PROLAKTİNOMA
Tedavisinde Yenilikler

Prof. Dr. Erdinç ERTÜRK
Uludağ Üniversitesi Tıp Fakültesi
Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı
9. Hipofiz Sempozyumu 9-10 Kasım 2013, Ankara

Prolaktinoma Tedavisinde Amaçlar

- Prolaktin seviyesinin normale getirilmesi
  - Gonadal fonksiyonların normale getirilmesi
- Tümör boyutunun küçültülmesi
  - Baskı semptomlarının giderilmesi

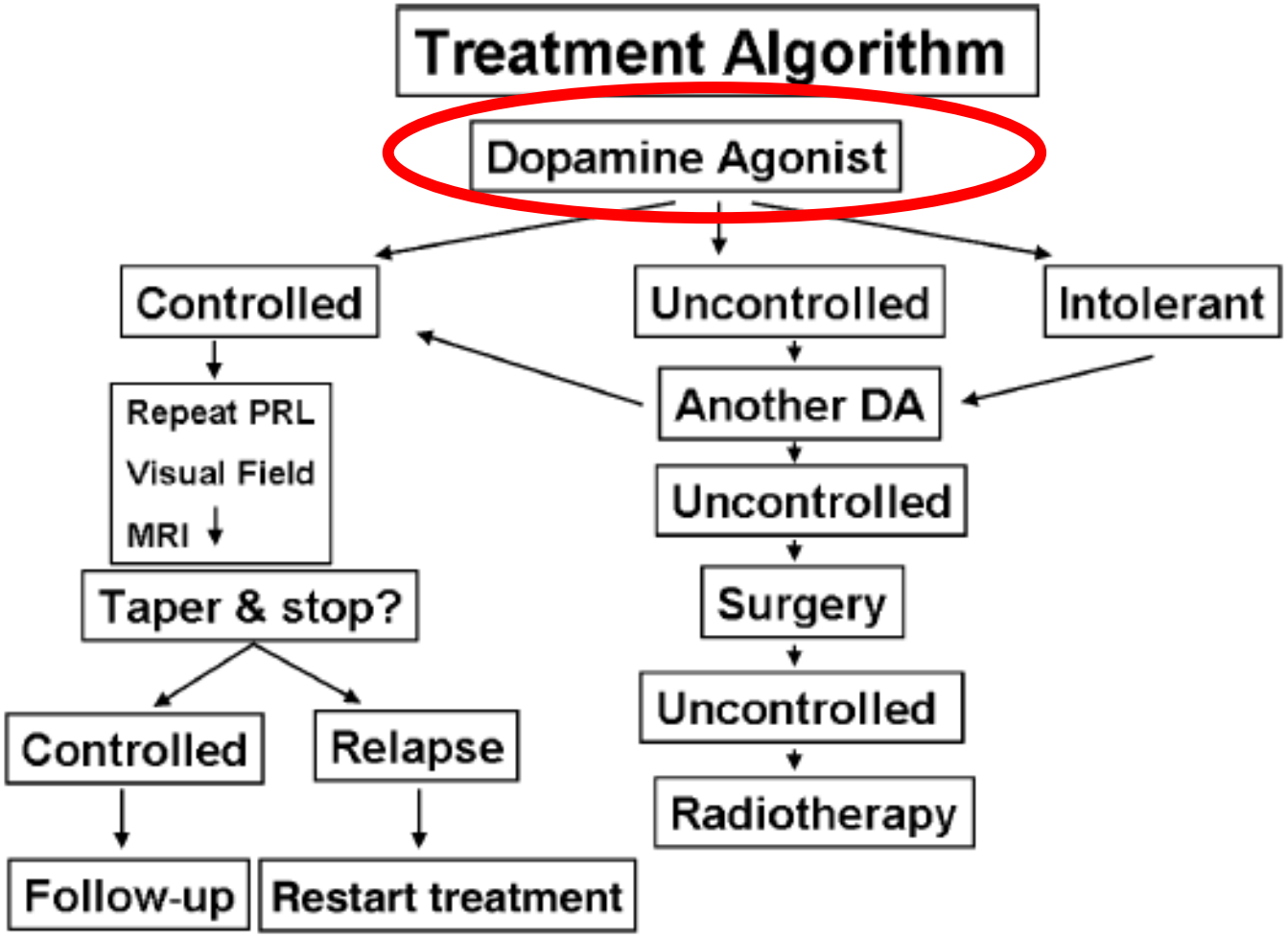
Prolaktinomada dopamin agonistleri

- Prolaktin seviyesinin normalleşmesi
- Tümör boyutunun küçülmesi

  - Galaktorenin düzelmesi
  - Gonadal fonksiyonların iyileşmesi
  - Fertilitenin sağlanması

