

Akromegalinin deęiřen yz

Prof. Dr. Erdińç Ertrk

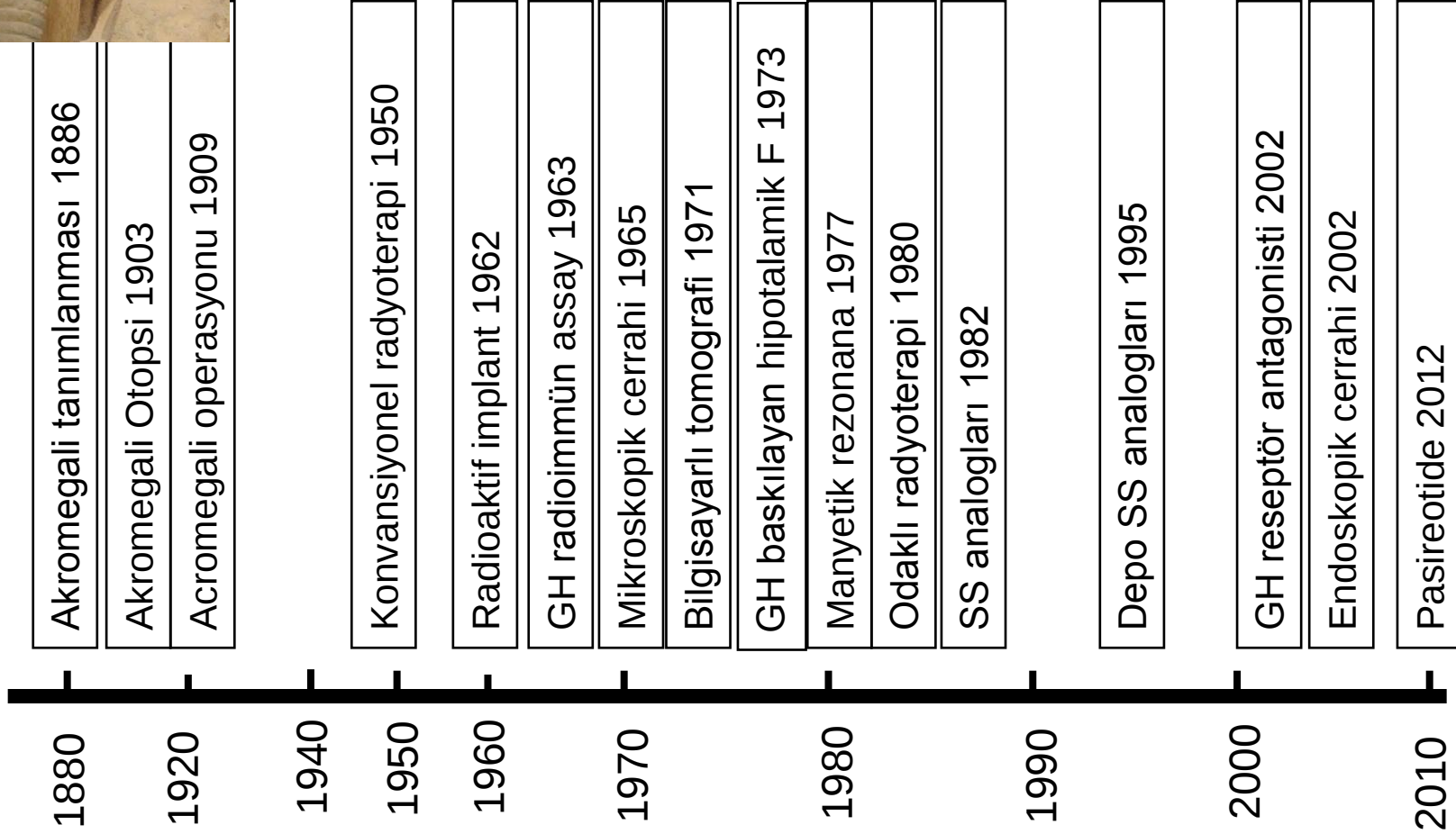
Uludaę niversitesi Tıp Fakltesi

Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı

10. Hipofiz Kongresi, 8 Kasım 2014 - ANKARA

Akromegali tanı ve tedavisindeki gelişmeler

Tarih çizgisi



Akromegalinin deęiřen yz

- Tanıdaki deęiřiklikler
- Tedavideki deęiřiklikler

Akromegalinin değişen yüzü

- Tanı kriterleri
 - IGF-1 seviyesinin $> N$
 - OGTT süpresyonu sonrası GH $> 1 \text{ ng/mL}$

Akromegali tanısında beklenti

- Erken tanı
 - Hastaların erken tanı ile komorbiditelerin gelişmesi önlenmelidir
 - Mikroadenom iken saptanıp operasyon ile küratif başarı olasılığı artırabilmeli

Akromegali tanısı sırasındaki bulgularda değişenler

- Semptomlar
- GH ortalaması
- IGF-1 ortalaması
- Komorbiditeler
- Adenom çapı
- Semptomlar ile tanı arası süre

Tanıdaki değişikliklerin sebepleri

- Halk ve hekimler arasında farkındalığın artması
- GH/IGF ölçümünün güvenilirliği yaygınlaşması
- Görüntüleme yöntemlerinin yaygınlaşması

Akromegali epidemiyolojisi

Eski

- Milyon nüfusta
Yıllık insidans 1-3
Prevalans 30-40

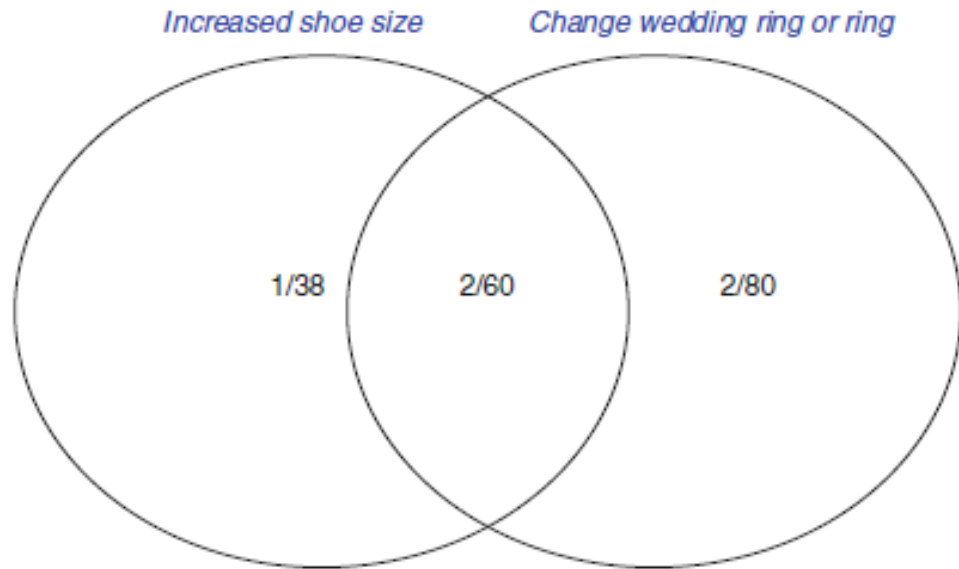
Yeni

- Milyon nüfusta
Yıllık insidans 2-4
Prevalans 40-90

Akromegalide ilk başvuru

	Erkek	Kadın	Toplam
Yüz görünümünde değişiklik	5	12	17
El ve ayaklarda büyüme	6	5	11
Boyda hızlı büyüme	3	1	4
Görme alanı daralması	5	2	7
Baş ağrısı	11	7	18
Karpal tünel sendromu	7	9	16
Osteoartrit	3	3	6
Kalp yetmezliği	2	5	7
Diyabetes mellitus	8	7	15
Tiroid hastalığı	2	3	5
Amenore	-	18	18
Hirsutizm	-	3	3
Libido kaybı	3	-	3
Doktor ikazı	67	47	114
Diş hekimi	2	2	4

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 Aşkar klinik
5 Anket ile tanı

Prevalans

Aşkar 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 ($\times$ ULN)	GH nadir (μ g/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

High prevalence of biochemical acromegaly in primary care patients with elevated IGF-1 levels

6773 olgu	1 Aşık klinik
IGF-1: 125 (+)	6 Tarama ile tanı
	Prevalans: Aşık 147/ m
	Toplam 1034/m

Table 1. Clinical features of the patients with biochemical acromegaly

Sex	Age	Diagnostic status on acromegaly	IGF-1	IGF-1 SDS	Repeat IGF-1 xULN	GH nadir OGTT	MRI findings	Acromegalic features	Other diseases
M	80	New	254	2.60	1.66	3.7	ND	No	Diabetes, dyslipidaemia, thyroid disease, chronic kidney failure, liver disease, depression
F	80	New	239	2.76	1.61	2.4	ND	No	Dyslipidaemia, hypertension, arthritis, depression, osteoporosis
F	62	New	337	3.07	1.66	4.5	ND	No	None
F	74	New	223	2.27	1.22	1.3	Normal	No	Diabetes, dyslipidaemia, CAD, CLL
F	50	New	961	6.85	9.55	2.7	Microadenoma	Increased finger size, face changes	Diabetes, dyslipidaemia, hypertension, thyroidectomy, hysterectomy
F	66	New	780	6.51	4.37	24.9	Macroadenoma	Increased finger and foot size, face changes	Diabetes, dyslipidaemia, hypertension, papillary thyroid cancer, myoma, sleep apnea syndrome
F	54	Known	351	2.85	ND	ND	ND	ND	Hypertension, CAD, arthritis

Akromegali epidemiyolojisi

Eski

- Milyon nüfusta
Yıllık insidans 1-3
Prevalans 30-40

Yeni

- Milyon nüfusta
Yıllık insidans 2-4
Prevalans 40-90
Sorgulama 365
Biyokimyasal ≈ 1000

Akromegali Taraması

- IGF-1 taraması (?)
 - Uyku apnesi
 - Karpal tünel sendromu
 - Diyabetes melitus
 - Osteoartropati
 - Sol ventrikül büyümesi
 - Diş değişiklikler
- Hatalı pozitiflikler
- Maliyet

Akromegalinin değişen yüzü

- Tanıdaki değişiklikler
 - Tanı kriterleri
 - Tanı sırasındaki bulgular
 - Epidemiyolojik veriler
 - Tarama gerekliliği ?

