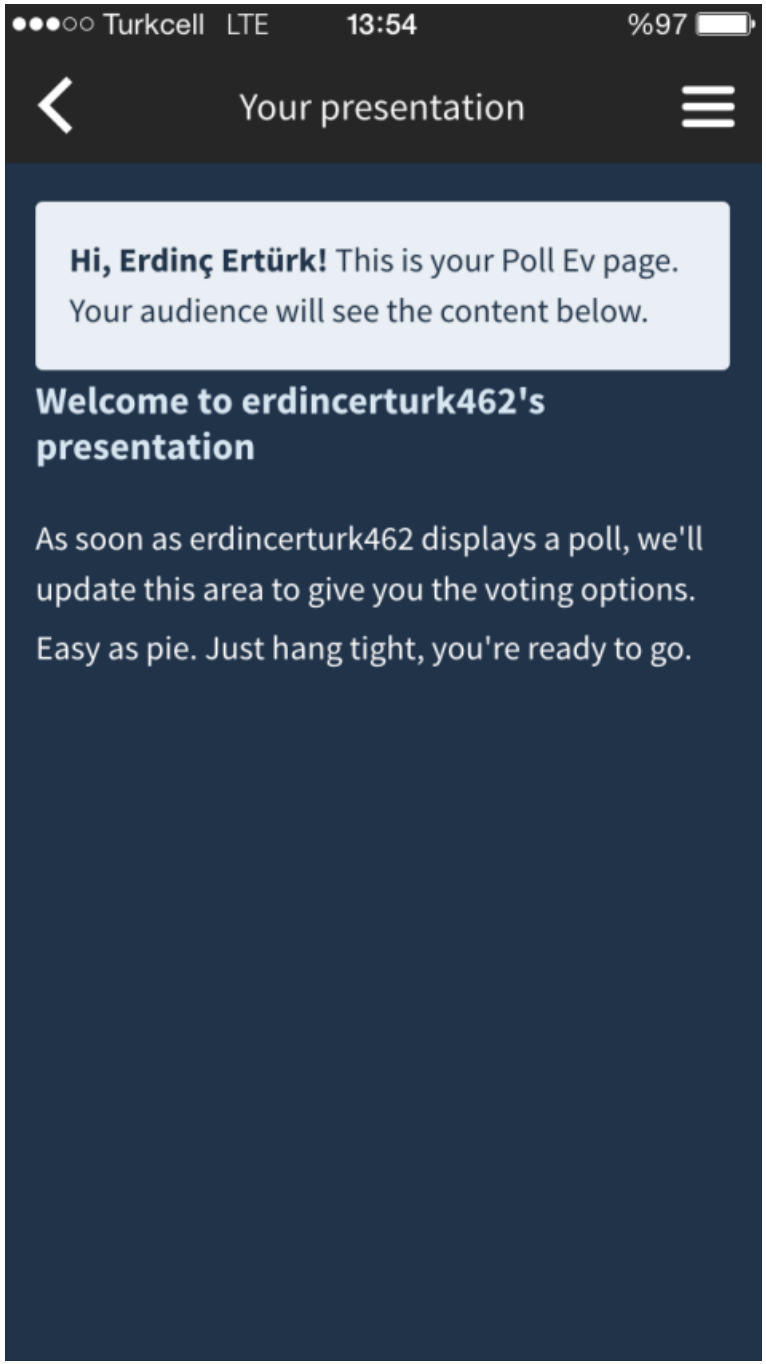
●●●○○ Turkcell LTE 13:54 %97
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HAZIRSINIZ

Kendinizi tanımlar mısınız?

a) Endokrinoloji Öğretim Üyesi

b) Endokrinoloji Uzmanı

c) Endokrinoloji Araştırma Görevlisi

d) İç Hast. Uzmanı

e) Beyin Cerrahı

f) Diğer

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Çalıştığınız bölge?

a) İç Anadolu

b) Marmara

c) Ege

d) Karadeniz

e) Akdeniz

f) Doğu Anadolu

g) Güneydoğu Anadolu

Cep telefonu ile Keypad uygulaması

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Gigantizme sebep olan somatotrof adenomlar daha agresif olma eğilimindedir.

a) Doğru

b) Yanlış

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Akromegali yapan sebepler

- GH hipersekresyonu
  - Somatotrof adenoma
    - Sporadik
    - Herediter akromegali
      - FIPA (AIP)
      - MEN1
      - Carney kompleksi
      - McCune Albright
      - X-LAG
      - Diğer genetik nedenler (SDH, NF, VHL)
  - Ektopik GH salan tümör
- GHRH hipersekresyonu (< % 1)
  - Hipotalamik tümör
    - Hemartom, gliom, gangliositom
  - Ektopik GHRH hipersekresyonu
    - Karsinoid, Adacık hücre tm, Feo

Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients

Table 1 Clinical characteristics of patients with pituitary gigantism

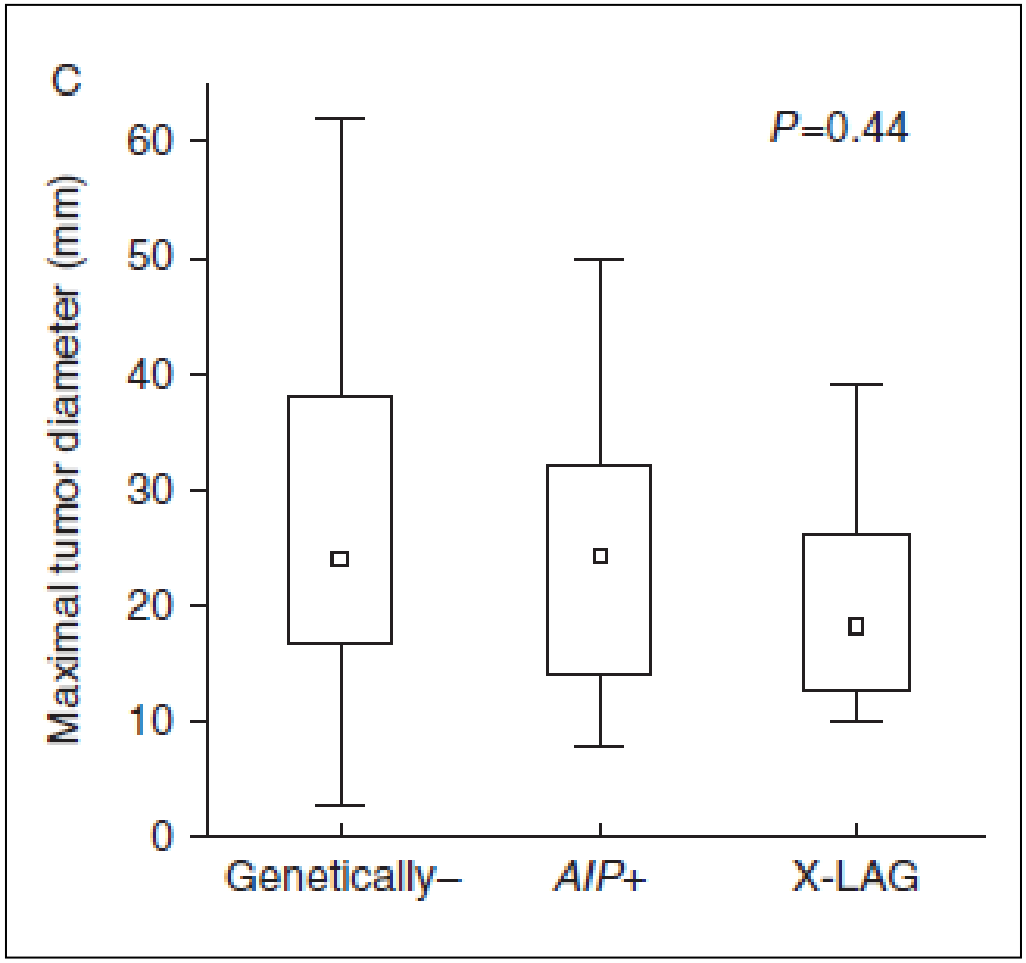
Study criteria	Total group	Males (n=163) 78%	Females (n=45) 22%
Age at rapid growth onset (year)[a]	13 (9; 15)	13 (10; 15)	11 (3; 14)
Patients who had not attained final height (%)	15.9%	13.5%	25.6%
Age at which final height was attained (year)	20 (18; 22)	20 (18; 22)	18.5 (16; 23)
% from MPH	11.6 (8.5; 14.8)	11.2 (8.4; 13.7)	12.9 (8.7; 16.4)
Maximal dimension of PA (mm)	22 (14; 34)	21 (14; 32)	24.5 (15; 36)
Macroadenoma (%)	84.3%	85.1%	81.6%
Giant adenoma (%)	15%	14.6%	16.7%
Extension (%)	77.2%	77%	78%
Invasion (%)	54.5%	54.9%	53.3%
GH level at diagnosis (ng/ml)[a]	35.5 (14; 83)	29 (12.3; 64)	62.3 (27.8; 95)
IGF1 level at diagnosis (% ULN)	254.5 (189.5; 359.5)	250 (188; 358.5)	268 (198; 421)
Prolactin co-secretion (%)	34%	31%	46.9%
GH/IGF1 controlled $\leq$19 years (%)	36.6%	32.1%	55%
GH/IGF1 controlled before final height (%)	20.8%	19.2%	26.8%
Long-term control (%)	39%	42%	30%

Macroadenoma (%) 84.3%
Giant adenoma (%) 15%
Extension (%) 77.2%
Invasion (%) 54.5%

Long-term control (%) 39%

Rostomyan L, End Rel Ca 22:745, 2015

Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients



Rostomyan L, EndRelCa 22:745, 2015

- Akromegalide cerrahi başarıyı **en az** etkileyen faktör aşağıdakilerden hangisidir?