  - Görme alanının iyileşmesi

Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas



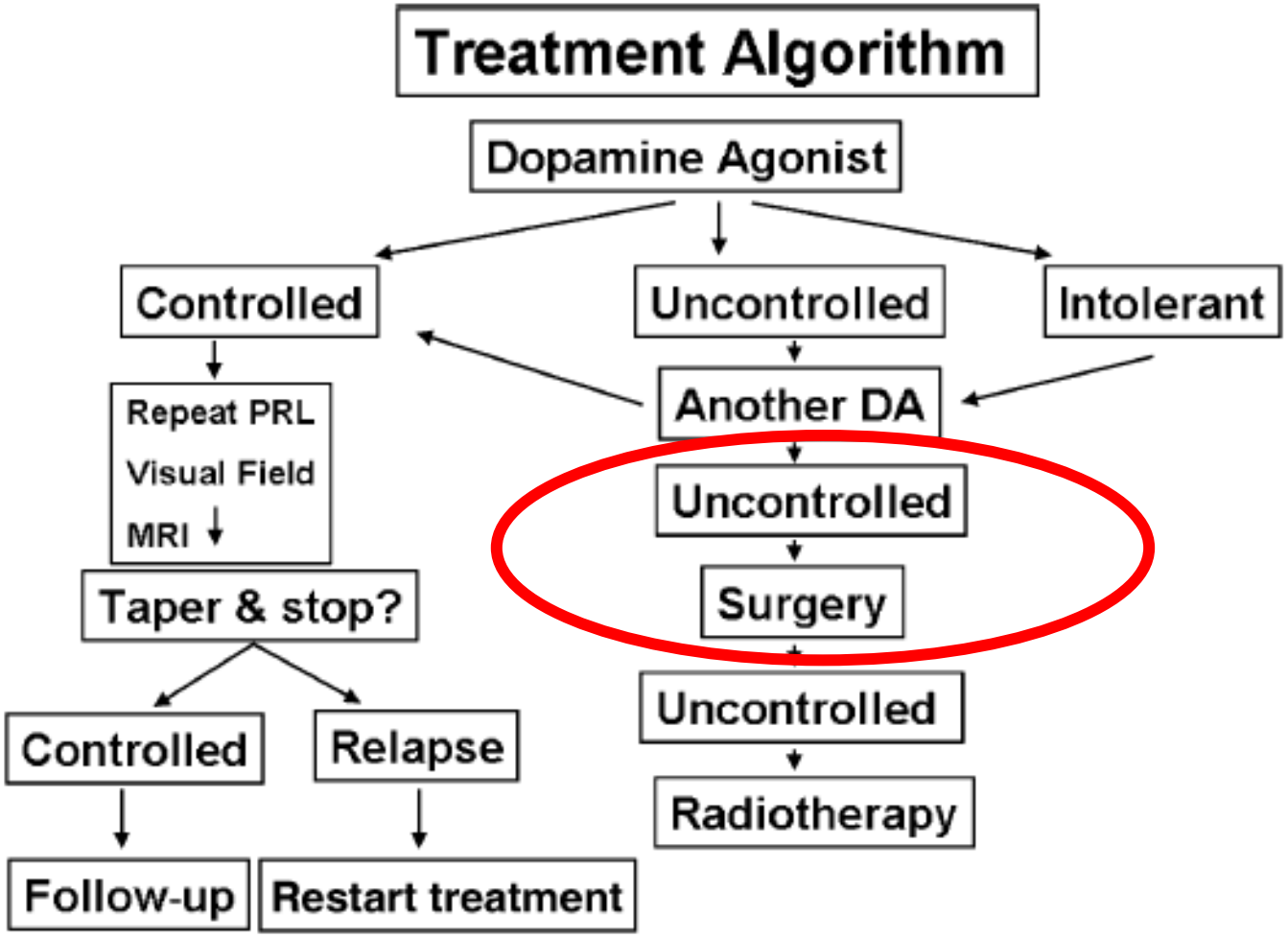
Casaneuva F, Clin Endo , 2006

DA dışında tedavi seçimi

- Hasta tercihi
- Makroadenomda hamilelik isteği
- Acil pitüiter apopleksi

- DA intoleransı
- DA direnci

Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas

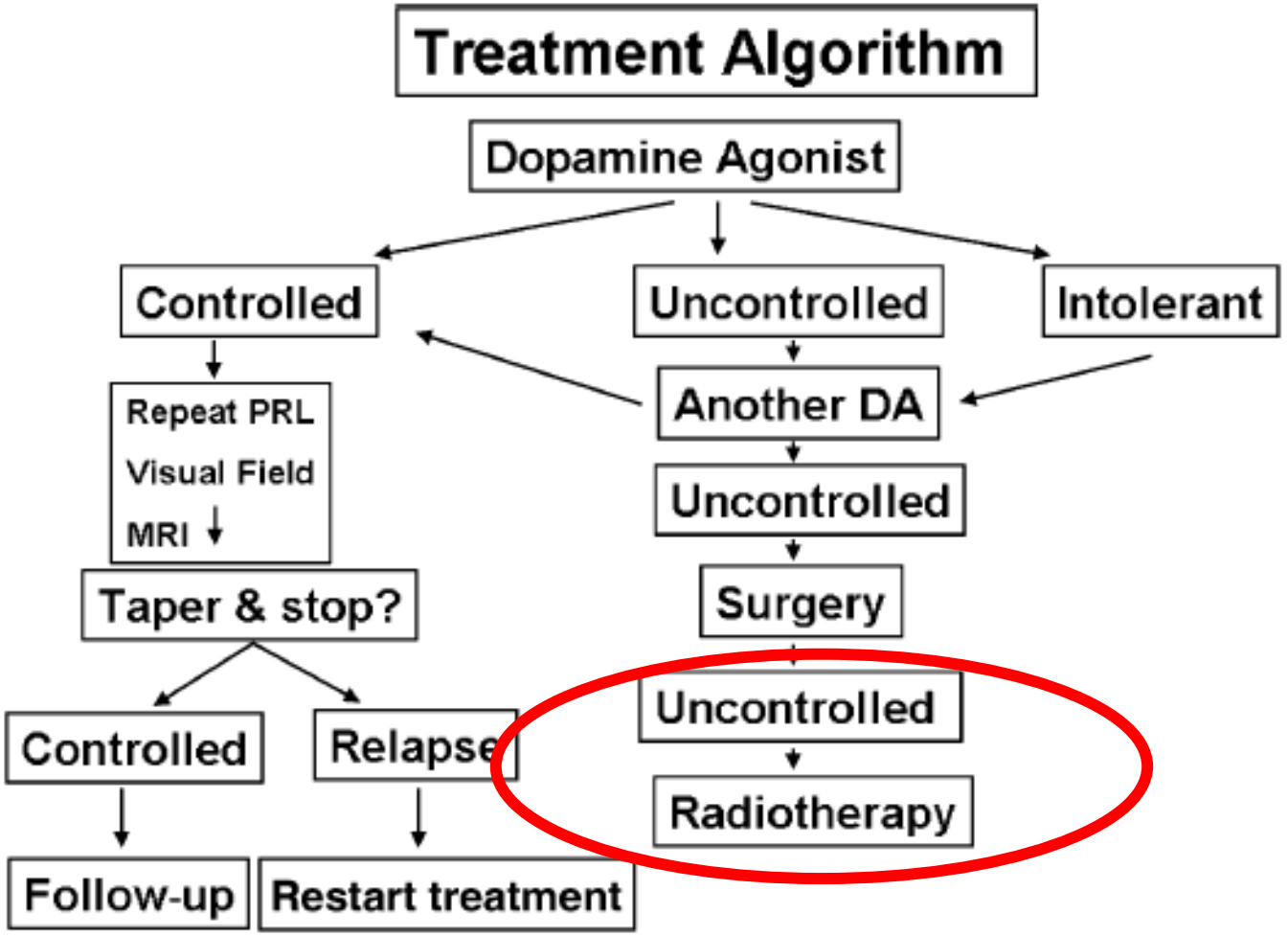


Casaneuva F, Clin Endo , 2006

Prolaktinomada ikincil tedavi tercihi

- Cerrahi tedavi
  - Tümör boyutunun küçülmesi
  - Prolaktin seviyesinin normalleşmesi
    - Görme alanının iyileşmesi
    - Galaktorenin düzelmesi
    - Gonadal fonksiyonların iyileşmesi
    - Fertilitenin sağlanması
  - Düşük cerrahi komplikasyon olasılığı

Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas

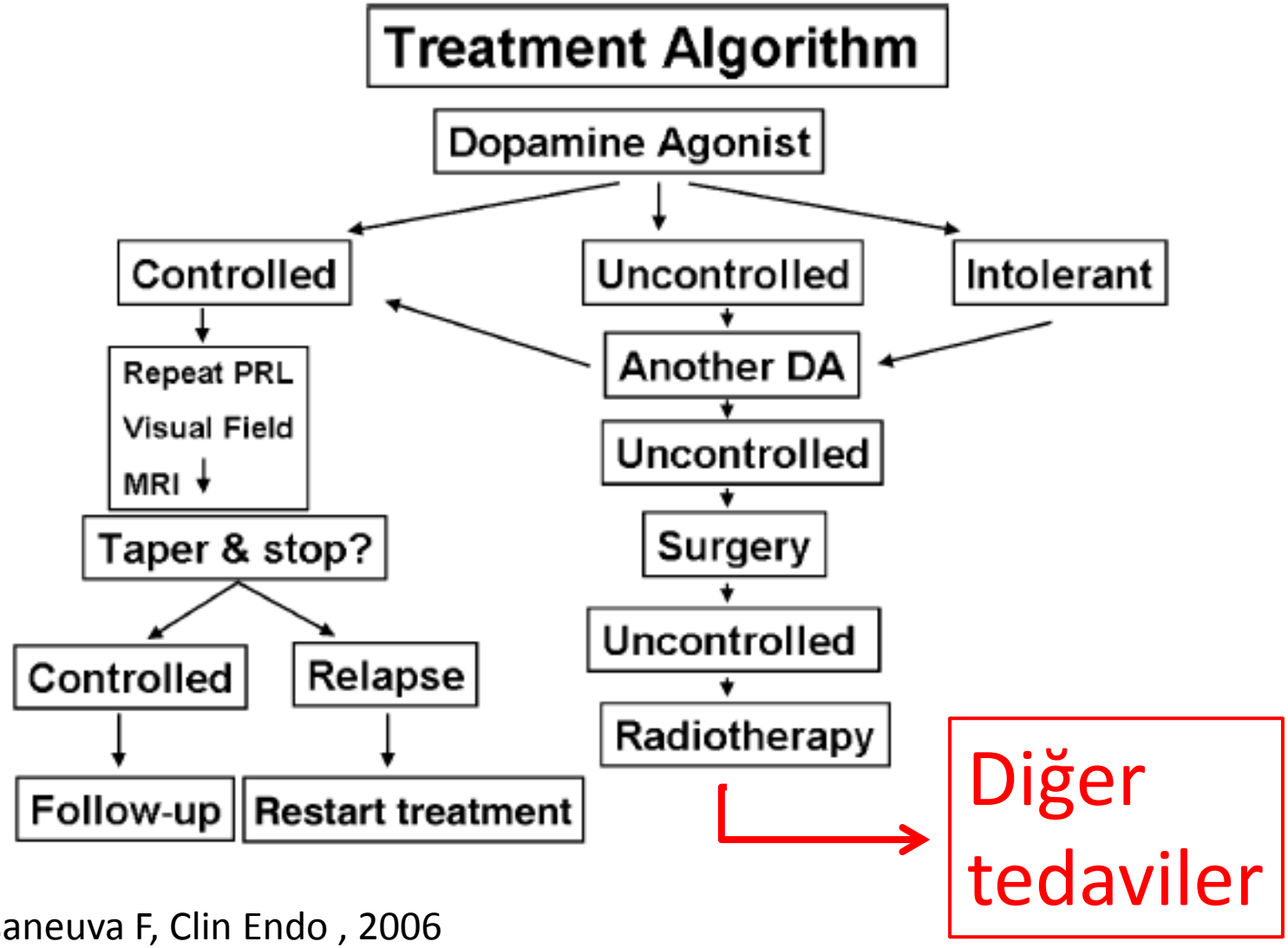


Casaneuva F, Clin Endo , 2006

Prolaktinomada radyoterapi

- Etkinliği düşük
- Gecikmeli etkinlik
- Hipopitüitarizm olasılığı yüksek
- Diğer olası komplikasyonlar

Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas



Casaneuva F, Clin Endo , 2006

Prolaktinomada diğer tedavilerin kullanımı

- Medikal tedaviye (DA) dirençli
- Cerrahi tedavi ile küratif sonuç alınamamış
- Radyoterapi ile kontrol altına alınamayan

- Agresivite gösteren
- Çevre dokulara baskı bulguları giderek artan

Prolaktinomada uygulanabilen Diğer Tedavi Seçenekleri

- Somatostatin analogları
- Sitostatik kemoterapötikler
- Temozolomide

- Hibrid moleküller (SS+DA)
- Prolaktin reseptör antagonisti
- Gen tedavisi

Somatostatin Receptor Subtype Gene Expression In Pituitary Adenomas*

TABLE 2. SRIF receptor subtype expression in pituitary adenomas

Tumor type	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatotroph	6/8	8/8	1/8	0/8	8/8
Nonfunctioning	5/11	9/11	0/11	0/11	8/11
Lactotroph	8/8	8/8	0/8	0/8	7/8
Corticotroph	3/5	5/5	0/5	0/5	4/5
Normal pituitary	4/4	4/4	0/4	0/4	4/4
Islet cell tumor	+	+	+	−	+
Normal human pituitary cDNA library	+	+	−	−	+
Human genomic DNA	+	+	+	+	+

Miller GM. JCEM, 1995

Somatostatinergic ligands in dopamine-sensitive and -resistant prolactinomas

Table 3 Quantitative RT-PCR of dopamine receptor 2 (D2DR), somatostatin receptor (SSTR1), SSTR2, SSTR3, and SSTR5 mRNA expression in ten prolactinomas (a) and four mixed growth hormone and prolactin (GH and PRL) adenomas (b).

	D2DR and SSTR mRNAs (copy/copy β-Gus)				
Tumor	D2DR	SSTR1	SSTR2	SSTR3	SSTR5
(a)					
DA sensitive					
P2	65	0.1	0.1	0.1	0.1
P3	144	0.1	6.5	0	0.1
P4	445	0.1	1.0	0	2.1
P6	26	0.4	0.1	0	4.3
P8	13	0.2	0.5	0.1	0.5
P9	ND	0.9	0.1	0	0.1
DA resistant					
P1	15	12.4	0.1	0	1.3
P5	17	0.3	0.6	0	0.1
P7	12	3.9	0.1	0.1	4.3
P10	29	13.6	0.1	0	0.1
(b)					
A1	ND	0	0.4	0.3	15.2
A2	ND	1.4	0.8	0	0.5
A3	4	0.4	2.2	0	2.5
A4	13	0.4	6	1.1	1.5