Akromegalinin deęiřen yz

- Tanıdaki deęiřiklikler
- Tedavideki deęiřiklikler

Akromegalinin komorbiditeleri

- Kardiyovasküler hastalıklar
 - Hipertansiyon, kardiyomiyopati, aritmiler
- Diyabetes mellitus
- Obstrüktif uyku apnesi
- Osteoartropatiler
- Karpal tünel sendromu
- Kolonik polipler
- Kolon ca, tiroid ca

Mortality in Acromegaly: A Metaanalysis

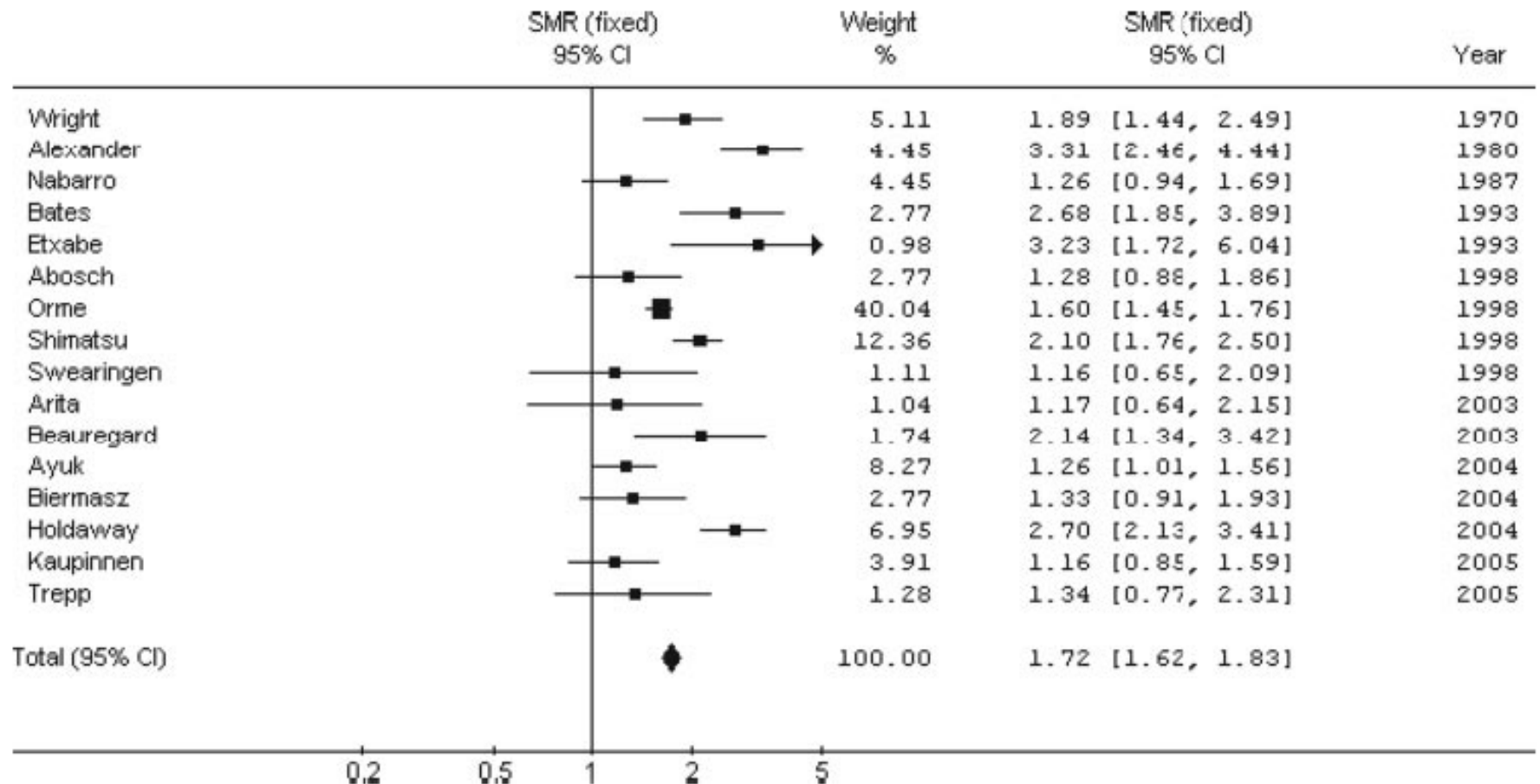
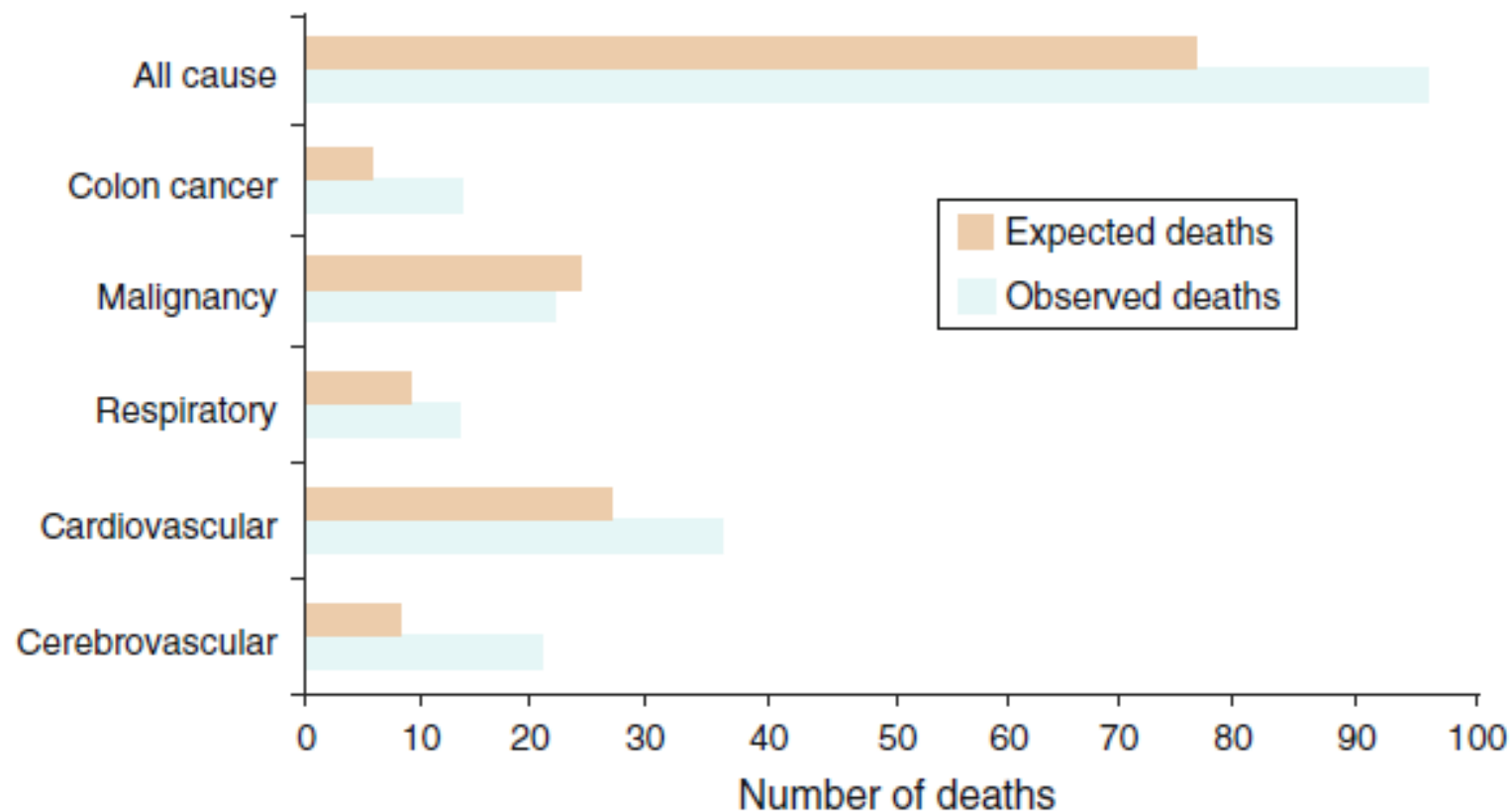


FIG 2. Metaanalysis of SMRs in acromegaly.

Clinical, quality of life, and economic value of acromegaly disease control



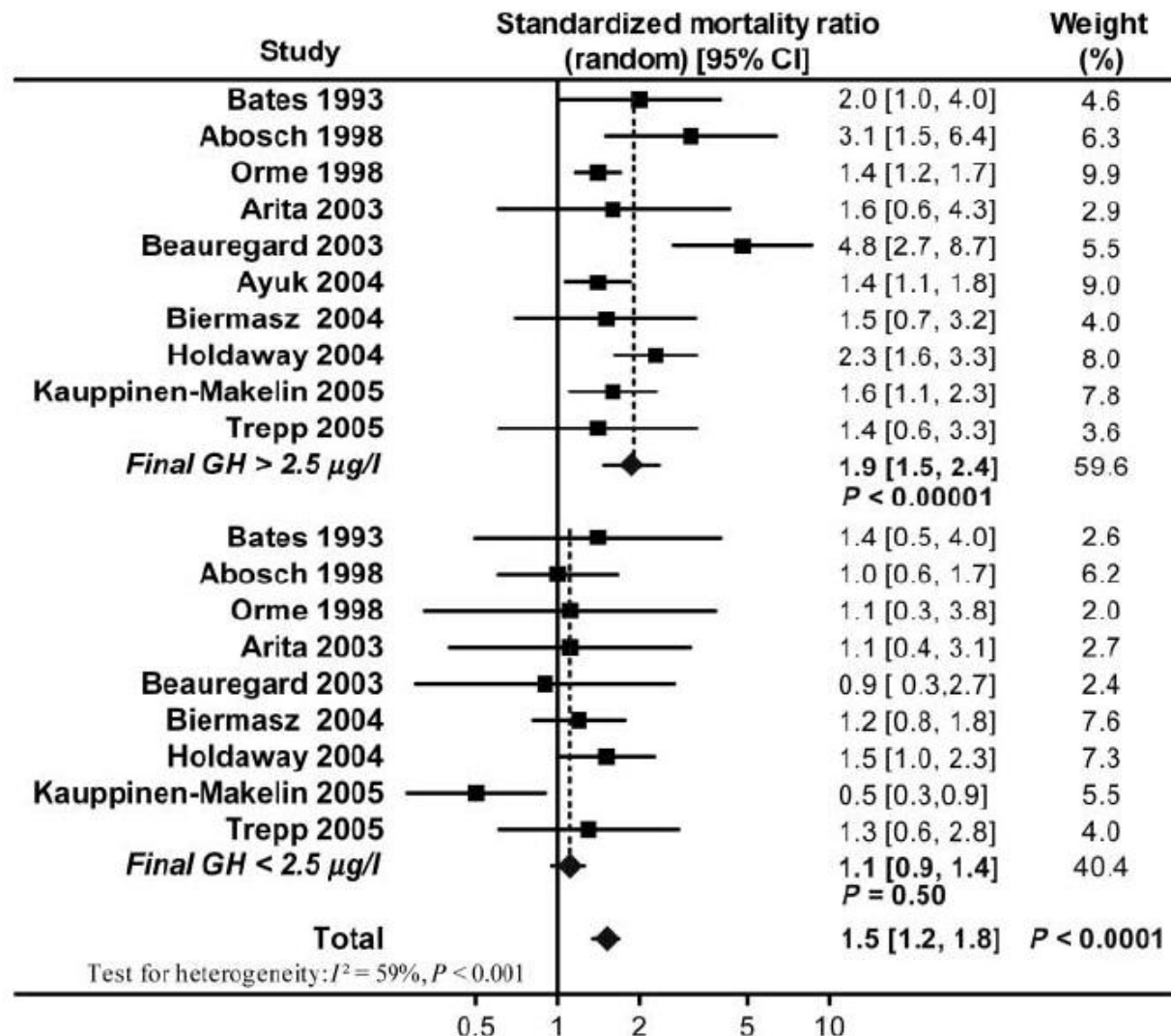
Akromegali Tedavi hedefleri

- Belirti ve bulguların iyileştirilmesi
 - Tümör çapının küçültülmesi
 - Komorbiditelerin tedavisi
 - Mortalitenin normale indirilmesi
-
- Pitüiter fonksiyonların korunması
 - Yan etkilerin olmaması