a) Serum GH düzeyi

b) Serum IGF-1 düzeyi

c) Adenom boyutu

d) Adenomun kavernöz sinüs invazyonu

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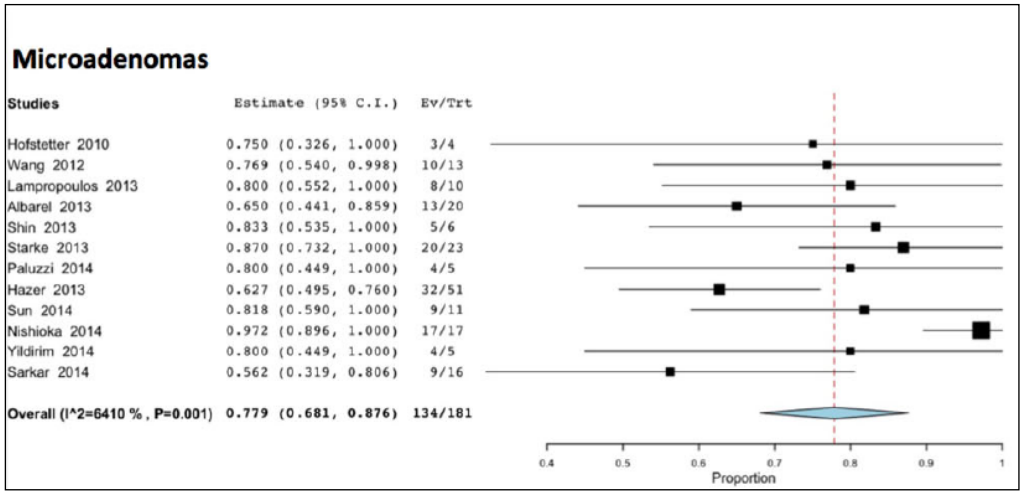
The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'

	Microadenoma	Macroadenoma	Giant adenoma
n	142 (27%)	378 (70.7%)	12 (2.2%)
Diameter (mm)	2–9	10–37	41–60
Average diameter (mm)	7.6±1.75	16.7±5.6^{+++}	50.9±9.5^{++}
GH level (μg/l)	1–142	4–357	10–398
Average GH level (μg/l)	16.4±15.2	42.6±38.4^{+++}	102.4±64.3^{++}
Remission rate (*n*)	107 (75.3%)	186 (48.6%)	1 (8.3%)

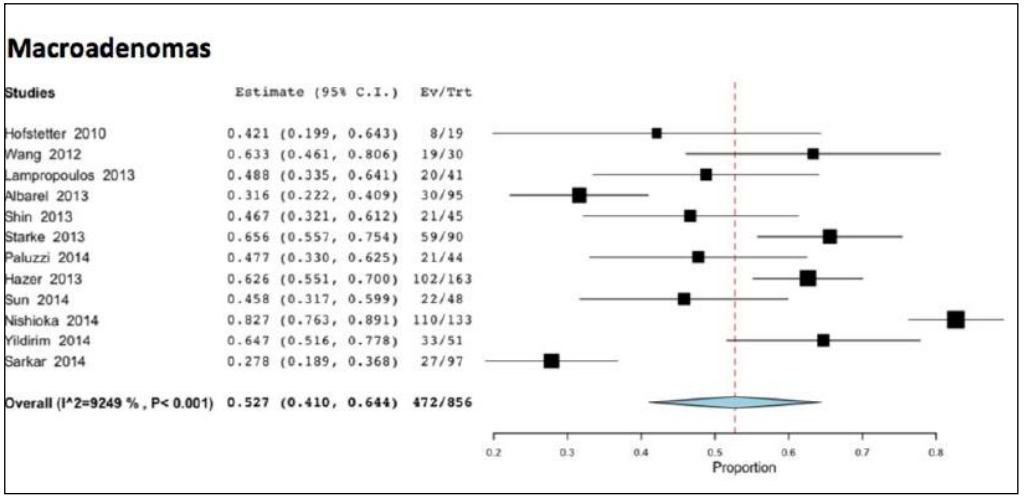
Nomikos P, EJE 152:379, 2005

Surgical treatment of acromegaly according to the 2010 remission criteria: systematic review and meta-analysis



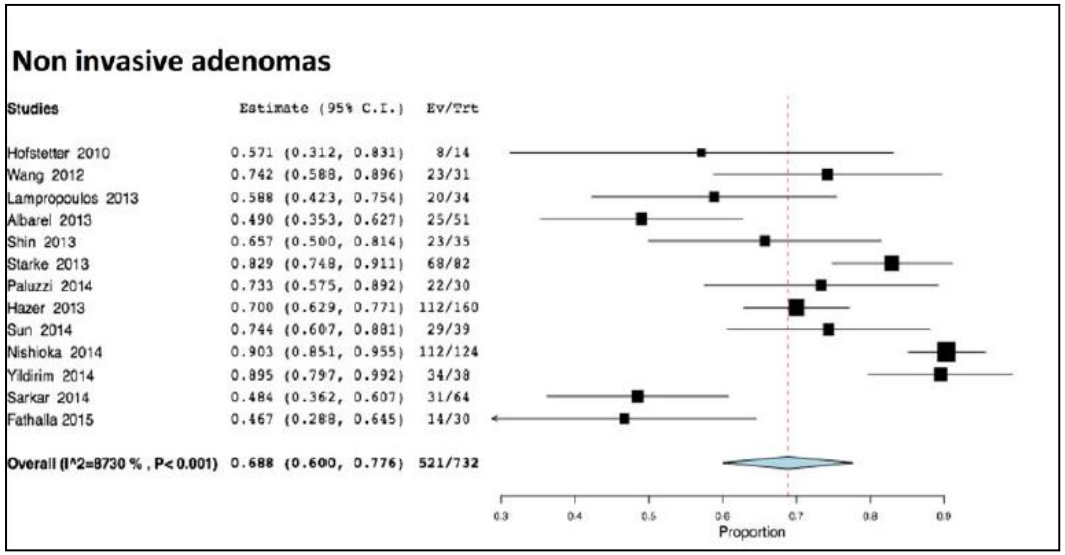
Mikroadenom % 78

Makroadenom % 53



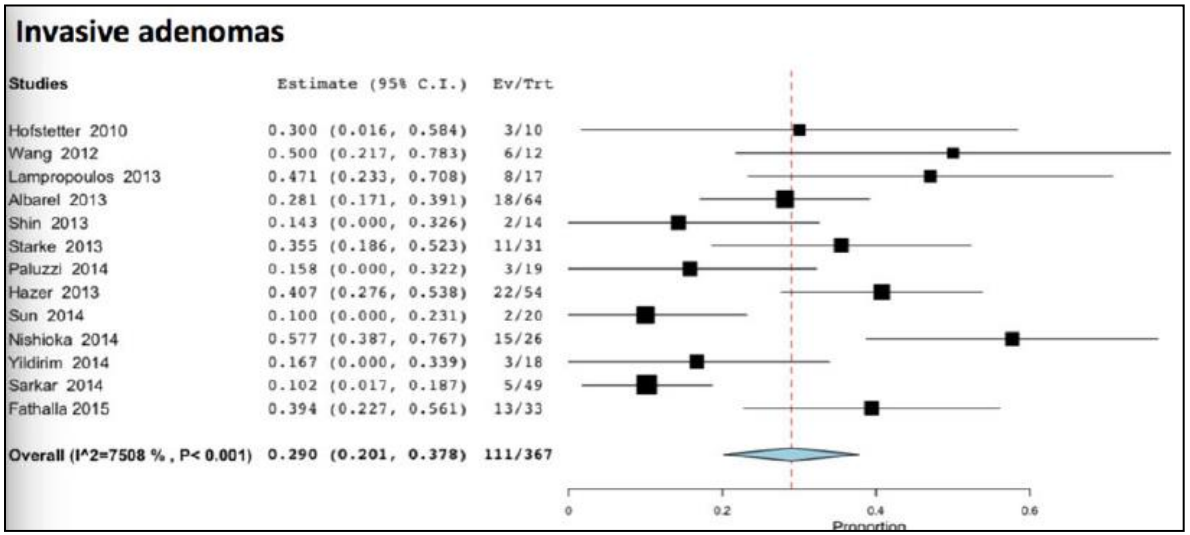
Starnoni D, Acta Neuroschir. 158:2109, 2016

Surgical treatment of acromegaly according to the 2010 remission criteria: systematic review and meta-analysis