Fusco A. EJE, 2008

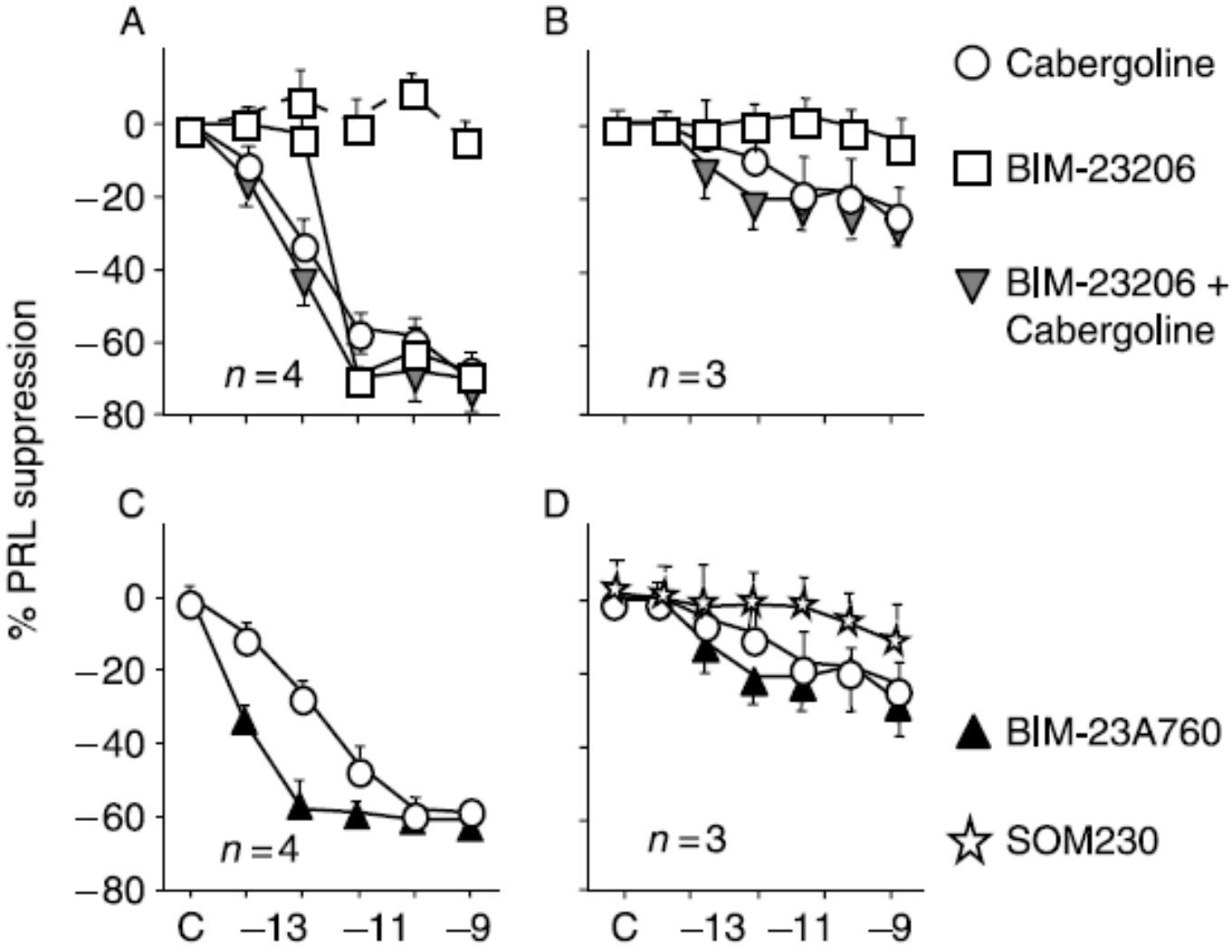
Somatostatinergic ligands in dopamine-sensitive and -resistant prolactinomas

Table 2 Human dopamine receptor 2 (D2DR) and somatostatin receptor (SSTR) binding affinities of dopamine agonist (DA) and SST analogs.

Compound	Dopamine receptor (IC50: nmol/l)	Human somatostatin receptor subtype (IC50: nmol/l)				
	D2DR	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin-14		1.9	0.2	1.2	1.8	1.4
BIM-23926		3.6	>1000	>1000	833	788
BIM-23197		6016	0.19	26.8	3897	9.8
BIM-23206		1152	166	1000	1618	2.4
BIM-23A760	15	622	0.03	160	1000	3.7
SOM230		9.3	1	1.5	>100	0.2
Cabergoline	0.3					

Fusco A. EJE, 2008

Somatostatinergic ligands in dopamine-sensitive and -resistant prolactinomas



Fusco A. EJE, 2008

Sitostatik tedaviler

- 5 Florourasil
- Procarbazine
- Vincristine
- Cisplatin
- Etoposite
- Lomustine
- Doxorubusin
- Siklofosfamit

The Role of Cytotoxic Chemotherapy in the Management of Aggressive and Malignant Pituitary Tumors