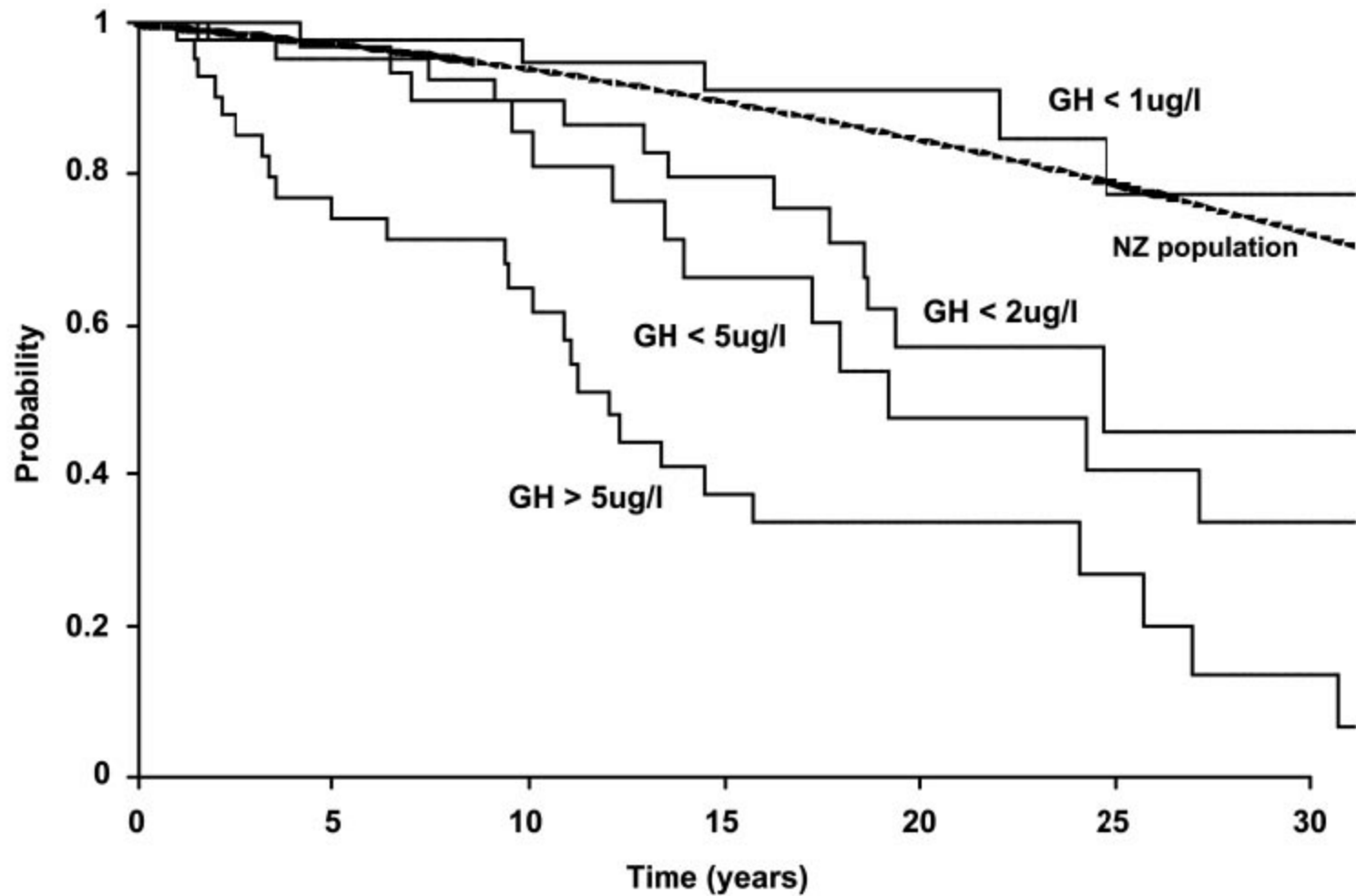
Akromegali tedavisinde amaç

- Biyokimyasal kontrol
 - IGF-1 < N
 - GH < 1 ng/mL

A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly



Factors Influencing Mortality in Acromegaly



Recent developments in acromegaly: a review¹

Guidelines for Acromegaly Management: An Update

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE
DIAGNOSIS AND TREATMENT OF ACROMEGALY—2011 UPDATE**

**A consensus on the diagnosis and treatment of acromegaly
complications**

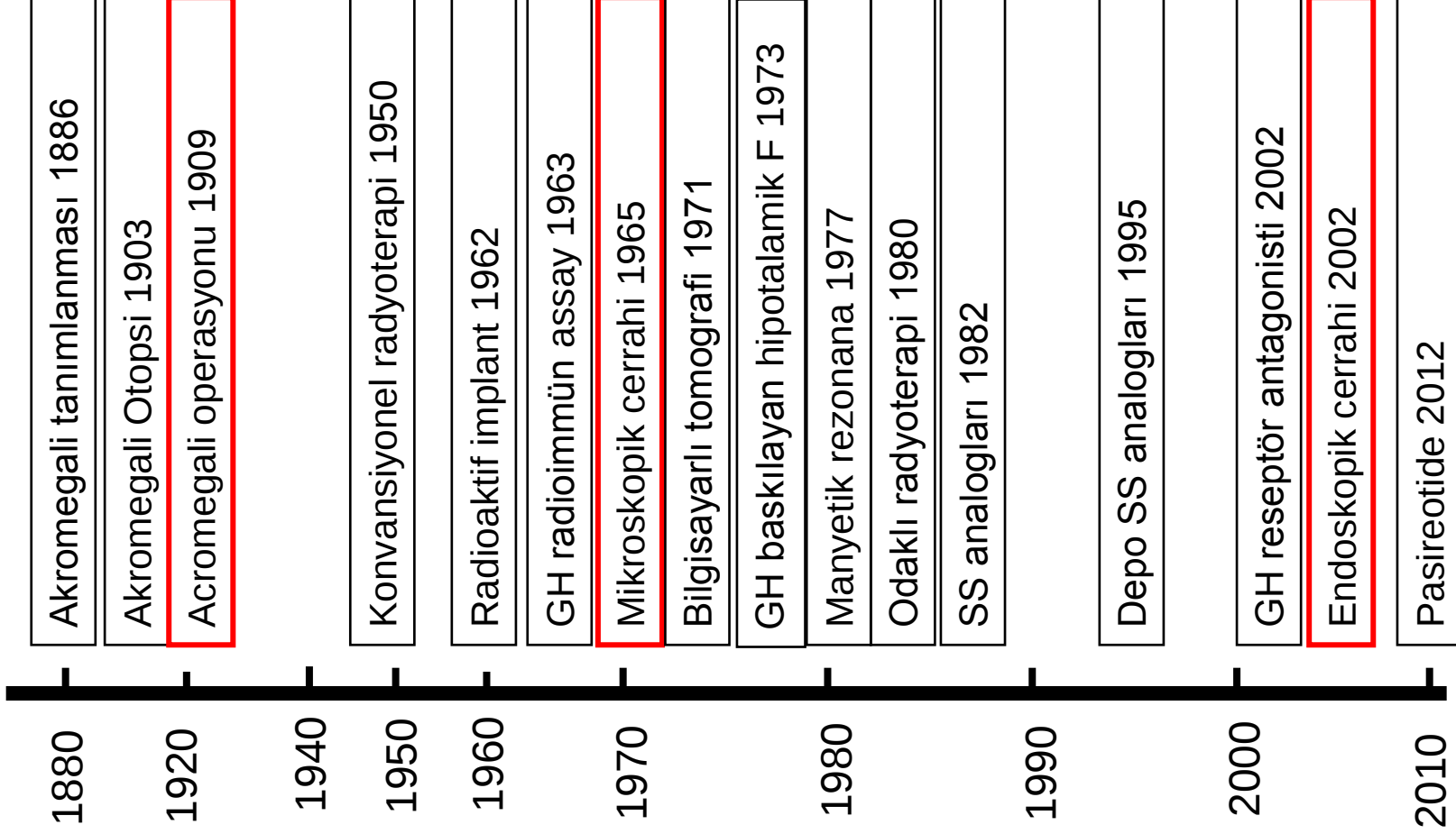
**A consensus on the medical treatment
of acromegaly**

Akromegali tedavisinde ilk basamak öneri

OPERASYON

Akromegali tanı ve tedavisindeki gelişmeler

Tarih çizgisi

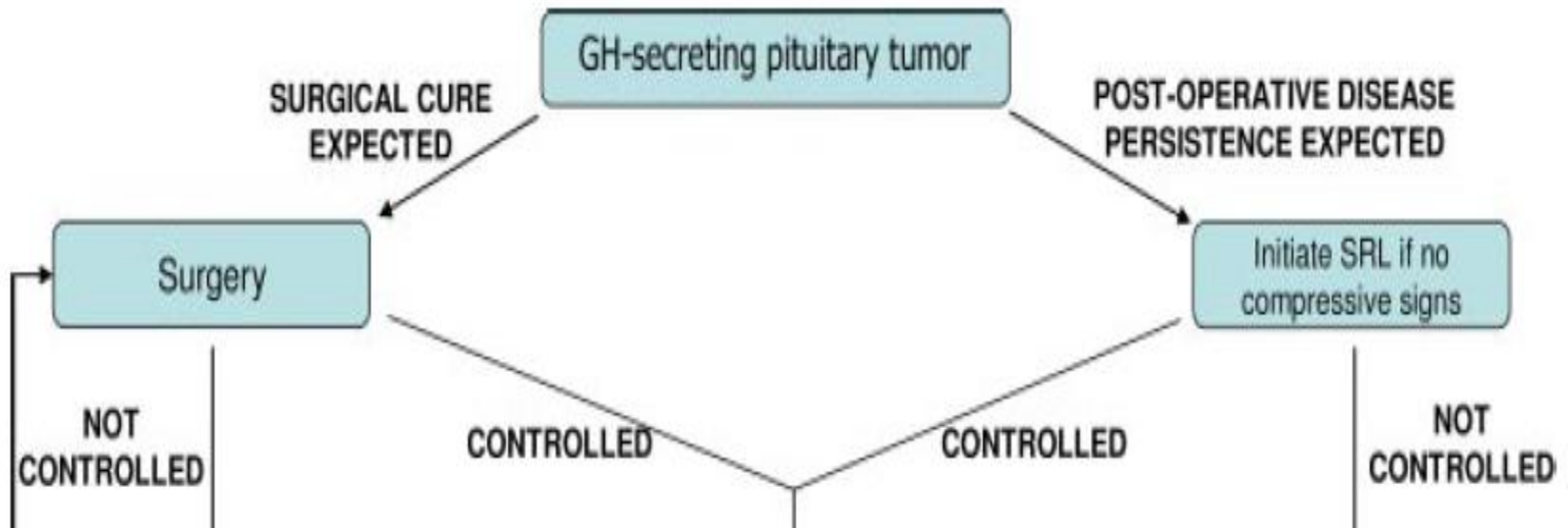


Endoscopic Transsphenoidal Surgery for Acromegaly: Remission Using Modern Criteria, Complications, and Predictors of Outcome