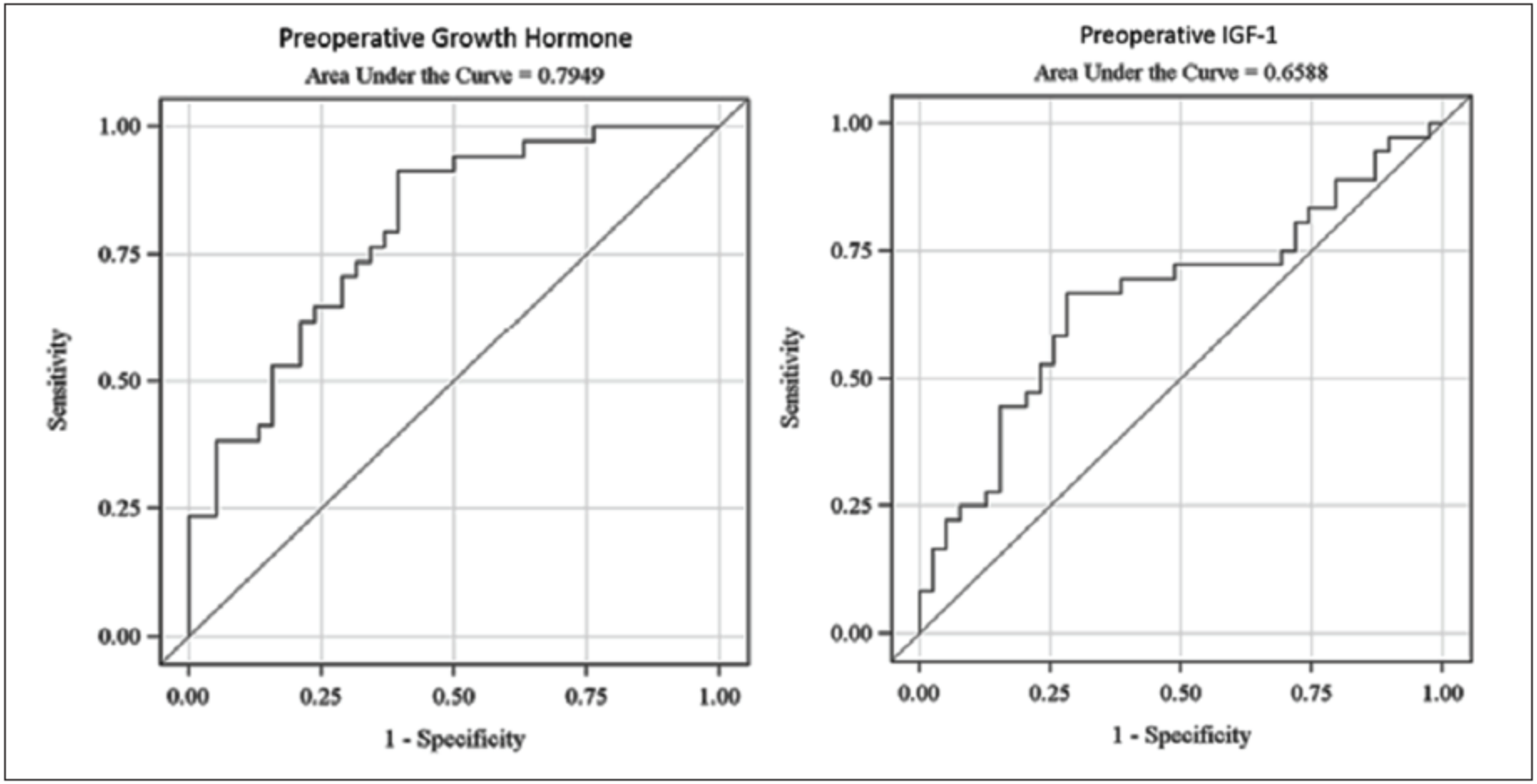
Non İnvasif % 69

İnvazif % 29



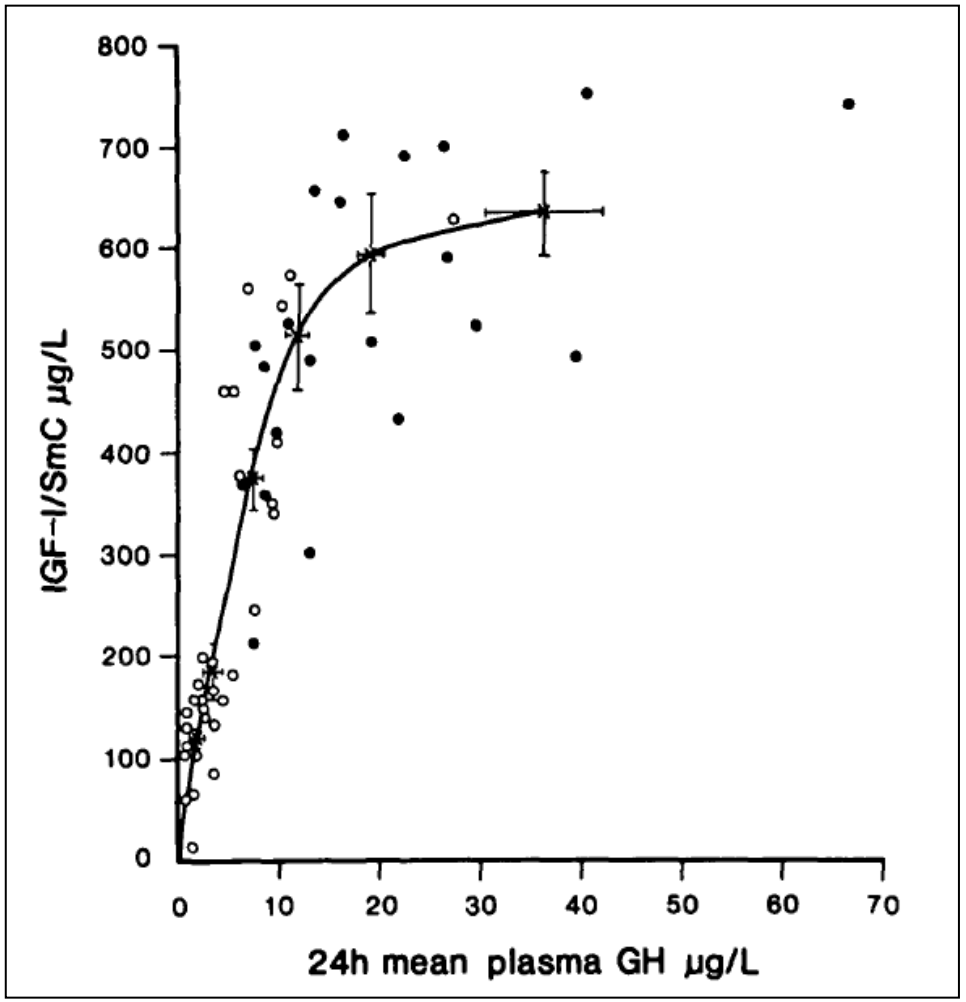
Starnoni D, Acta Neuroschir. 158:2109, 2016

SIGNIFICANT ELEVATION OF GROWTH HORMONE LEVEL IMPACTS SURGICAL OUTCOMES IN ACROMEGALY



Anthony JR, Endocr Pract, 21:1001, 2015

Plasma Insulin-Like Growth Factor-I/Somatomedin-C in Acromegaly: Correlation With the Degree of Growth Hormone Hypersecretion*



Barkan A, JCEM, 67:99, 1988

SIGNIFICANT ELEVATION OF GROWTH HORMONE LEVEL IMPACTS SURGICAL OUTCOMES IN ACROMEGALY

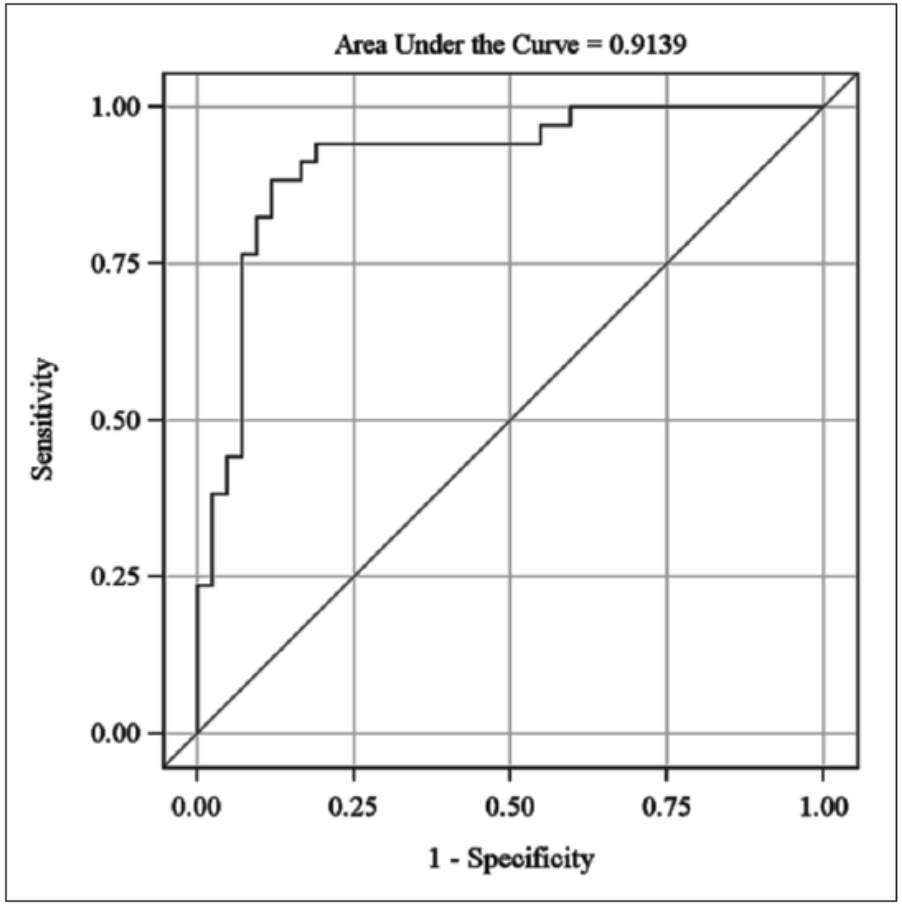
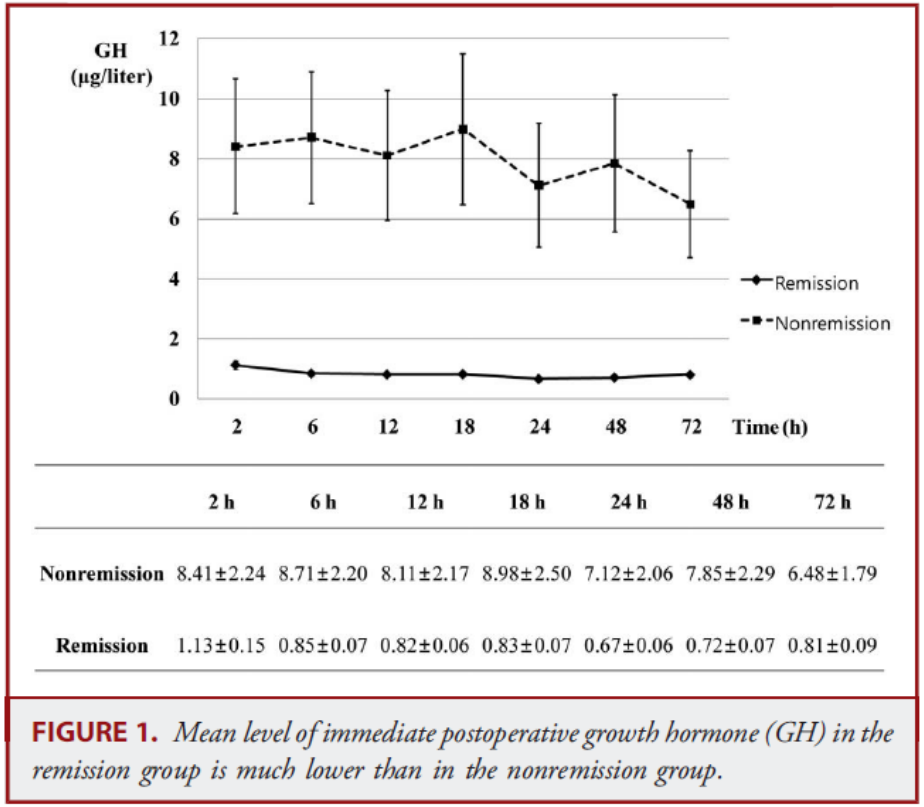


Fig. 2. Receiver operating characteristic curve for immediate postoperative growth hormone levels (ng/mL) drawn on postoperative day 2 and long-term remission.