Patient no.	Chemotherapy	Extent of disease	Side effects	Response to chemotherapy	Outcome
(1) PRL mU/L	CCNU/5-FU × 2 cycles	Pituitary fossa Liver, Lungs	None	Cl: ? Improved but liver mets noted Hor: PRL ↓ from 550000 to 90000 mU/L Rad: No change CT pituitary	Died 4 weeks after liver mets noted and 3 months after initiation of chemotherapy
(2) PRL	CCNU/5-FU × 1	Pituitary fossa Thoracic, Lumbar Spine	None	Cl: No change Hor: No change PRL 720000 mU/L Rad: No change MRI pituitary	Died 5 months after spinal mets noted (6 months after initiation of chemotherapy)
(3) PRL	CCNU/5-FU × 6	Frontal lobe Parietal lobe Orbit (left)	None	Cl: Vision improved Hor: No change PRL 45000 mU/L Rad: No change CT pituitary	Died 11 yr after CNS mets noted (11 yr post-chemotherapy)
	Carboplatin × 5		None	Cl: No progression Hor: PRL ↓ from 97000 to 79000 mU/L Rad: No change CT pituitary	
	Carboplatin × 3		None	Cl: Deterioration of vision Hor: No change in PRL levels Rad: ? Reduction tumor size	
	5-FU/α-INF × 8		Epilepsy WBC ↓	Cl: no progression. ? Improved Hor: PRL ↑ from 400000 to 641000 mU/L Rad: No change CT pituitary	
	Carboplatin/α-INF × 4		WBC ↓	Cl: Worsening cerebral function Hor: PRL 350000 mU/L Rad: Progression	
(4) ACTH (ng/L)	CCNU/5-FU × 6 cycles	Thoracic spine Liver	Nausea	Cl: No change Hor: ACTH from 500 to 472 ng/L Rad: No change in size	Died 18 months after spinal mets noted (3 yr postchemotherapy)