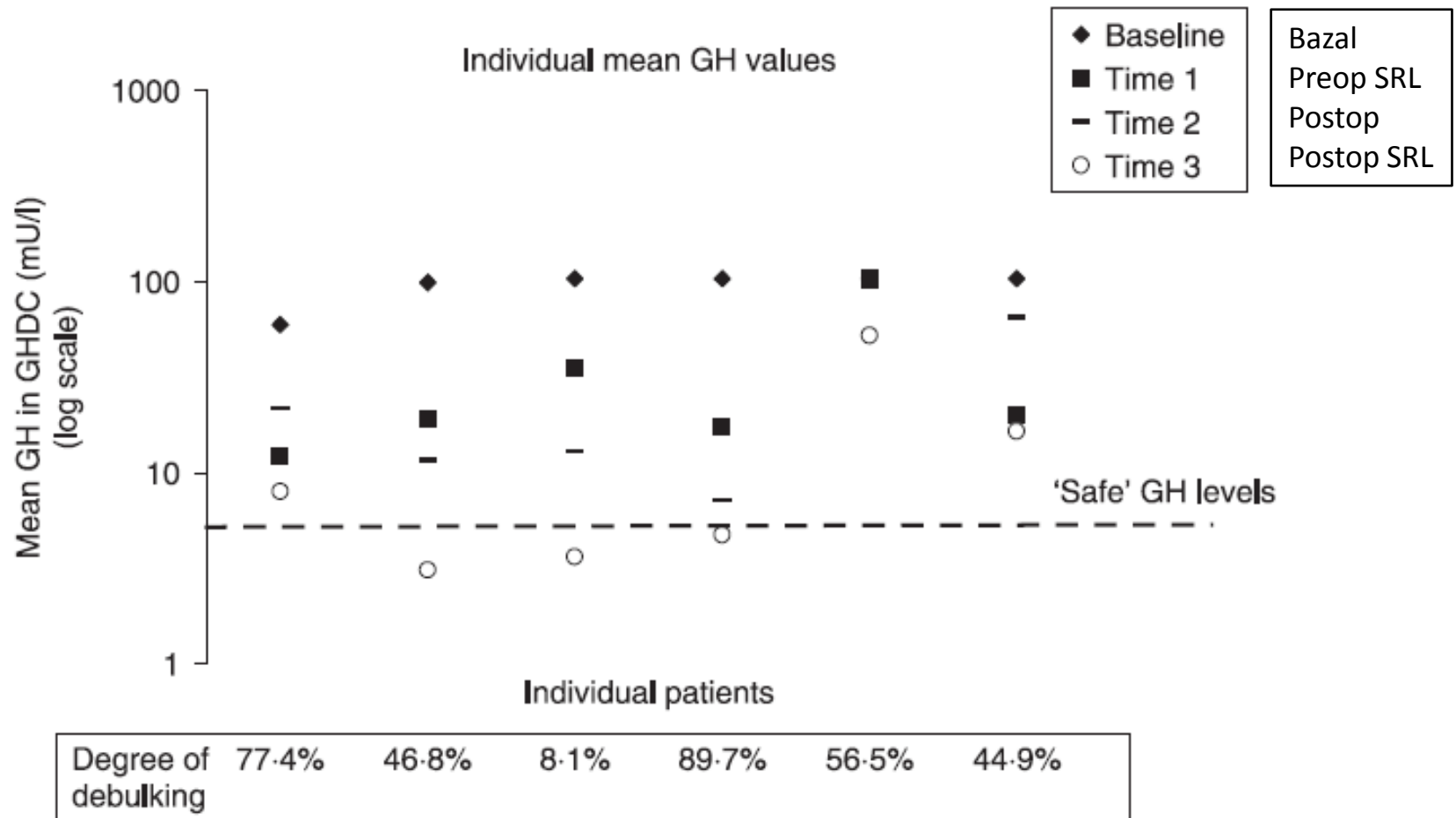
TABLE 5. Biochemical remission: modern surgical series

Author/year	n	Size micro/macro	Remission		
			Overall	Microadenoma	Macroadenoma
Microscopic series					
Kim <i>et al.</i> (41), 2009 ^a	42	12/30	64%	67%	60%
Ludecke and Abe (9), 2006 ^a	147	21/126	72%	95%	68%
Trepp <i>et al.</i> (22), 2005 ^a	69	5/64	42%	80%	39%
Nomikos <i>et al.</i> (10), 2005 ^a	506	142/364	57%	75%	50%
Esposito <i>et al.</i> (20), 2004 ^a	67	13/54	57%	77%	52%
De <i>et al.</i> (7), 2003 ^a	90	29/61	63%	79%	56%
Beauregard <i>et al.</i> (4), 2003 ^a	103	22/81	52%	82%	47%
Kaltsas <i>et al.</i> (42), 2001 ^a	67	17/42	34%	59%	26%
Shimon <i>et al.</i> (11), 2001 ^a	88	44/44	74%	84%	64%
Kreutzer <i>et al.</i> (37), 2001 ^a	57	19/38	70%		
Endoscopic series					
Hofstetter <i>et al.</i> (17), 2010 ^b	24	4/20	38%		
Gondim <i>et al.</i> (24), 2010 ^a	67	14/53	75%	86%	72%
Campbell <i>et al.</i> (5), 2010 ^a	26	4/22	58%	75%	55%
Tabaee <i>et al.</i> (16), 2009 ^a	6		83%		
Yano <i>et al.</i> (12), 2009 ^a	31		71%		
Dehdashti <i>et al.</i> (8), 2008 ^a	34	8/26	71%	83%	65%
Frank <i>et al.</i> (23), 2006	83	24/59	70%	83%	65%
Kabil <i>et al.</i> (25), 2005	48	13/35	85%	100%	80%
Rudnik <i>et al.</i> (26), 2005	12	4/8	83%		
Cappabianca <i>et al.</i> (15), 2002 ^a	36	6/30	64%	83%	60%
Cappabianca <i>et al.</i> (6), 2002 ^a	23	3/20	57%	67%	55%
Current series ^b	60	14/46	70%	100%	61%

Akromegali tedavisinde ilk basamak



Surgical debulking of pituitary macroadenomas causing acromegaly improves control by lanreotide



Comparison of the effects of primary somatostatin analogue therapy and pituitary adenomectomy on survival in patients with acromegaly: a retrospective cohort study

438 olgu
1999-2009 arası
Mortalite 20 (% 4.5)

SMR 0.70

MI	4
CVO	5
Ca	6
Adenom	4
Diğer	1

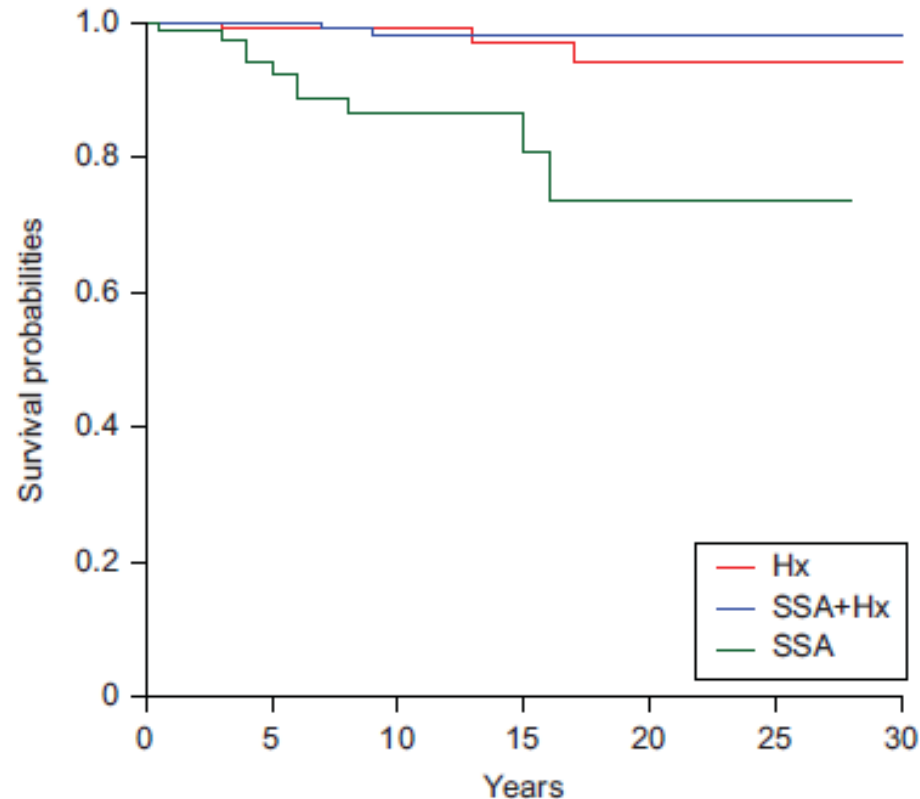


Figure 1 Survival of acromegalic patients over a 30-year period. Effect of different therapies on mortality: neurosurgery (Hx), neurosurgery followed by external radiotherapy and/or somatostatin analogue therapy (Hx+ SSA) and treatment with primary SSA therapy.

Akromegali tedavisinde ilk basamak öneri

- Cerrahi kür şansı yüksek
- Cerrahi kür şansı düşük

Operasyon

- Cerrahi kontrendikasyon varsa

Primer medikal tedavi

Operasyon öncesi medikal tedavi ?

- Yapılan çalışmalar yeterli bulunmamıştır
- Anestezi komplikasyonu riski olabilecek seçilmiş hastalarda önerilir
 - Şiddetli farengeal kalınlık
 - İleri derecede uyku apnesi
 - Yüksek kardiyak output

Akromegalide operasyon tipi

- Mikroskopik cerrahi
- Endoskopik cerrahi

Endoscopic Transsphenoidal Surgery for Acromegaly: Remission Using Modern Criteria, Complications, and Predictors of Outcome

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Akromegalide operasyon tipi

- Mikroskopik cerrahi
- Endoskopik cerrahi

Tecrübeli cerrah

Akromegalinin değişen yüzü

- Tanıdaki değişiklikler
- Tedavideki değişiklikler
 - Cerrahi tedavi
 - Medikal tedavi

Akromegalide Medikal Tedavi

- Somatostatin analogları
- Dopamin agonistleri
- GH reseptör antagonisti

- Pasireotide
- Oral octreotide

Long-Acting Somatostatin Analog Therapy of Acromegaly: A Meta-Analysis

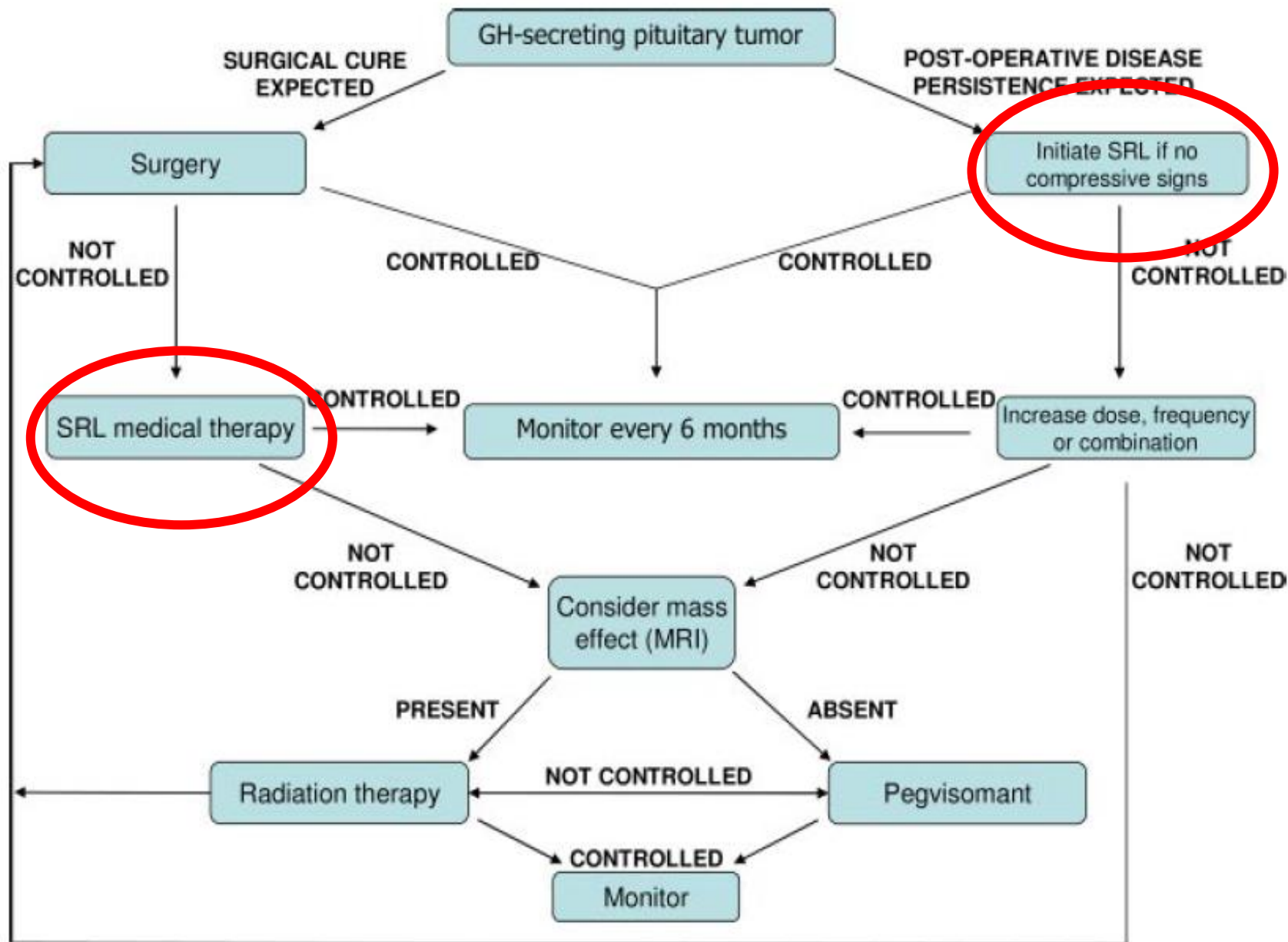
TABLE 1. Biochemical efficacy of somatostatin analog therapy for acromegaly