Postoperatif GH düzeyi

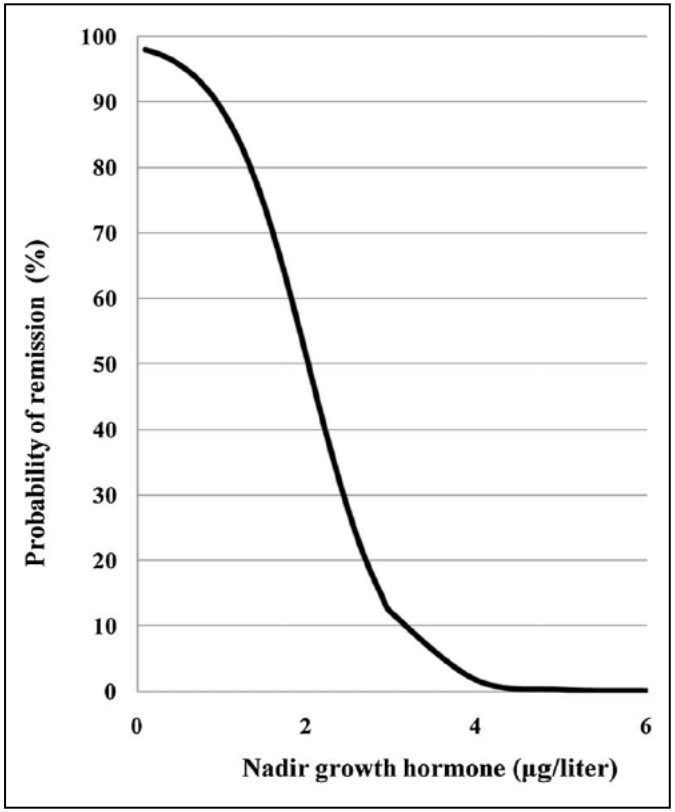
Anthony JR, Endocr Pract, 21:1001, 2015

Predicting Long-term Remission by Measuring Immediate Postoperative Growth Hormone Levels and Oral Glucose Tolerance Test in Acromegaly



	2 h	6 h	12 h	18 h	24 h	48 h	72 h
Nonremission	8.41±2.24	8.71±2.20	8.11±2.17	8.98±2.50	7.12±2.06	7.85±2.29	6.48±1.79
Remission	1.13±0.15	0.85±0.07	0.82±0.06	0.83±0.07	0.67±0.06	0.72±0.07	0.81±0.09

FIGURE 1. *Mean level of immediate postoperative growth hormone (GH) in the remission group is much lower than in the nonremission group.*



Kim EH, Neurosurgery, 70:1106, 2012

Akromegalide
Cerrahi için Prognostik faktörler

- Hastanın yaşı
- Adenomun boyutu
- İnvazyon varlığı
- Preop serum GH düzeyi
  - Preop serum IGF1 düzeyi
- **Postop serum GH düzeyi**
  - ~~Postop (erken) serum IGF1 düzeyi~~

- Akromegalide cerrahi başarıyı olumlu/olumsuz yönde **<u>en fazla</u>** etkileyen faktör aşağıdakilerden hangisidir?

a) Mikroskopik / Endoskopik cerrahi

b) İntraoperatif MR navigasyonu

c) Preoperatif SRL tedavisi

d) Tecrübeli / Az tecrübeli cerrah

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Cerrah tecrübesi

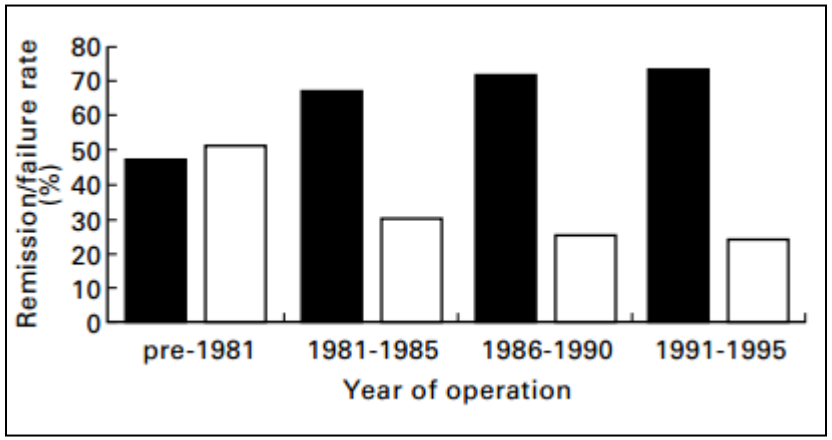
Outcome of surgery for acromegaly—the experience of a dedicated pituitary surgeon

Gittoes NJL. QJM, 92:741, 1999

	One of eight surgeons	Single surgeon	*p*
Overall cure	26/78 (33%)	42/66 (64%)	<0.0005
Microadenomas	7/13 (54%)	19/22 (86%)	<0.05
Macroadenomas			
+SS	1/13 (8%)	12/19 (63%)	<0.005
−SS	9/20 (45%)	11/25 (44%)	N/S

Overall cure rates are shown along with data relating to tumour size. Microadenomas were <1 cm; macroadenomas were $\geqslant 1$ cm. +SS, suprasellar extension present; −SS, suprasellar extension absent.

Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience*



Ahmed S Clin Endocr 50:561, 1999

Mikroskopik / Endoskopik

Endoscopic vs Microsurgical Transsphenoidal Surgery for Acromegaly: Outcomes in a Concurrent Series of Patients Using Modern Criteria For Remission

Table 6. Biochemical Remission After Resection of GH-Secreting Adenomas in Modern Surgical Series

Author/Year	n	Size Microadenoma/ Macroadenoma	Remission		
			Overall	Microadenoma	Macroadenoma
Series using 2010 consensus criteria					
Microscopic series					
Current series	43	11/32	70%	82%	66%
Endoscopic series					
Wang et al, 2012 (23)	43	13/30	67%	77%	63%
Hofstetter et al, 2010 (8)	24	4/20	38%		
Current series	72	13/59	71%	88%	66%
Series using 2000 consensus criteria					
Microscopic series					
Kim et al, 2009 (41)	42	12/30	64%	67%	60%
Ludecke and Abe, 2006 (29)	147	21/126	72%	95%	68%
Trepp et al, 2005 (31)	69	5/64	42%	80%	39%
Nomikos et al, 2005 (25)	506	142/364	57%	75%	50%
Esposito et al, 2004 (28)	67	13/54	57%	77%	52%
De et al, 2003 (27)	90	29/61	63%	79%	56%
Beauregard et al, 2003 (34)	103	22/81	52%	82%	47%
Kaltsas et al, 2001 (47)	67	17/42	34%	59%	26%
Shimon et al, 2001 (42)	88	44/44	74%	84%	64%
Kreutzer et al, 2001 (32)	57	19/38	70%		
Endoscopic series					
Wagenmakers et al, 2011 (43)	40	0/40	56%		56%
Gondim et al, 2010 (44)	67	14/53	75%	86%	72%
Campbell et al, 2010 (5)	26	4/22	58%	75%	55%
Tabaee et al, 2009 (9)	6		83%		
Yano et al, 2009 (10)	31		71%		
Dehdashti et al, 2008 (12)	34	8/26	71%	83%	65%
Frank et al, 2006 (13)	83	24/59	70%	83%	65%
Rudnik et al, 2005 (17)	12	4/8	83%		
Cappabianca et al, 2002 (45)	36	6/30	64%	83%	60%
Cappabianca et al, 2002 (46)	23	3/20	57%	67%	55%

Starke RM. JCEM, 98:3190, 2013

Endoscopic vs Microsurgical Transsphenoidal Surgery for Acromegaly: Outcomes in a Concurrent Series of Patients Using Modern Criteria For Remission

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Microscopic series					
[illegible]	43	11/32	70%	82%	66%
Dehdashti et al, 2008 (12)	34	8/26	71%	83%	65%
Frank et al, 2006 (13)	83	24/59	70%	83%	65%
Rudnik et al, 2005 (17)	12	4/8	83%		
Cappabianca et al, 2002 (45)	36	6/30	64%	83%	60%
Cappabianca et al, 2002 (46)	23	3/20	57%	67%	55%

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(94, 95). There is no definitive evidence of superiority of the endoscopic vs the microscopic approach with regard to short- and long-term remission rates, recurrence, or complications. The experience of the pituitary surgeon is the major determinant in achieving successful outcomes (96,

Starke RM. JCEM, 98:3190, 2013

İntraoperatif navigasyon (MR)

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

Fahlbusch R. EJE, 153:239, 2005

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.

Intraoperative magnetic resonance imaging–assisted transsphenoidal pituitary surgery in patients with acromegaly