	Carboplatin × 6			Cl: Visual deterioration Hor: ACTH ↑ from 1892 to 2951 ng/mL Rad: Progression	
	DTIC × 2			Cl: Deterioration Hor: ACTH 3000 ng/L Rad: Progression	
(5) PRL	CCNU/5-FU × 2 cycles	Retrosellar and brainstem extensions	None	Cl: Improvement Hor: PRL ↓ from 21078 to 4746 mU/L Rad: Reduction in size	Died from other cause (6 months after initiation of chemotherapy)
(6) GH (mU/L)	CCNU/5-FU × 2 cycles	Max extension into cavernous sinus (right)	None	Cl: Uncontrolled acromegaly Hor: No change in GH levels Rad: No change in size	Alive (5 yr after initiation of chemotherapy)
(7) ACTH	CCNU/5-FU × 4 cycles	Pituitary fossa and both cavernous sinuses	None	Cl: No change in pigmentation Hor: No change in ACTH levels Rad: No change in size	Alive (4 yr after initiation of chemotherapy)
	Carboplatin/5-FU × 6		Microscopic hematuria	Cl: No change in pigmentation Hor: No change in ACTH levels Rad: No change in size	

Kaltsas GA. JCEM, 1998

Temozolomide

- İkinci jenerasyon alkilleyici ajan
- Dakarbazin derivesi
- Tümör hücre siklusunun tüm evrelerinde etkili
- 1999 yılından beri kullanımda
- Kan beyin bariyerini kolaylıkla geçer
- Glioblastome multiforme tedavisinde endike

Temozolomide in the treatment of an invasive prolactinoma resistant to dopamine agonists

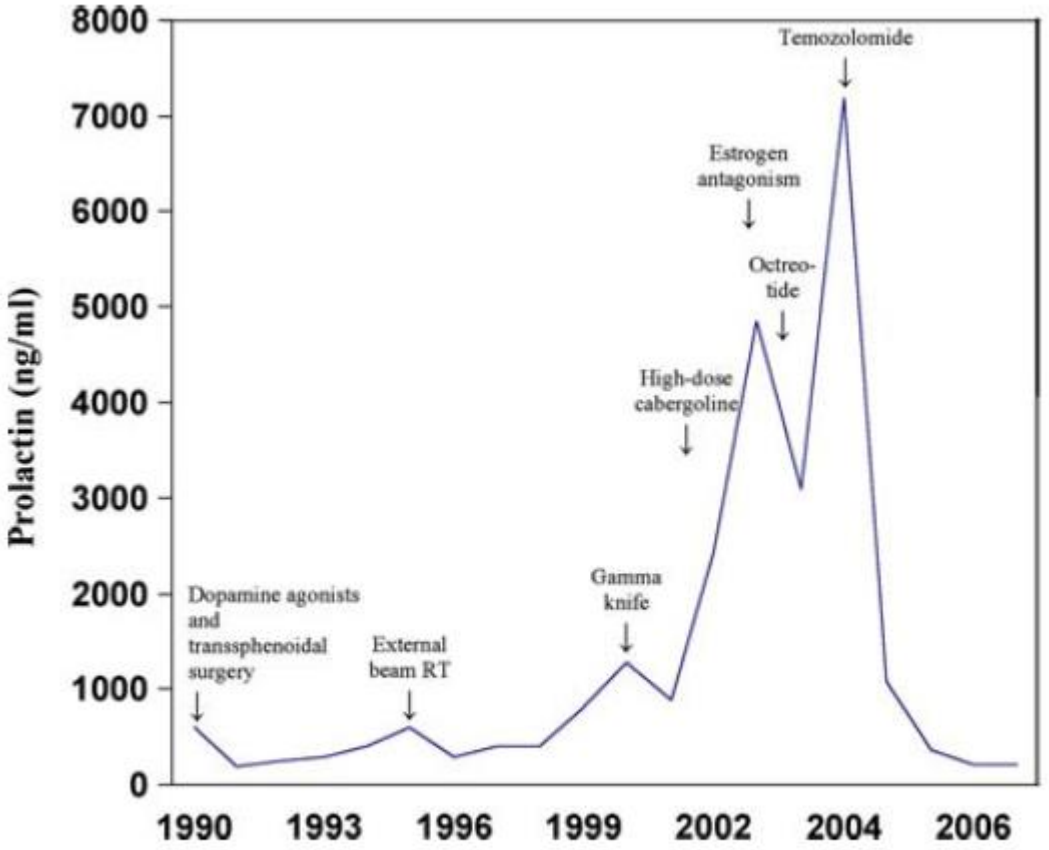
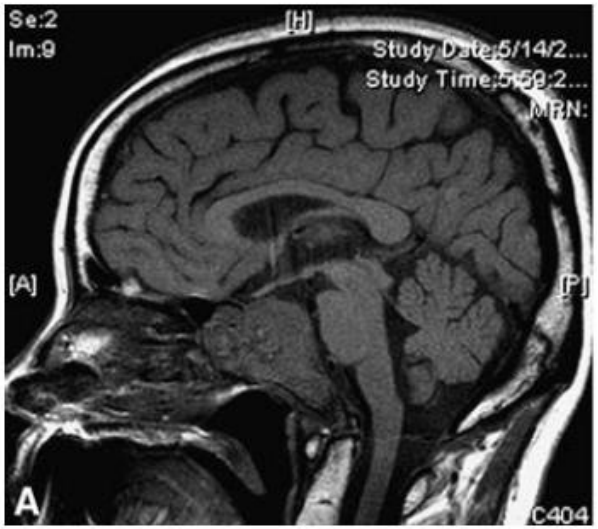
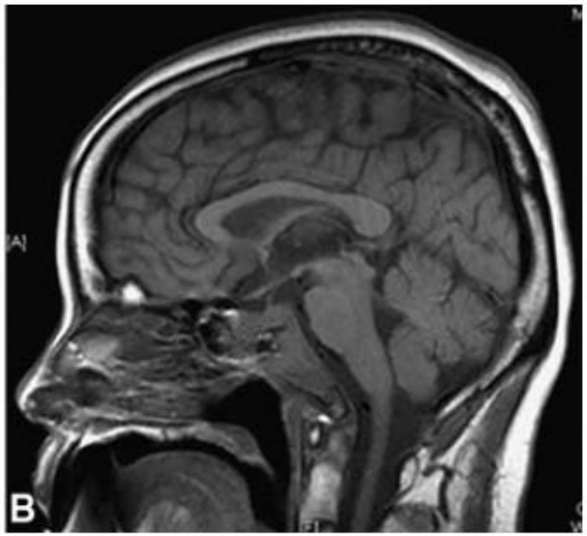