	% of subjects meeting efficacy criteria	
	GH	IGF-I normalization
Octreotide LAR		
Unselected (n = 126)	54 ± 0.002 ^a	63 ± 0.002 ^b
Preselected (n = 486)	58 ± 0.003	68 ± 0.003
All subjects (n = 612)	57 ± 0.05 ^c	67 ± 0.05 ^d
Lanreotide SR		
Unselected (n = 609)	48 ± 0.002	42 ± 0.002
Preselected (n = 305)	50 ± 0.005	56 ± 0.003
All subjects (n = 914)	48 ± 0.04	47 ± 0.03
Octreotide (sc) (primary therapy only)		
All subjects (n = 266) (unselected, n = 252, preselected, n = 14)	53 ± 0.05	54 ± 0.05

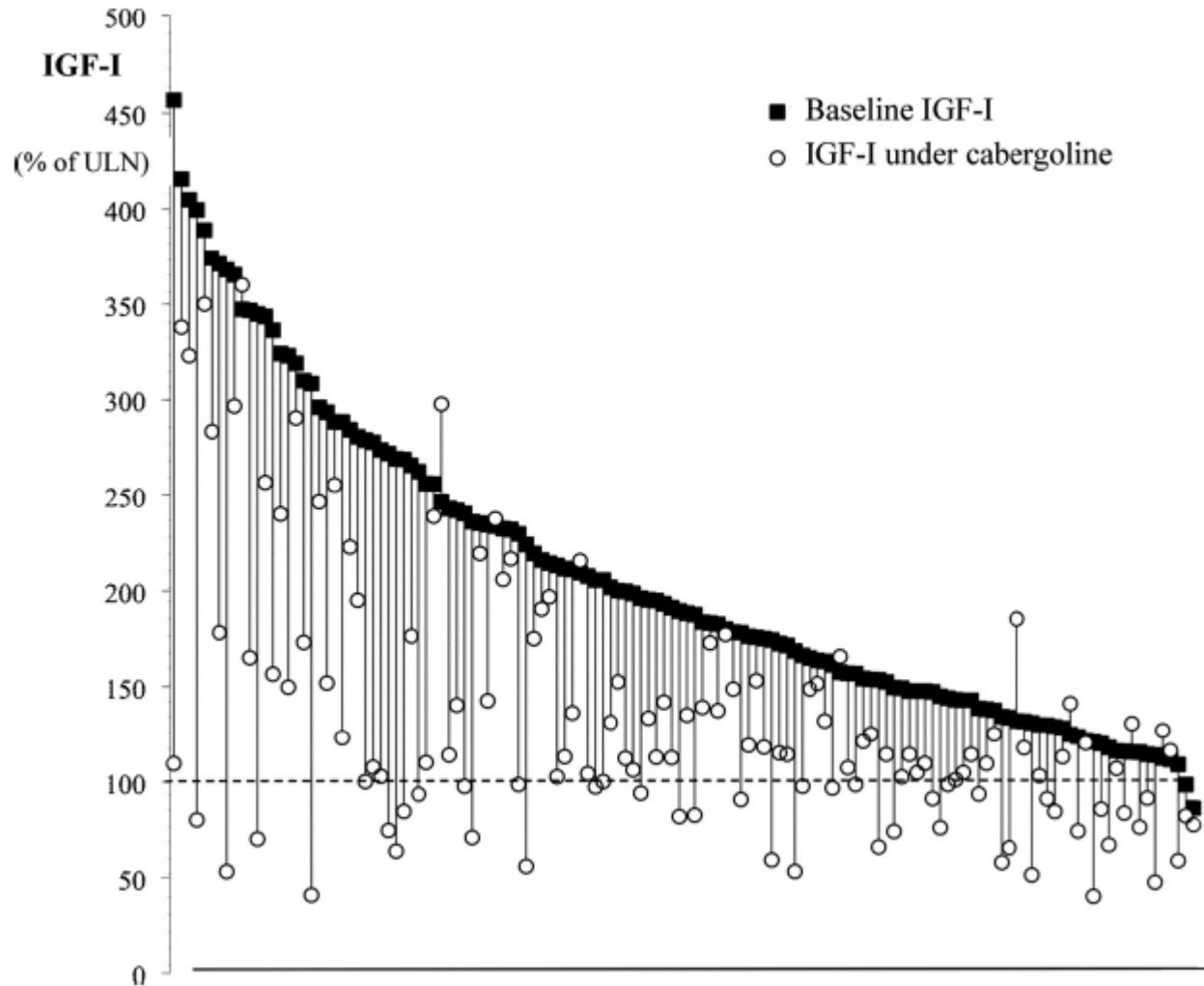
Clinical, quality of life, and economic value of acromegaly disease control

Table 2 Influence of disease control and somatostatin analogue use on mortality in patients with acromegaly [23]

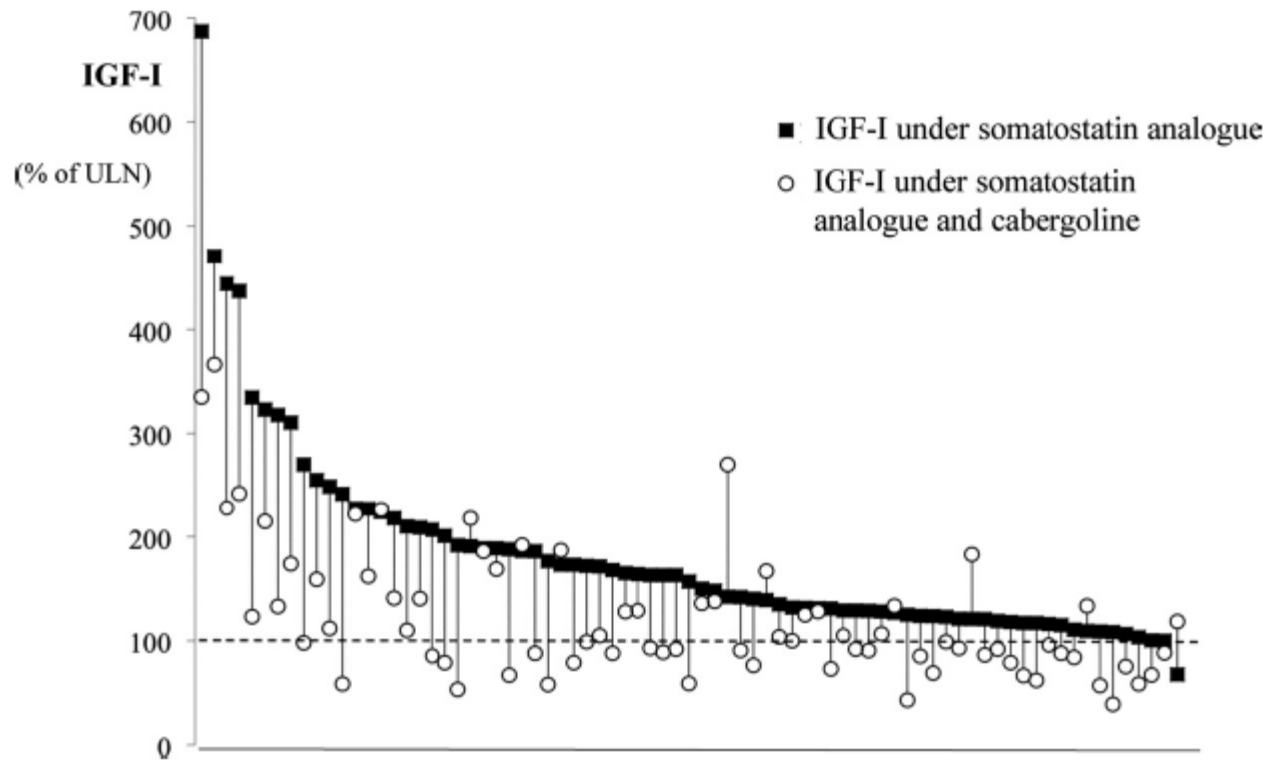
Acromegaly population	SMR (95% CI)	Risk ratio (<i>P</i> value)
Remission in >70% of patients	1.2 (1.0–1.5)	1.7 (<0.05)
Remission in <70% of patients	2.0 (1.6–2.3)	
GH < 2.5 µg/l	1.1 (0.9–1.4)	1.7 (<0.05)
GH > 2.5 µg/l	1.9 (1.5–2.4)	
Normal IGF-I	1.1 (0.9–1.4)	2.3 (<0.05)
Increased IGF-I	2.5 (1.6–4.0)	
Somatostatin analogue use in >30% patients	1.2 (1.0–1.5)	1.7 (<0.001)
Somatostatin analogue use in <30% of patients	2.0 (1.6–2.3)	