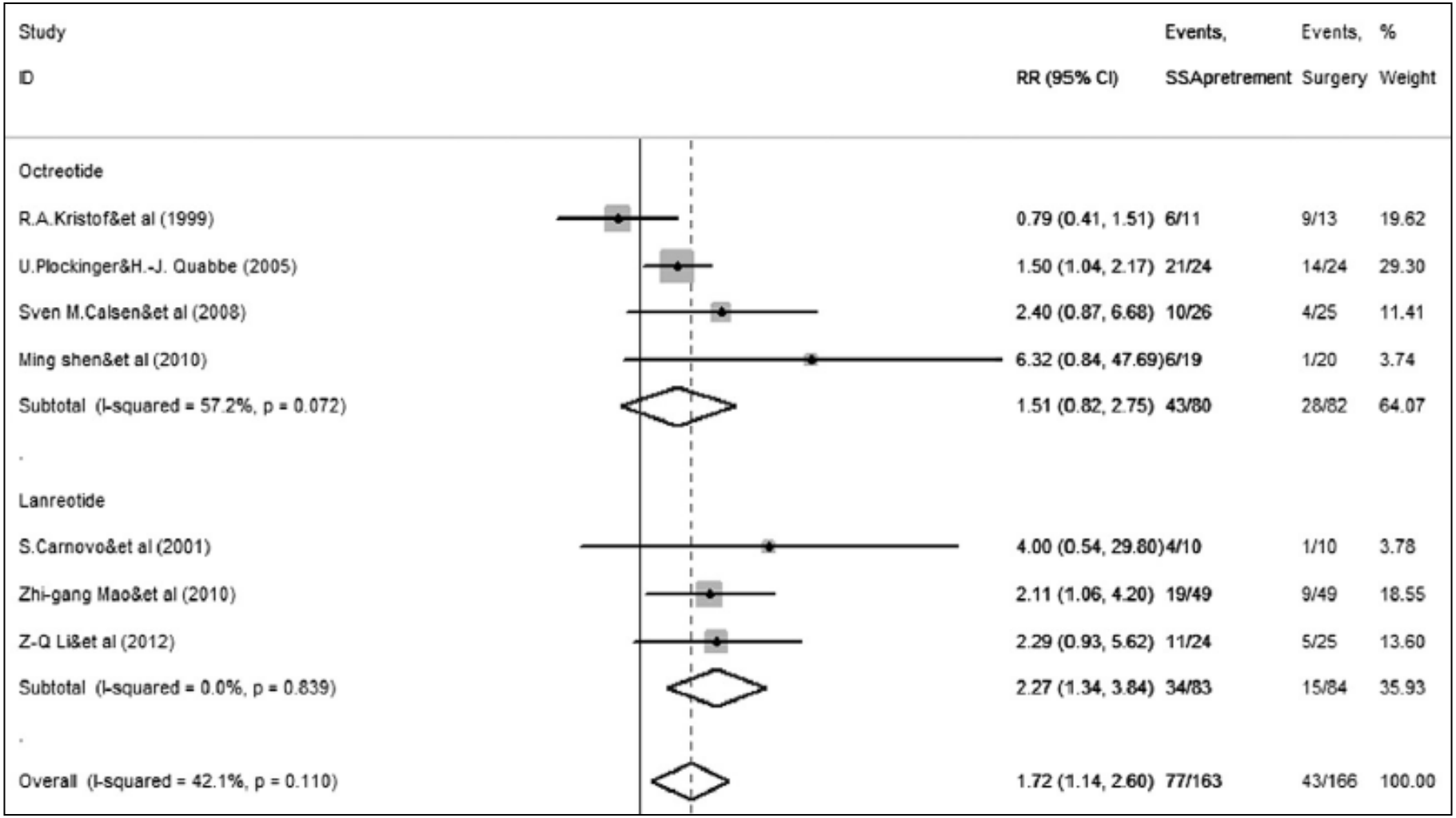
Bellut D. Neurosurg Focus, 29:E9, 2010

Results. Thirty-seven patients with acromegaly underwent 39 transsphenoidal surgeries for pituitary adenomas. During a median follow-up period of 30 months (range 9–56 months), the remission rate was 73.5% in 34 patients with primary surgery and 20% in 5 cases with previous surgery; overall the remission rate was 66.7%. There were no serious postoperative complications. Detection of tumor remnant on iMR imaging led to a 5.1% increase in remission rate.

Conclusions. In this largest study to date of GH-producing pituitary adenomas in which iMR imaging–guided

Preop SRL tedavisi

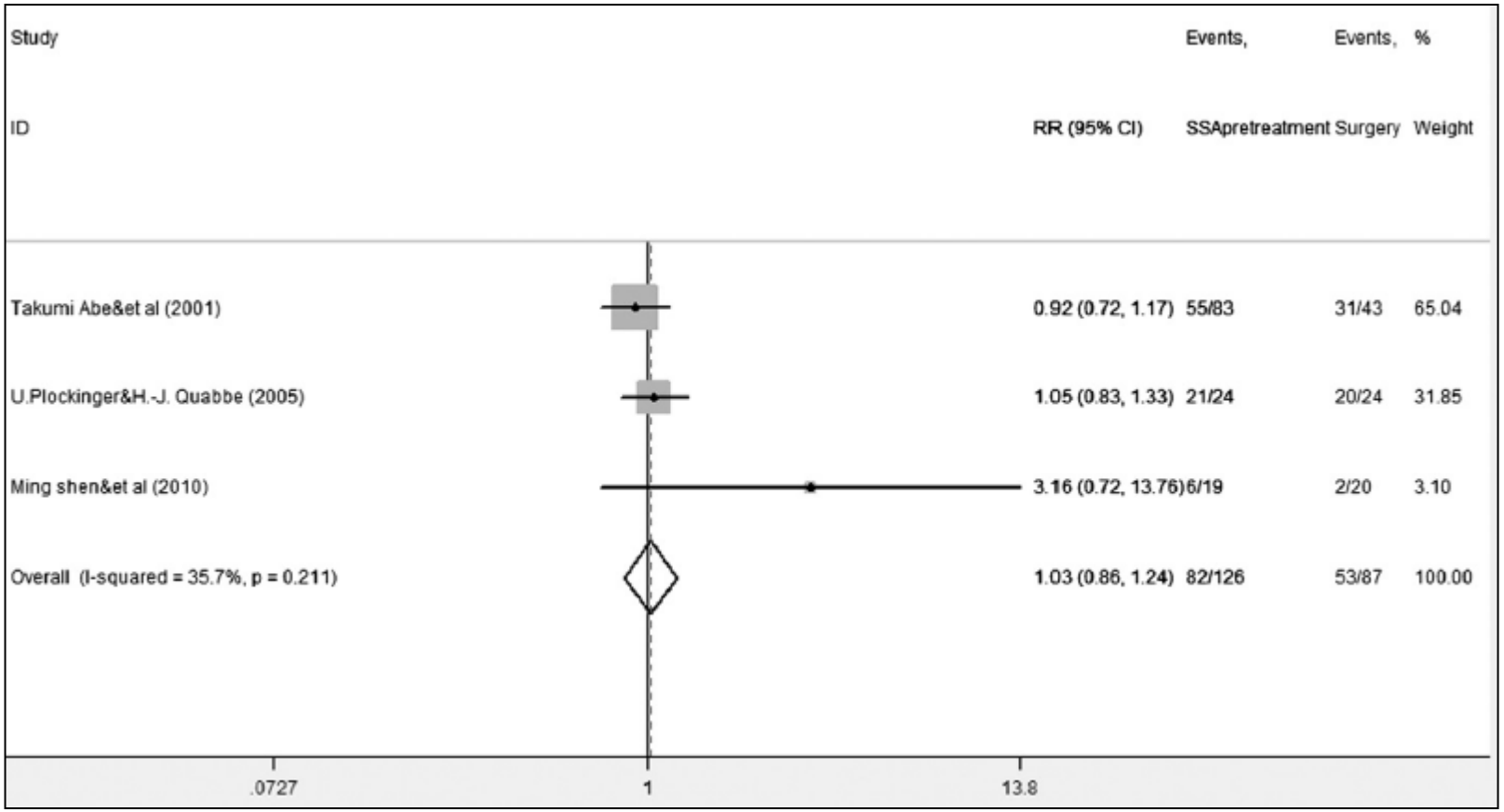
Preoperative somatostatin analogs treatment in acromegalic patients with macroadenomas. A meta-analysis



Lei Z. Brain Dev, 37:181, 2015

Preoperative somatostatin analogs treatment in acromegalic patients with macroadenomas. A meta-analysis

Geç dönem



Lei Z. Brain Dev, 37:181, 2015

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Preoperative medical therapy

4.3 We suggest against the routine use of preoperative medical therapy to improve biochemical control after surgery. (2|⊕⊕◯◯)

Katznelson L, JCEM 99:3933, 2014

Akromegalide
Cerrahi için Prognostik faktörler

- Hastanın yaşı
- Adenomun boyutu
- İnvazyon varlığı
- Preop serum GH düzeyi
  - Preop serum IGF1 düzeyi
- **Postop serum GH düzeyi**
  - ~~Postop (erken) serum IGF1 düzeyi~~
- **Cerrah tecrübesi**
  - ~~Cerrahi teknik (Mikroskopik/Endoskopik)~~
  - ~~İntraoperatif MR navigasyon sistemleri~~
  - ~~Preoperatif SRL ile tedavi~~

Acromegaly: An Endocrine Society Clinical Practice Guideline

4.0 Surgery

Indications

4.1 We recommend transsphenoidal surgery as the primary therapy in most patients. (1|⊕⊕⊕◯)

5.0 Medical therapy

5.1 We recommend medical therapy in a patient with persistent disease following surgery. (1|⊕⊕⊕⊕)

Katznelson L, JCEM 99:3933, 2014

Akromegalide medikal tedavi seçenekleri

- Somatostatin analogları
  - Octreotid, Lanreotid, Pasiretotid
- Dopamin agonistleri
  - Kabergolin
- GH reseptör antagonistleri
  - Pegvisomant

- Akromegalide cerrahi kür beklenmeyen invazif adenomlu bir hastada debulking cerrahisi daha sonra uygulanacak SRL tedavisinin etkinliğini artırabilir mi?

a) Evet arttırabilir

b) Hayır arttırmaz

c) Yeterli çalışma bulunmamaktadır

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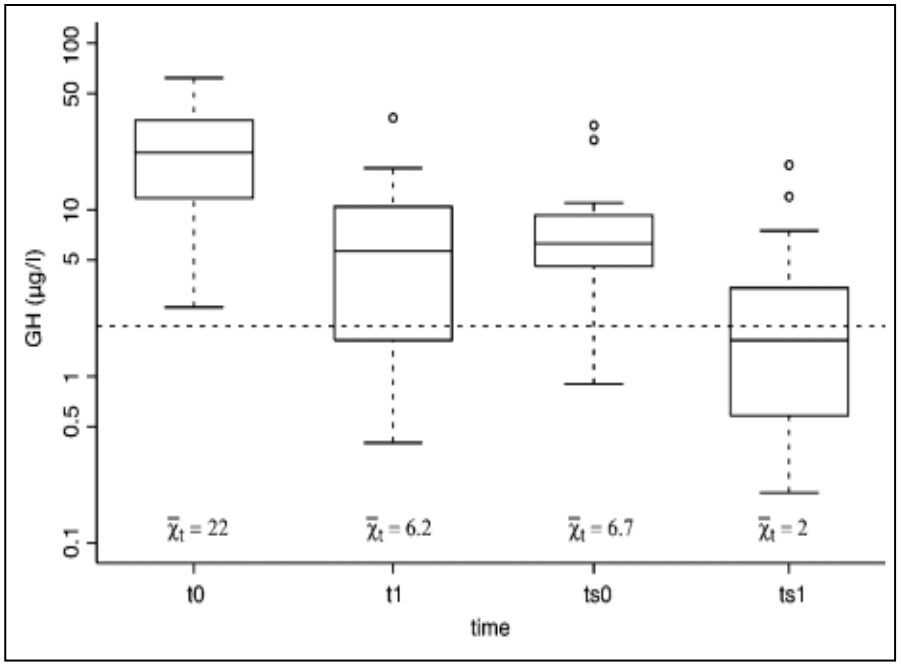
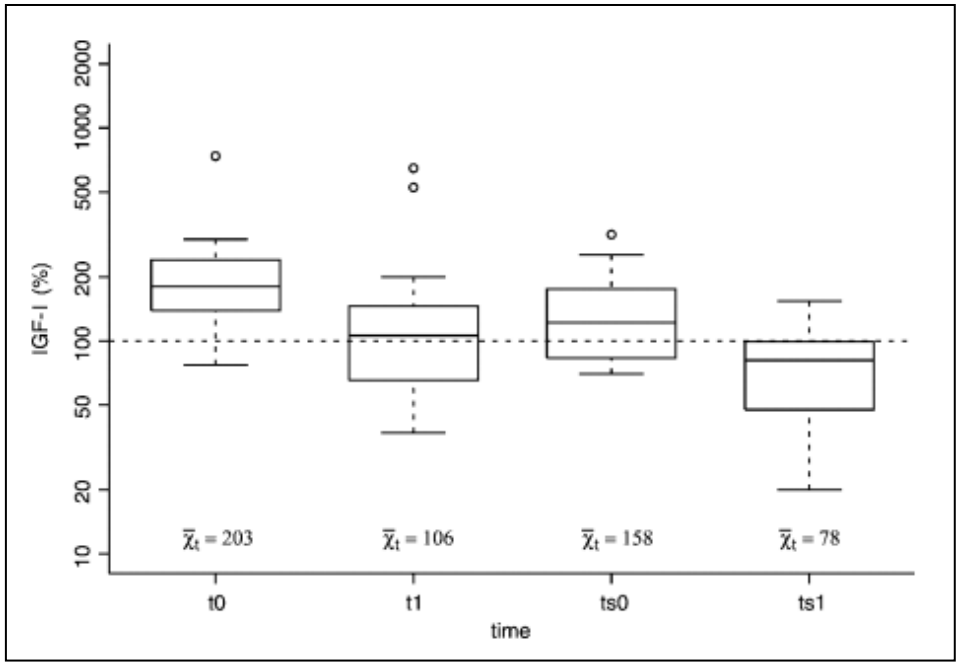
Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs



preop pre+SRL postop post+SRL



preop pre+SRL postop post+SRL

Petrossians P, EJE 152:61, 2005

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Surgical debulking

4.5 In a patient with parasellar disease making total surgical resection unlikely, we suggest surgical debulking to improve subsequent response to medical therapy. (2|⊕⊕◯◯)

Katznelson L, JCEM 99:3933, 2014

Akromegalide
SRL tedavisi için Prognostik Faktörler

- Debulking cerrahi

- Aşağıdakilerden hangi faktörler SRL tedavisine yanıtı **en fazla** gösterebilen kriterdir?

a) Sella MR da T2 de sinyal intensitesi

b) Somatostatin sintigrafisi

c) Octreotid süpresyon testine yanıt

d) İmmünositokimyasal yoğun/gevşek granüllü boyanma

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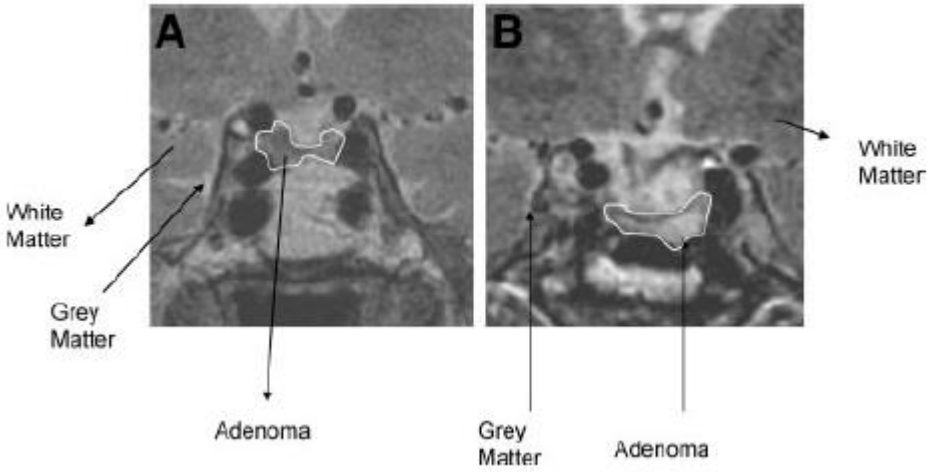
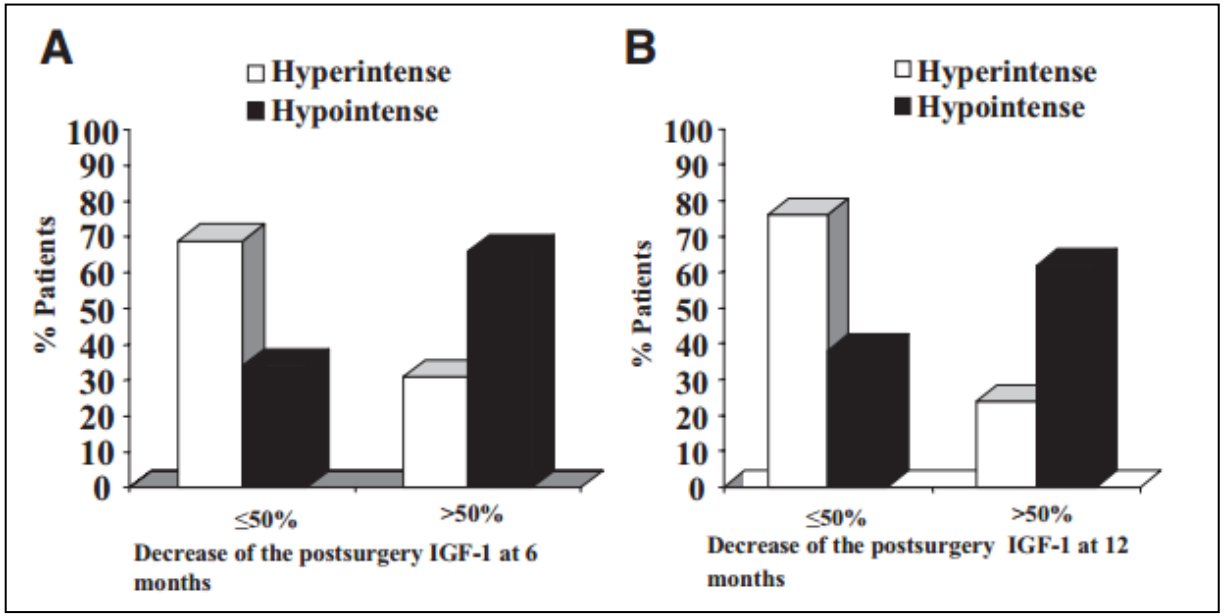
Sella MR; T2 de sinyal yoğunluğu

Magnetic Resonance Imaging as a Predictor of Response to Somatostatin Analogs in Acromegaly after Surgical Failure





Puig-Domingo M, JCEM, 95:4973, 2010

Somatostatin sintigrafisi

Results of somatostatin receptor scintigraphy do not predict pituitary tumor volume- and hormone-response to ocreotide therapy and do not correlate with tumor histology.

mixed somatotrope/lactotrope, plurihormonal) or in 22 NF-A (null-cell adenomas, gonadotropinomas silent hormonal adenomas). We conclude that 111In-pentetreotide SRS reflects tumor volume poorly in GH-A and not at all in NF-A. It does not predict the effect of Oct-Tx on the volume of both GH-A and NF-A, nor on the GH concentration in GH-A. 111In-pentetreotide SRS is unable to identify post-operative tumor remnants not visible on MRI.

Plöckinger U, EJE 136:369, 1997

Octreotid test dozu

The octreotide test dose is not a reliable predictor of the subsequent response to somatostatin analogue therapy in patients with acromegaly

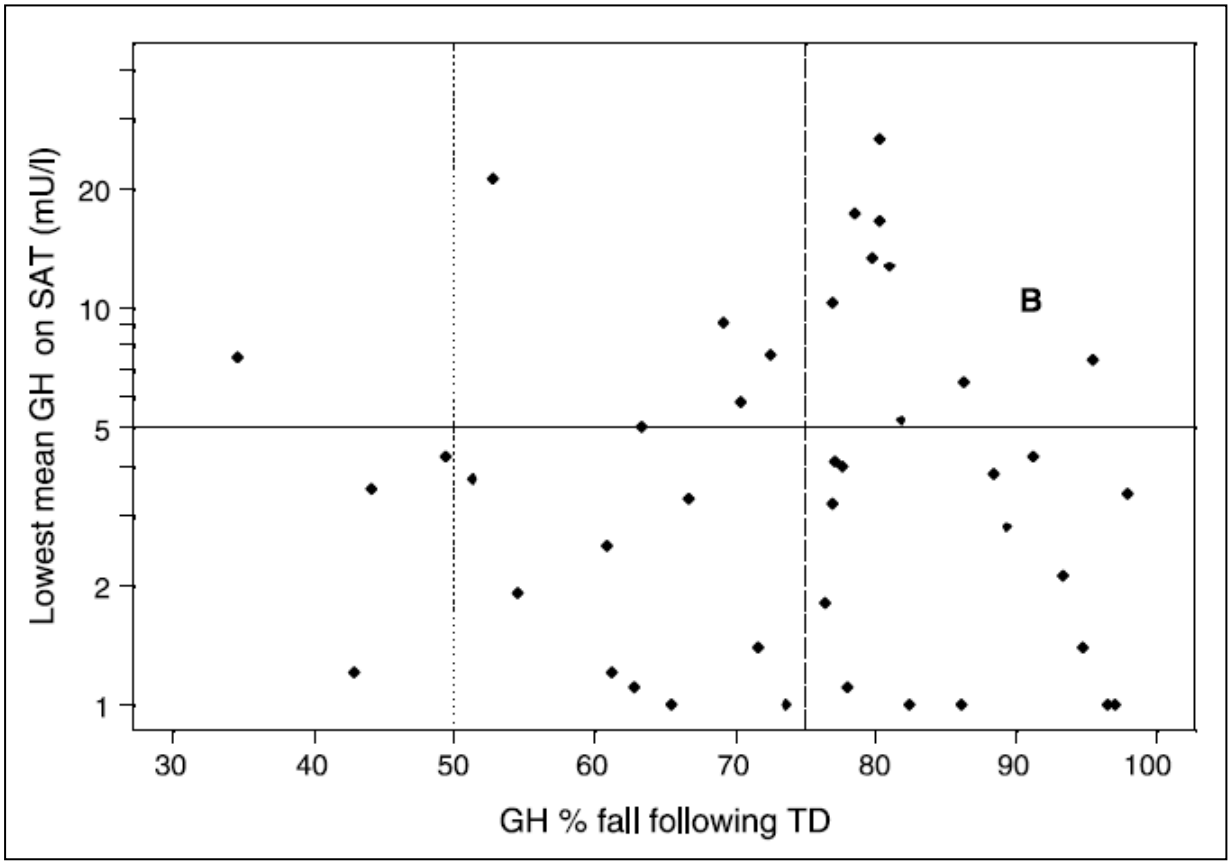


Figure 3 No significant correlation ($r = -0.06$, $P = 0.72$) is seen between the percentage fall in GH after the TD and mean GH on SAT. Despite falls in GH values following the TD of > 75%, patients in quadrant B failed to normalise GH during treatment.

control does not equate to no benefit, as biochemical improvement was seen in every patient; therefore, no patient should be deprived of octreotide therapy because of the result of a TD. In conclusion, our data indicate that the octreotide TD has no place in selecting patients for SAT.