Fig. 2 Serum prolactin level over the course of treatment since 1990





Neff LM, Pituitary, 2007

Treatment of Pituitary Neoplasms With Temozolomide

A Review

Patient	Reference(s)	Tumor	Age, y	Sex	Time From Disease Onset to TMZ Treatment, y	Previous RT	No. of Previous Surgeries	Response	Treatment	Follow-Up
1	Lim 2006,[17] Zhu 2004[25]	PRL carcinoma	72	Man	12	Yes	3	Yes	18 Mo	–
2	Fadul 2006[13]	LH carcinoma	38	Man	8	Yes	2	Yes	12 Cycles	16 Mo; free of disease
3	Fadul 2006[13]	PRL carcinoma	26	Man	7	Yes	2	Yes	10 Cycles	15 Mo; free of disease
4	Byrne 2009,[10] McCormack 2009[19]	PRL carcinoma	64	Man	23	Yes; ×2	6	Yes	12 Mo	Controlled
5	Hagen 2009[14]	PRL carcinoma	48	Woman	8.5	Yes	1	Yes	23 Mo	Free of disease ≥3 y
6	Takeshita 2009[24]	CCA, ACTH carcinoma	46	Woman	9	Yes; gamma ×3	3	Yes	Monthly for 1 y; bimonthly for 2 y	Good at 2 y 3 mo