Place of Cabergoline in Acromegaly: A Meta-Analysis

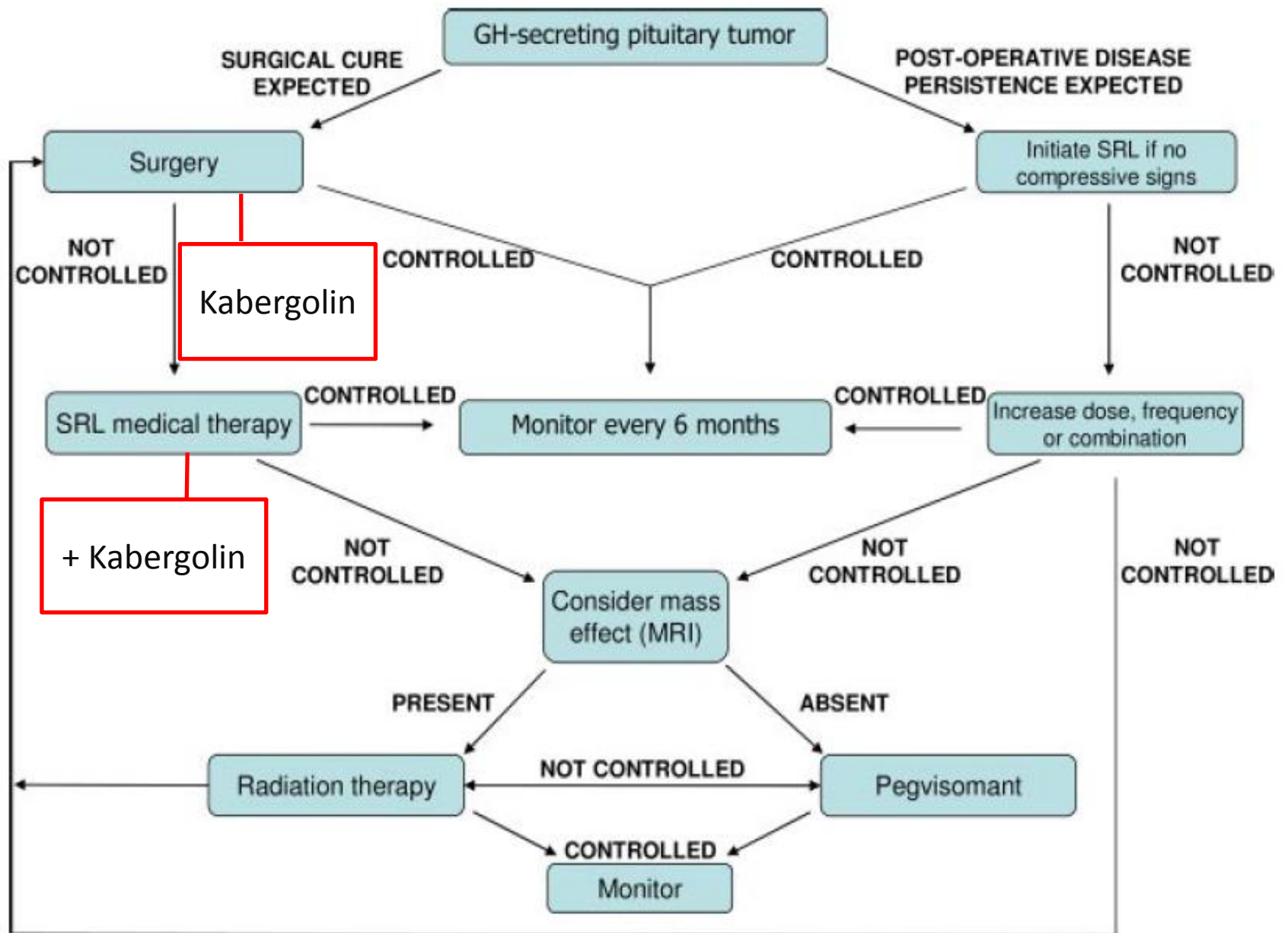


Place of Cabergoline in Acromegaly: A Meta-Analysis



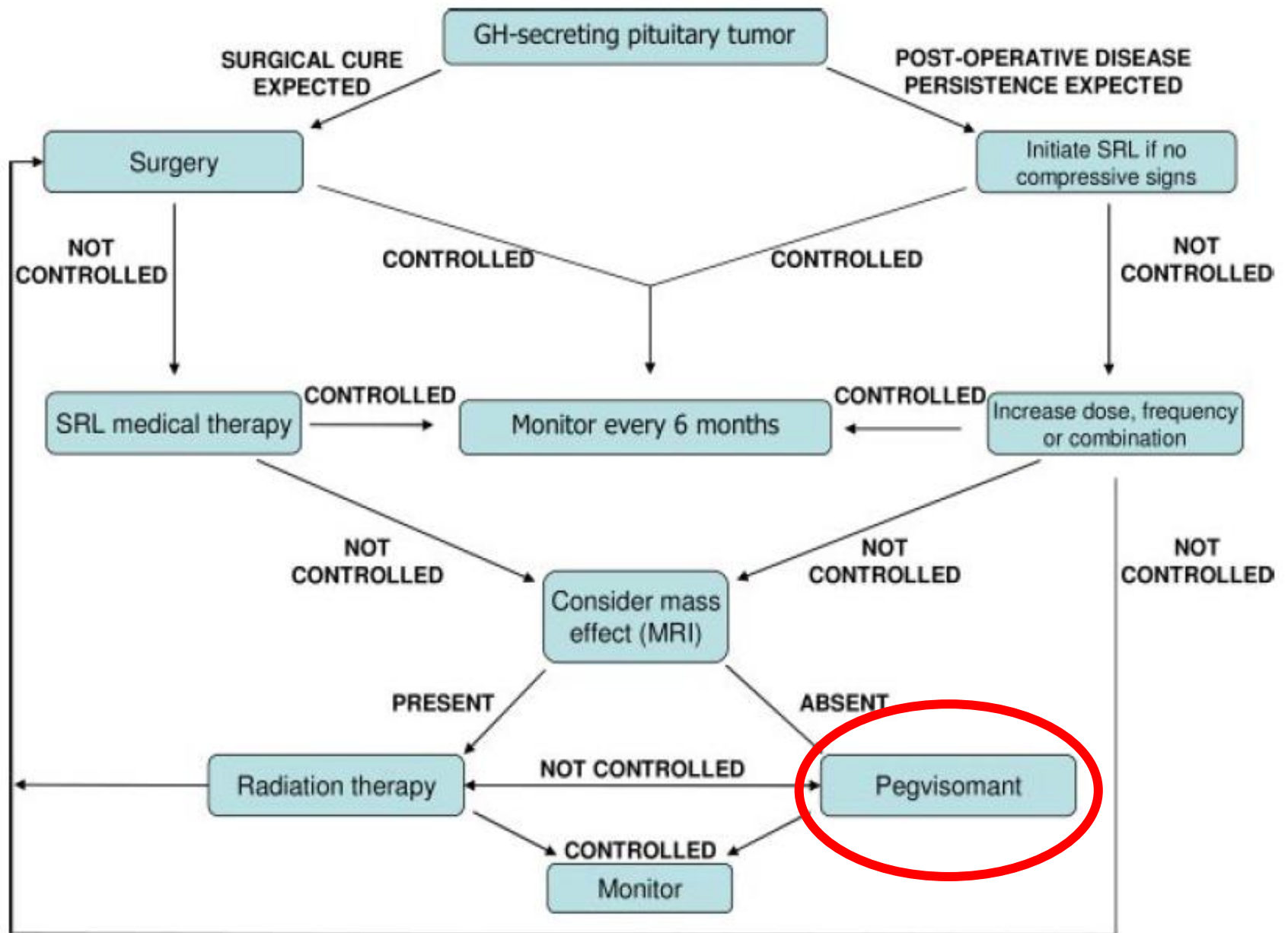
Akromegalide Kabergolin

- Yeterli etkinlik olasılığı düşük
- Hafif GH/IGF-1 yüksekliklerinde
- Hiperprolaktinemi eşlik ediyorsa
- SRL kullanamayan hastalarda
- SRL kombine olarak



Akromegalide Medikal Tedavi

- Somatostatin analogları
- Dopamin agonistleri
- GH reseptör antagonisti



Pegvisomant

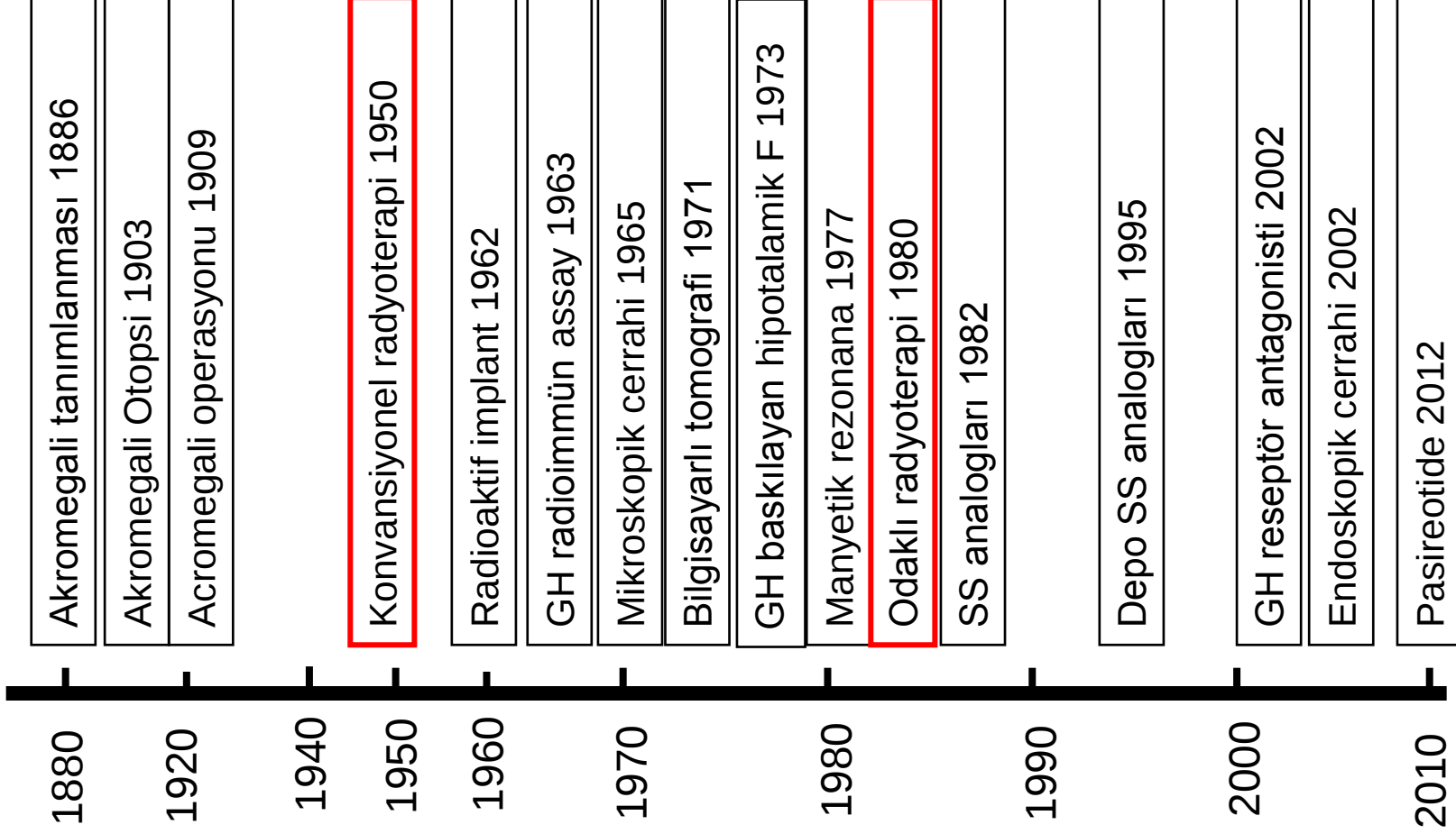
- IGF-1 normalizasyonu % 90
- GH izlemi yapılamaz
- Tümör çapı izlenmesi gerekir
- KC toksisitesi nadir bildirilmiş
- Çalışmalar ile uygulamada etkinlik diskordansı
- Hasta uyumu
- Pahası

Akromegalinin değişen yüzü

- Tanı kriterlerindeki değişiklikler
- Tedavideki değişiklikler
 - Cerrahi tedavi
 - Medikal tedavi
 - Radyoterapi

Akromegali tanı ve tedavisindeki gelişmeler

Tarih çizgisi



Successful Treatment of Acromegaly: Metabolic and Clinical Studies in 145 Patients

JOHN H. LAWRENCE, CORNELIUS A. TOBIAS, JOHN A. LINFOOT,
JAMES L. BORN, JOHN T. LYMAN, CLAUDE Y. CHONG,
EDWARD MANOUGIAN, AND WEN C. WEI

(J Clin Endocr 31: 180, 1970)

Journal of the Royal Society of Medicine Volume 76 November 1983 947

Recent developments in acromegaly: a review¹

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and Royal East Sussex Hospital, Hastings, East Sussex TN34 1ER*

Radiation Therapy in the Management of Pituitary Adenomas

TABLE 3. Continued

Follow-up, Median	LC (%)	LC median	Hormone normalization (%)	Hormone normalization time
7.5 yr, mean	100		50%	7.1 yr, mean
?	100			1.4 yr, mean
5.2 yr, mean			43.7%	5.6 yr, mean
			50%	2.9 yr, mean
			0%	1.2 yr
			0%	3.6 yr
53.7 months, mean	100		67.4%	5 yr
			85.7%	8 yr
82 months, mean	97		33.0% CR	42.8 months
12 months, min			49.8% NL	36.1 months
6.3 yr	100		95% any	
			59% CR	
			36% PR	
			67% CR	5 yr
63 months	100		11%	2 yr
			60%	5 yr
			50%	36 months, mean
25.4 months, mean			44.4% CR, 11.1% PR	12 months, mean
5.5 yr, mean	100		58%	5 yr
			86%	10 yr
69 months	97.6		52.6%	5 yr
		5 yr	84.8%	10 yr
96 months, mean	100		42% CR	42.6 months, mean (mix)
5 yr, min				48 months, estimate
114 months	100	10 yr	43%	130 months, mean
104 months, mean				7 yr
			64% CR/NL	10 yr
			46% CR	10 yr
			82% CR/NL	
84 months	96		16.9%	5 yr
24 months, min			47.4%	10 yr
31 months	90.3		53% CR	29.8 months
6 months, min				
11.5 yr, mean			35%	5 yr
			53%	10 yr
			66%	15 yr
14 yr	96?		16%	10 yr
10 yr			58%	8 yr
15 yr, min			65%	15 yr
82 months; 4 yr, mean	100	82 months, median	29% CR	6.7 yr
12 yr	95	5 yr	31%	5 yr
	95	10 yr	55%	10 yr
	95	15 yr	83%	15 yr
7 yr			60%	10 yr
			74%	15 yr
			77%	20 yr
47 months, imaging	100		45% CR	5 yr
83 months, H nl			36% PR	
4 yr; 5.9 yr, mean	100		54%	Raw
			40%	5 yr
			63%	10 yr
			67%	15 yr

Akromegalide Radyoterapi

- Radyonekroz
- Hipopitüitarizm
- Sekonder tümörler
- Vasküler komplikasyonlar
- Kognitif değişiklikler

Could different treatment approaches in acromegaly influence life expectancy?