Pokrajak A, EJE 154:267, 2006

Yoğun / Gevşek granüllü

Growth hormone tumor histological subtypes predict response to surgical and medical therapy

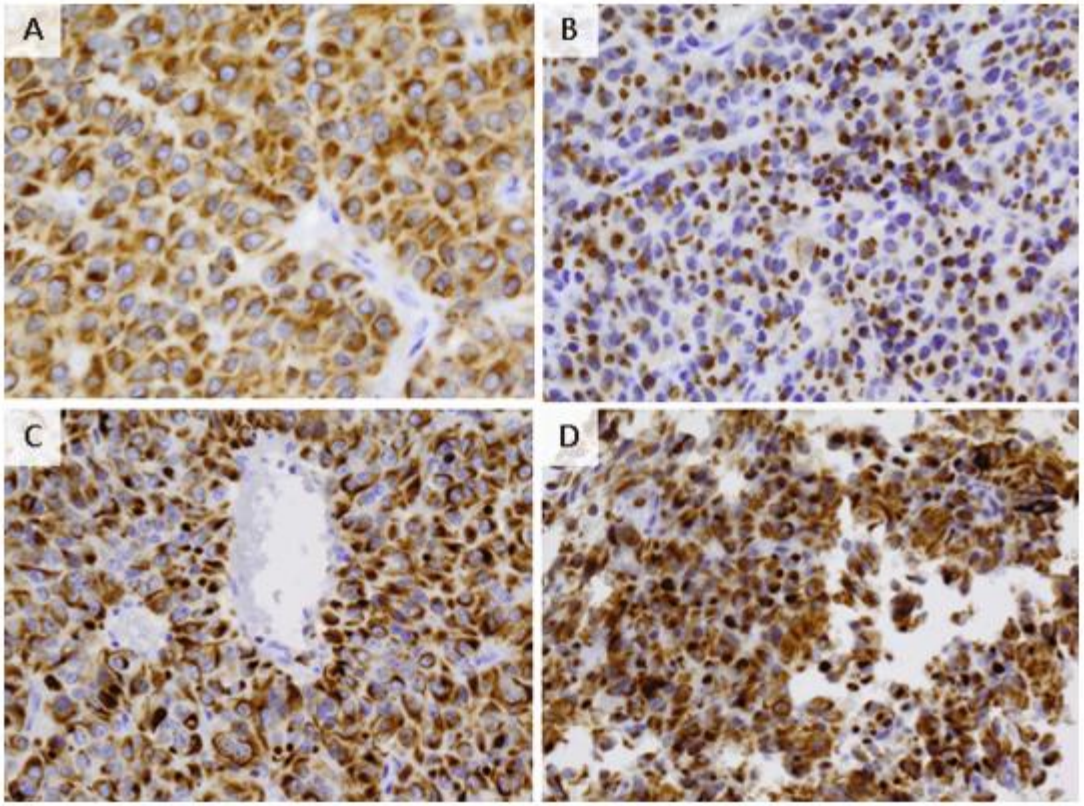
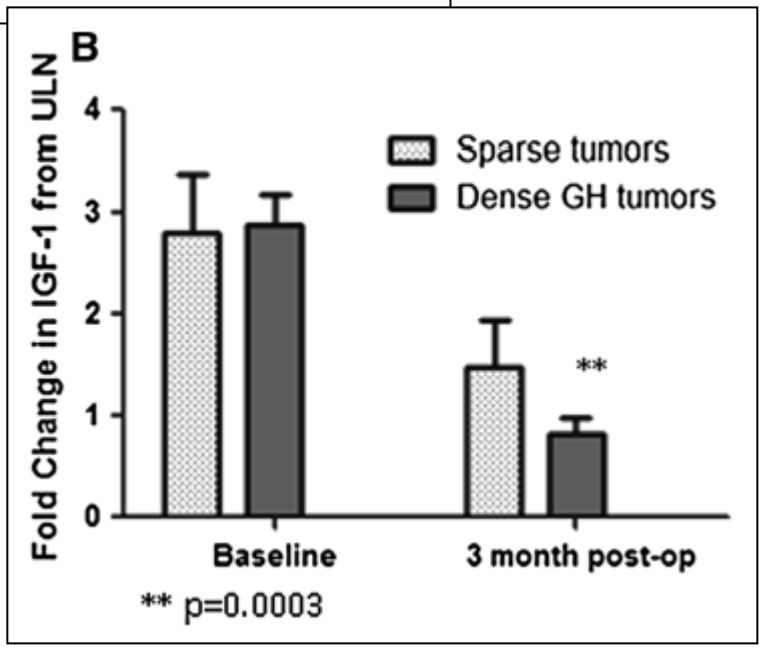


Fig. 1 Cam5.2 staining of growth hormone adenoma. **a** Densely granulated tumor (×60) shows keratins diffusely distributed throughout cytoplasm and perinuclear distribution pattern. **b** Sparsely granulated adenoma (×60) with characteristics dot-like keratin immunoreactivity representing fibrous bodies. **c** Intermediate tumors (×40) typically comprised of two keratin pattern populations with dot-like pattern and perinuclear pattern interspersed. **d** Intermediate tumors (×60) with DG and SG pattern

Vassiliadis KK, Endocrine 49:231, 2015

Growth hormone tumor histological subtypes predict response to surgical and medical therapy

Variable	Sparse GH	Dense GH	*p* value
Age (Mean ± SD)	40.4 ± 13.7	50.0 ± 12.8	**0.0010**
Gender (*N*: % Female)	16 (53.3 %)	34 (47.9 %)	0.62
Mean follow-up (Years ± SD)	3.2 ± 2.3	2.4 ± 2.5	0.19
Tumor volume (mm^3)* Geo. mean (95 % CI)	2,392, $N = 23$ (1,274–4,537)	665, $N = 60$ (428–1,043)	**0.0030**



Vassiliadis KK, Endocrine 49:231, 2015

Growth hormone tumor histological subtypes predict response to surgical and medical therapy

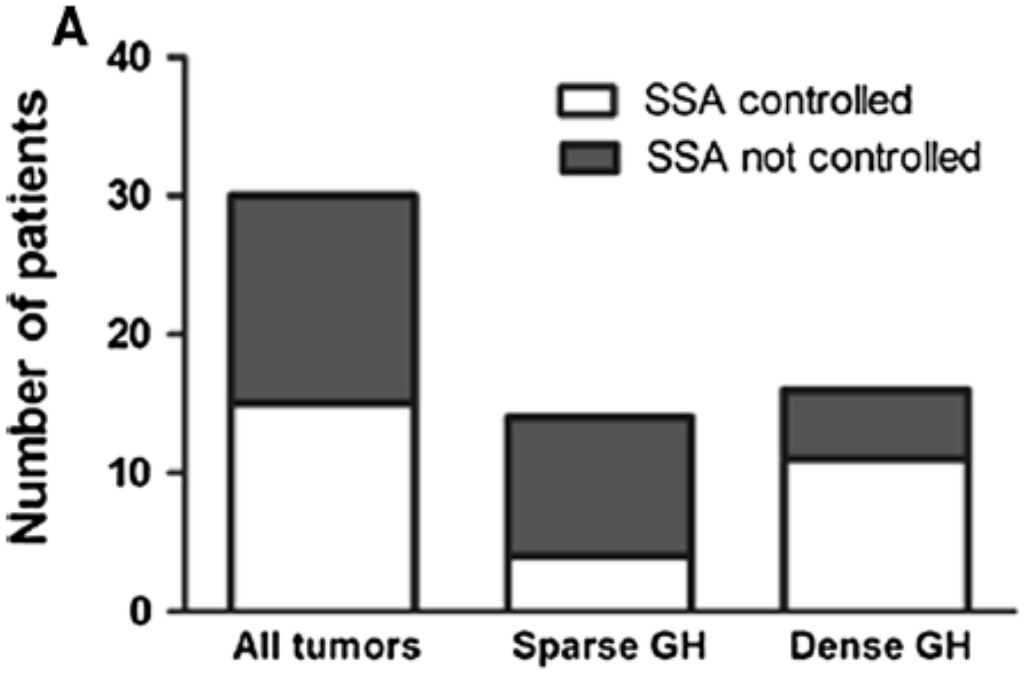


Fig. 4 **a** GH tumor response to somatostatin analogs (SSA). SG tumors were significantly less likely to be controlled with SSA compared to DG ($p = 0.028$). **b** GH adenoma subtypes and response

Vassiliadis KK, Endocrine 49:231, 2015

AIP gen mutasyonu

Clinical Characteristics and Therapeutic Responses in Patients with Germ-Line *AIP* Mutations and Pituitary Adenomas: An International Collaborative Study

TABLE 2. Comparisons between clinical characteristics at diagnosis of *AIPmut*-associated and non-*AIPmut* somatotropinoma groups

	Somatotropinoma group		
	***AIPmut* (n = 75)**	**Control (n = 232)**	***P* value**
Sex ratio (male/female)	1.6	0.87	0.027
Age at diagnosis (yr)	22.0 (8.0–60.0)	43.0 (16.0–72.0)	<0.000001
Age at first symptoms (yr)	17.5 (4.0–50.0)	38.0 (14.0–70.0)	<0.000001
Maximum tumor diameter (mm)	22.5 (7.0–60.0)	16.0 (3.0–48.0)	0.00026
Macroadenoma	93.1	80.8	0.026
Extrasellar extension (%)	65.1	49.8	0.018
Invasion (%)	51.7	38.8	0.11
GH level at diagnosis (ng/ml)	28.5 (3.3–183.0)	17.4 (1.7–180.0)	0.00068
IGF-I level at diagnosis (% ULN)	217.0 (116.0–1090.0)	210.5 (20.0–550.0)	0.48
Prolactin cosecretion (%)	56.1	28.9	0.00023
Gigantism (%)	32.0	6.5	<0.000001