A comparative study between Bulgaria and Campania (Italy)

	Bulgaristan	italya
n	407	220
Cerrahi	80.8	71.8
RT	26	15.5
SSAs	7.8	63.6
DAs	45.2	39.5
GHRa	0	12.7
SMR	2.0	
MI	2.31	
CVO	3.54	
Ca	1.43	

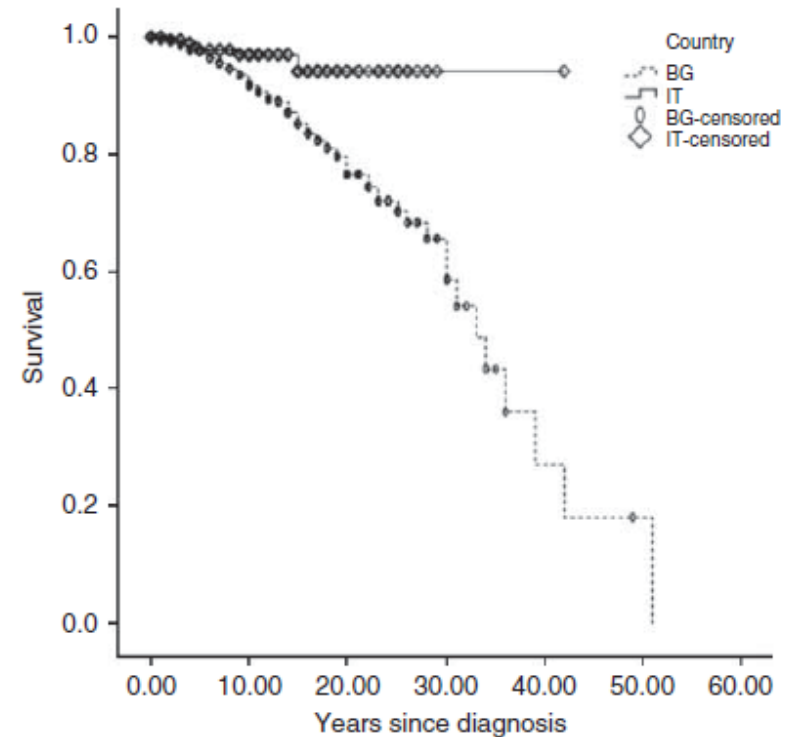
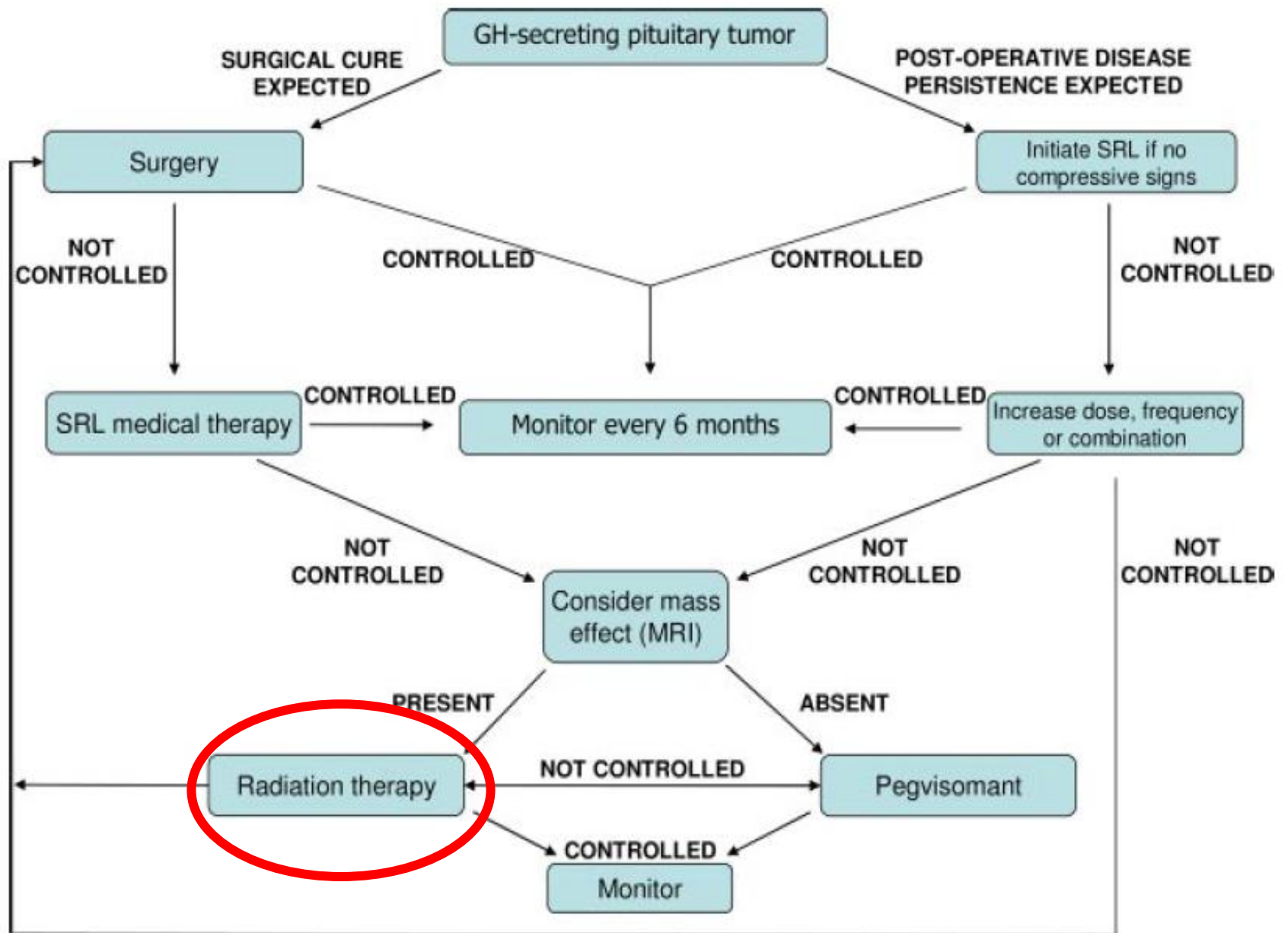


Figure 1

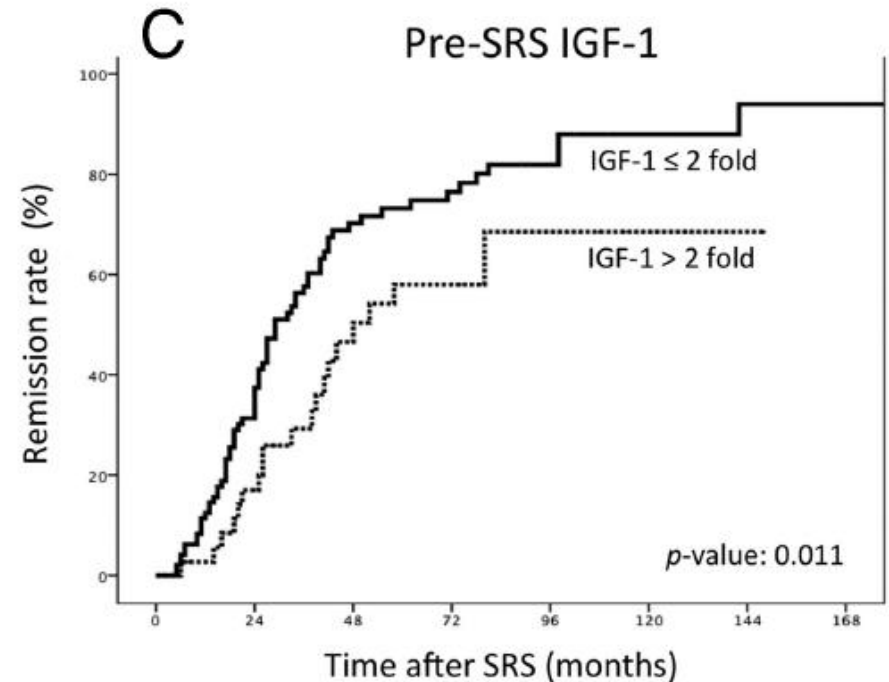
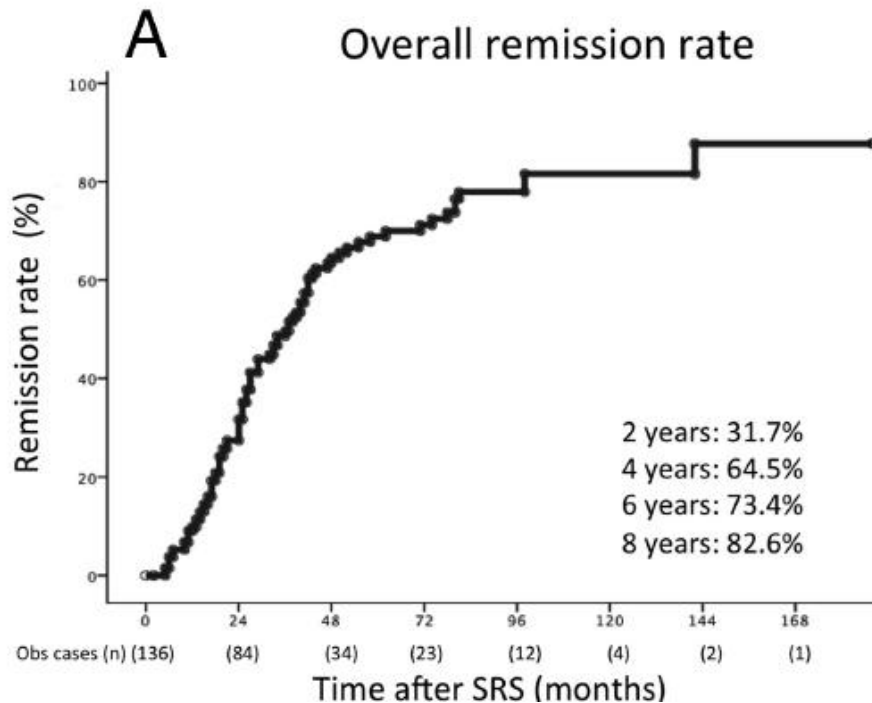
Kaplan-Meier survival analysis in the Bulgarian and the Italian cohorts.