Daly AF, JCEM 95:E373, 2010

Clinical Characteristics and Therapeutic Responses in Patients with Germ-Line *AIP* Mutations and Pituitary Adenomas: An International Collaborative Study

operative SSA use within each group. In the *AIPmut* group (n = 38), the median SSA-induced reductions in GH [40.0% (range 0.0–99.0%)] and IGF-I [47.4% (range 0.0–83.4%)] were significantly lower than those seen in the 164 control patients treated with long-term SSA [GH: 75.0% (range 0.0–99.0%); $P = 0.0004$; IGF-I: 56.0%

Daly AF, JCEM 95:E373, 2010

Akromegalide
SRL tedavisi için Prognostik Faktörler

- Debulking cerrahi
  - MRI; T2 de hipointensite
    - Somatostatin sintigrafisi
    - Octreotid süpresyon testi
- Yoğun / gevşek granüllü histoloji
- AIP gen mutasyonu

Akromegalide tedavi algoritmi

Cerrahi tedavi

SRL tedavisi

- Kabergolin eklemek
- SRL dozunu artırmak
- Pegvisomanta geçmek
- Radyoterapi vermek
- Pasireotide geçmek
- Farklı kombinasyonlar

- Akromegalili bir hastada hiperprolaktinemi varlığı kabergolinin etkinlik olasılığını artırır.

a) Doğru

b) Yanlış

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Place of Cabergoline in Acromegaly: A Meta-Analysis

TABLE 2. Characteristics of the published studies evaluating the effects of cabergoline in association with somatostatin analogs in patients with acromegaly

First author, year (Ref.)	Design of the study	No. of patients (M/F)	Mean age (yr)	Before cabergoline (under somatostatin analog alone)				
				Type of somatostatin analog treatment	IGF-I (ng/ml), mean (SD)	IGF-I (% of ULN), mean (SD)	GH (ng/ml), mean (SD)	No. of patients with hyperprolactinemia
Marzullo, 1999 (40)	Prospective	10 (7/3)	44.5	Lanreotide LP 30 mg/10 d	483 (264)	140 (64)	20.6 (29.5)	8
Cozzi, 2004 (37)	Prospective	19 (7/12)	54	Octreotide LAR 30 mg/28 d (n = 13) or lanreotide 60 mg/28 d (n = 6)	554 (188)	166 (63)	6.6 (3.7)	3
Selvarajah, 2005 (41)	Retrospective	4 (NA)	52.2	Octreotide LAR 30 mg/28 d	423 (175)	155 (23)	2.6 (0.3)	2
Gatta, 2005 (38)	Retrospective	10 (7/3)	40.6	Octreotide LAR 30 mg/28 d	524.4 (181)	216 (111)	4.1 (3.2)	0
Jallad, 2009 (39)	Prospective	34 (17/7)	47.7	Octreotide LAR 30 mg/28 d	571 (356)	197 (118)	5 (7.2)	13

late and multivariate analysis.

This meta-analysis shows that the efficacy of cabergoline is dependent on the IGF-I baseline level; as with all other treatments for acromegaly (19, 42, 43), the chances of achieving a normal IGF-I level increase as the basal IGF-I level decreases. However, IGF-I levels normalize in

Sandret L, JCEM 96:1327, 2011

Acromegaly: An Endocrine Society Clinical Practice Guideline

5.3 In a patient with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess, we suggest a trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy. (2|⊕⊕◯◯)

levels, with or without concomitant hyperprolactinemia (168). Despite initial efficacy of cabergoline, the response to cabergoline appears to decrease with time. In one study,

Katznelson L, JCEM 99:3933, 2014

Serum PRL seviyesi

Cabergoline Therapy of Growth Hormone & Growth Hormone/Prolactin Secreting Pituitary Tumors

Prolactin levels and relationship to efficacy of cabergoline

The presence of prolactin level greater than 20 at diagnosis or positive prolactin immunostaining of the tumor is shown in Table 1. Serum prolactin levels at the start of cabergoline therapy were normal (<20 ng/ml) in all patients and 12 of 14 patients had a drop of prolactin within the normal range while on cabergoline therapy. There was a significant fall overall in prolactin levels on cabergoline therapy ($p < .0027$). Neither positive prolactin immunostaining nor a prolactin level over 20 ng/ml at diagnosis correlated with normalization of serum IGF-I level on cabergoline therapy.

Freda PU, Pituitary 7:21, 2004

Akromegalide
Kabergolin tedavisi için Prognostik Faktörler

- Serum IGF-1 seviyesinin normale yakın olması
  - ~~Hiperprolaktinemi varlığı~~

Akromegalide tedavi algoritmi

Cerrahi tedavi

SRL tedavisi

- SRL dozunu artırmak
- Kabergolin eklemek
- Pasireotide geçmek
- Pegvisomanta geçmek
- Radyoterapi vermek
- Farklı kombinasyonlar

Multi-modal management of acromegaly: a value perspective

Treatment	Remission rate (%)	Cost (US$/year)
Dopamine agonist (DA) monotherapy	30	2,000
Somatostatin analogue (SSA) monotherapy	50	34,000
SSA plus dopamine agonist (DA)	60	34,000 + 2,000
SSA plus GH receptor antagonist (GHRA)	95	34,000 + 8,600
GHRA monotherapy	80	57,000
Surgery	60	15,216
Stereotactic radiosurgery (SRS)	40	21,857

Table 2 Life time cost of medical regimens for acromegaly

Treatment	Cost/year (US$)	Lifetime cost (US$)
SSA	34,000	1,292,000
SSA(I)	51,000	1,938,000
SSA(I) + DA	53,000	2,014,000
GHRA	57,000	2,166,000
GHRA + DA	59,000	2,242,000
SSA(I) + GHRA	59,600	2,264,000
SSA(I) + DA + GHRA	61,600	2,340,000
SSA(I) + GHRA + DA	64,000	2,432,000
SSA(I) + DA + GHRA(I)	65,900	2,504,200
GHRA(I)	85,500	3,249,000
GHRA(I) + DA	87,500	3,325,000

Kimmell KT, Pituitary, 18:658, 2015

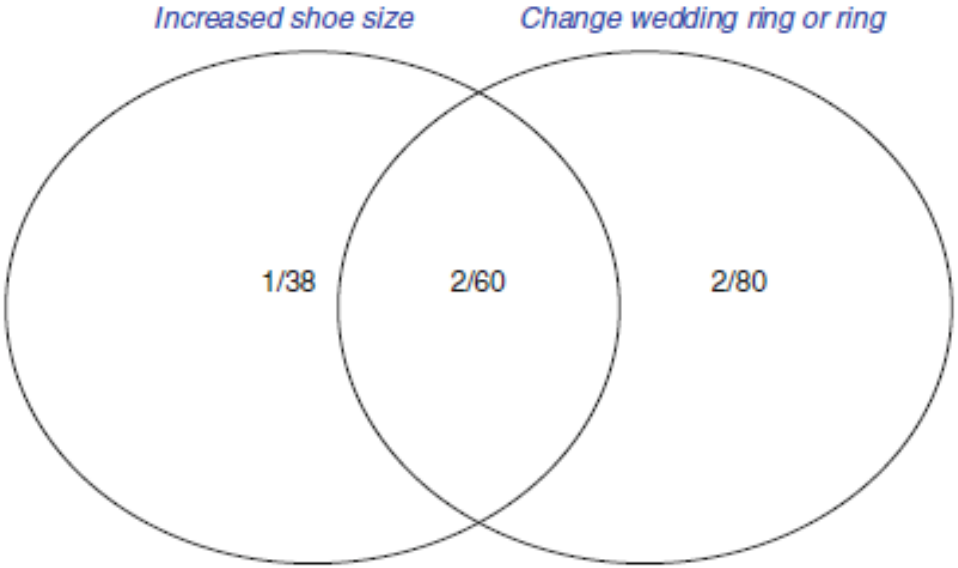
Akromegalide **en önemli** prognostik faktörler

- Adenom boyutu (Erken tanı)
- Postop GH seviyesi (Tecrübeli cerrah)

Akromegali erken tanısı mümkündür

- Kolay tanınabilir, aşikar semptomatoloji
  - Büyüyen el ve ayaklar
  - Uyku apnesi
  - Aşırı terleme
  - Dental malokluzyon
  - Karpal tünel sendromu
  - Dejeneratif artopati
- Hekimler aşikarı görmeli
- Basit tarama IGF-1.

Screening for acromegaly by application of a simple questionnaire evaluating the enlargement of extremities in adult patients seen at primary health care units



17 000 olgu
19-70 y (50,2)
Anket: 178 (+)
1 Aşikar klinik
5 Anket ile tanı

Prevalans
Aşikar 59/ m
Toplam 365/m

Table 1 Clinical features of the patients with persistently elevated IGF-1 and inadequate suppression of GH in the OGTT

Patient	Gender	Age (years)	IGF-1 (× ULN)	GH nadir (μg/L)	MRI	Acromegalic features	Symptoms and comorbidities
1	M	52	2.6	10.2	Macroadenoma	Yes	Headache[a], erectile dysfunction[a], visual field defects, hyperhidrosis, snoring, diabetes, hypertension
2	M	61	2.2	4.1	Macroadenoma	Yes	Decreased libido[a], hyperhidrosis, arthropathy[a], snoring
3	F	38	1.3	1.5	Normal	No	Headache[a], menstrual irregularity[a], hypertension
4	F	40	1.8	2.8	Macroadenoma	Yes	Menstrual irregularity[a], paresthesias, goiter[a]
5	F	62	2.5	8.5	Macroadenoma	Yes	Headache[a], hyperhidrosis, snoring[a], diabetes[a], goiter
6	F	54	2	6.5	Microadenoma	Yes	Headache[a], paresthesias[a], arthropathy, hypertension

Rosario PW. Pituitary, 2012

Pituitary surgery for acromegaly

Should be done by specialists

- Deneyimli pitüiter cerrah tanımı
  - 100 den fazla pitüiter operasyon yapmış olmak
  - Yılda 20 den fazla pitüiter cerrahi operasyon yapıyor olmak
  - Endokrinoloji, nöropatoloji ve radyasyon onkolojisi ile birlikte çalışıyor olmak

- Deneyimli cerrahi için merkez özellikleri
  - Yılda 20-30 operasyon için
  - 5 000 000 popülasyona 1 merkez
  - Her merkezde 2 cerrah

Clayton RN, BMJ 319: 589, 1999

Sonuç:

Akromegali tedavisinde iyi prognoz için

- Tanısı mümkün olduğunca erken konmalı
- Deneyimli cerrahlar tarafından opere edilmeli
- Uzman bir ekip tarafından takip edilmelidir