Akromegalide Radyoterapi

- Cerrahi/medikal tedaviye rağmen kontrol altına alınamamış hastada
- Adenomun büyüme riski olan hastada

Stereotactic Radiosurgery for Acromegaly



Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA)

Table 1 Baseline characteristics

n	1,658
Sex (F/M)	1,012/646 (61/39 %)
Age at diagnosis (yr)	45.5 (35–55)
Time of symptoms prior to diagnosis (yr)	6 (2–9)
Follow-up in REA (yr)	11 ± 9
Macro/microadenoma	75/25 %
Baseline GH (ng/mL)	17 (4–22)
Baseline IGF-1 (ng/mL)	767 (516–949)
GH nadir in OGTT (ng/mL)	15 (3–20)
First treatment received	
Surgery	895 (54 %)
Medical therapy	702 (42.3 %)
Surgery + medical	22 (1.3 %)
Radiation therapy	15 (0.9 %)

Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA)

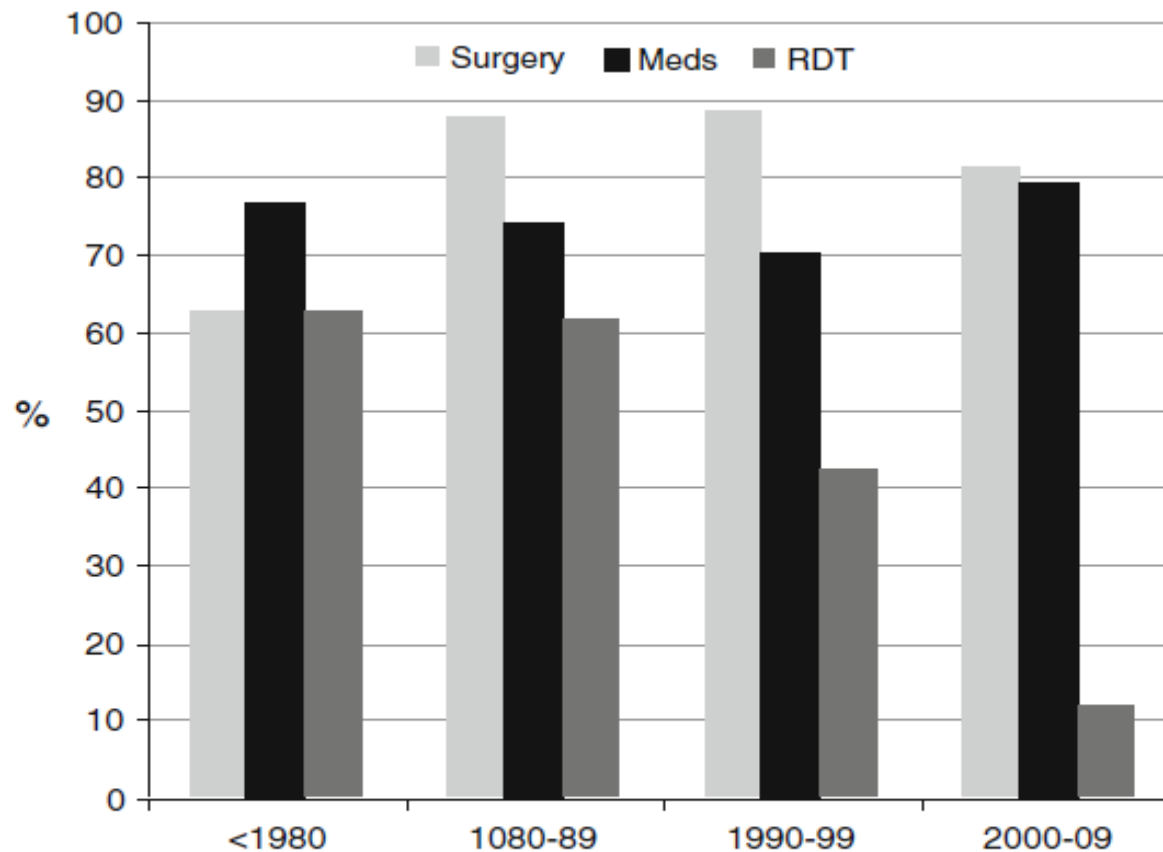


Fig. 2 Type of treatment received according to decade of diagnosis.
Meds medical therapy, *RDT* radiation therapy

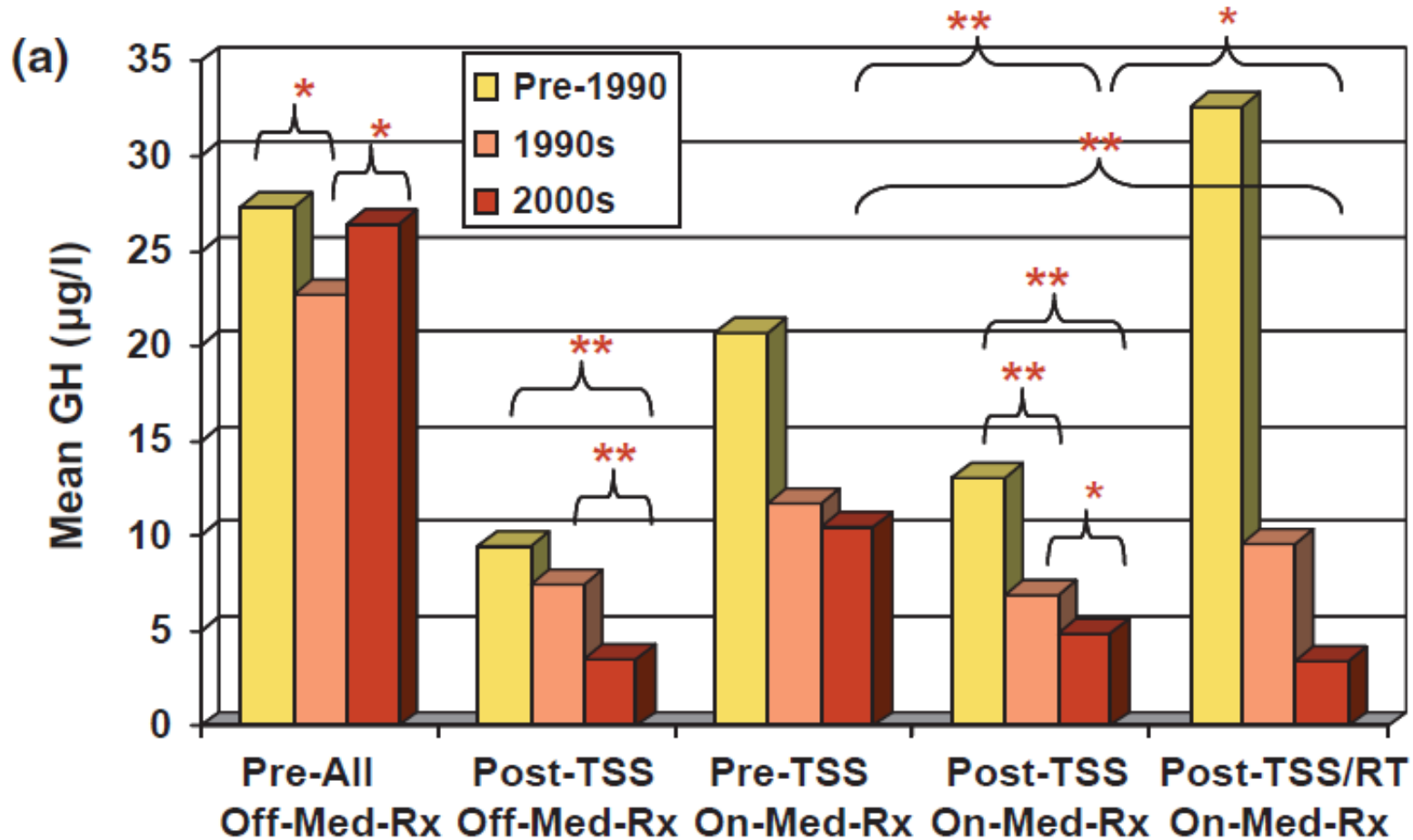
Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA)

Table 2 Treatment combinations

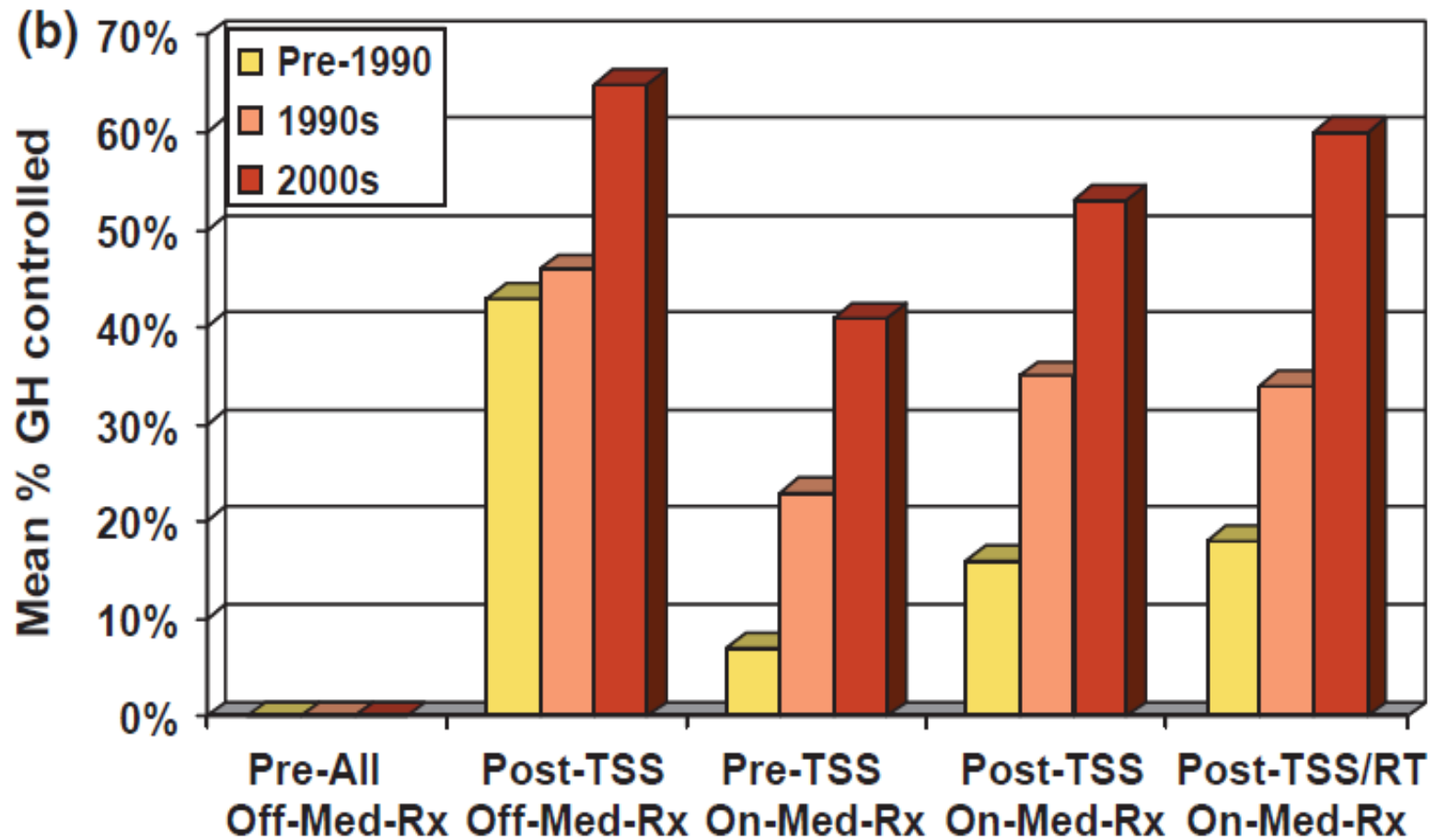
Type of treatment	Year of diagnosis			
	<1980	1980–1989	1990–1999	2000–2009
Surgery alone	2.4	14.2	24.4	16.4
Meds alone	7.3	6	7.2	14.7
RDT only	12.2	0.7	0	0
Meds + surgery	24.4	16.4	24.3	56.5
Med + SG + RDT	34.1	50.7	36.2	11.2
SG + RDT	4.9	9	4.1	0.9
Meds + RDT	14.6	3	2.7	0.4
n	41	134	221	232

SG surgery, *RDT* radiotherapy, *Meds* medical treatment

Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists



Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists



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