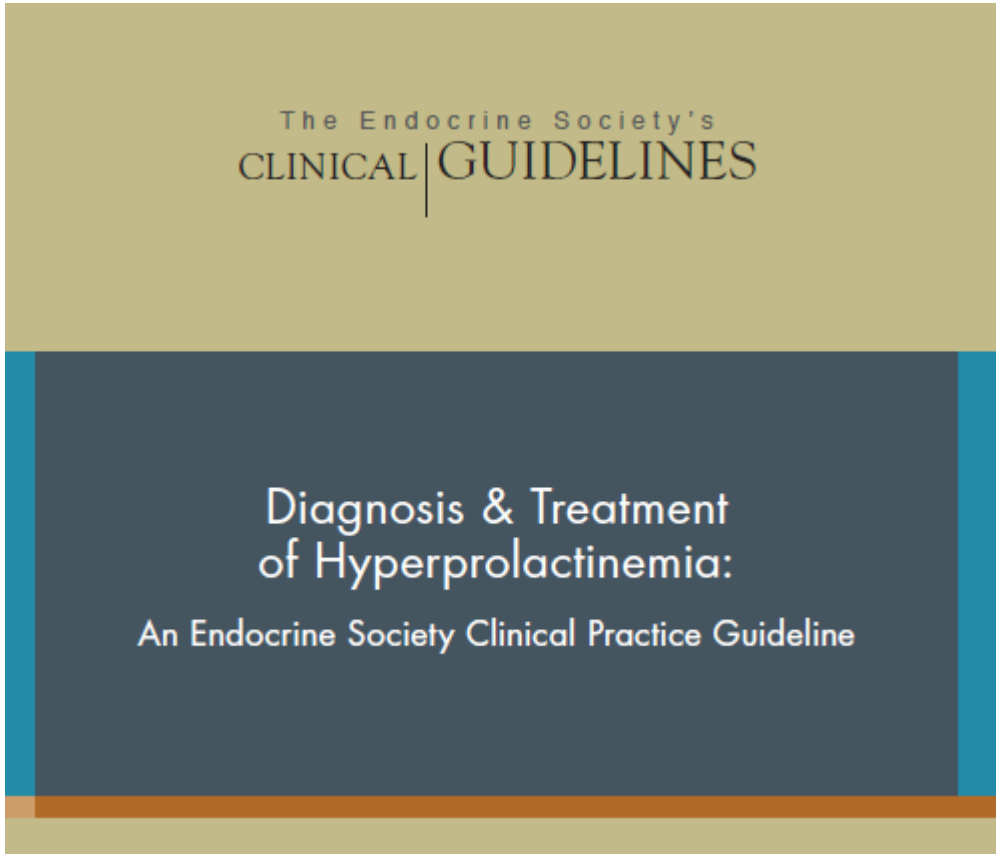
Syro LV. Cancer 2011

Treatment of Pituitary Neoplasms With Temozolomide

A Review

Patient	Reference(s)	Tumor	Age, y	Sex	Time From Disease Onset to TMZ Treatment, y	Previous RT	No. of Previous Surgeries	Response	Treatment	Follow Up	MGMT
1	Syro 2006[23]	PRL	46	Man	15	Yes	5	Yes	8 Cycles, +surgery, +24 cycles	Dead. 2 y; MI	Low
2	Neff 2007[21]	PRL	52	Woman	15	Yes+gamma	1	Yes	26 Mo	Controlled	–
3	Kovacs 2008[16]	Silent ACTH	41	Man	20	Yes	4	No	8 Cycles, +surgery, +16 cycles, +surgery, +6 cycles, +surgery	Cervical metastases, recurrence	High
4	Moyes 2009[20]	Nelson syndrome, ACTH	64	Woman	6	Yes	1	Yes	6 Cycles	No data	Low
5	Mohammed 2009[2]	ACTH	43	Woman	2	Yes	3	Yes	16 Mo	Free of disease	Low
6	Mohammed 2009[2]	ACTH, Nelson	60	Man	2	Yes	2	Yes; progression	12 Mo	Metastasis 4 mo after stopping TMZ	Intermediate
7	Mohammed 2009[2]	NFPA, incidental, glioma	28	Woman	0	No	0	Yes	10 Mo	Controlled	–
8	McCormack 2009[19]	GH	54	Man	6	Yes	4	No	3 Cycles	Dead	High
9	Debono 2008[11]	PRL	47	Man	23	Yes+gamma	1	Yes	11 Cycles	Recurrence 1 y after treatment; TMZ restarted	Low
10	Syro 2009[22]	Oncocytoma	61	Man	18	Yes	4	Yes	6 Cycles	Dead; pulmonary thromboembolism	Intermediate
11	Syro (unpublished results)	Oncocytoma	47	Man	23	Yes	4	Yes	4 Cycles	Improved; in treatment	Intermediate
12	Hagen 2009[14]	PRL	60	Man	19	No	1	Yes	12 Cycles	12 mo after treatment	Low
13	Hagen 2009[14]	NFPA	20	Man	5	Yes	6	Yes	15 Cycles	In treatment	Intermediate

Syro LV. Cancer 2011



Recommendation

5.4. In patients with malignant prolactinomas, we suggest temozolomide therapy (2 | ⊕◯◯◯).

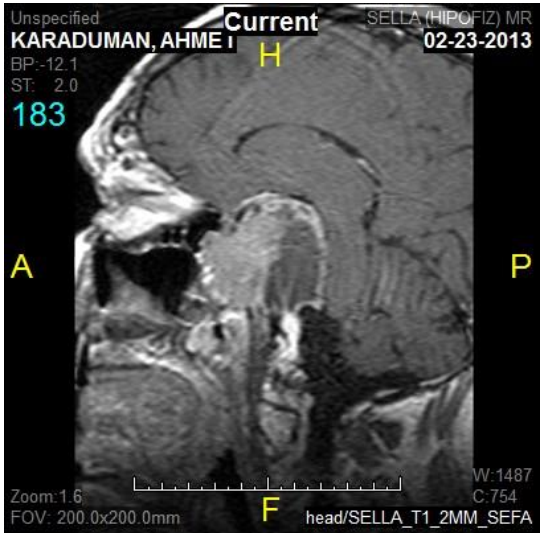
Temozolomide kullanılışı

- Temodal®, Temomid® cap (5-20-100-250 mg)
- 28 günlük sikluslarla 5 günlük tedavi (150-200 mg/m2)
- Genellikle iyi tolere edilir
  - GIS yakınmaları, Kİ depresyonu
- Etkinlik için 3-6 ay beklenmelidir (%50-70)

- Etkinlik (MGMT)
- Süre

Olgu:

- 53 y E, 1991 yılında saptanmış işlevsiz dev hipofiz makroadenomu
- 3 operasyon
  - 1991 transkranial,
  - 2006 transsfenoidal,
  - 2008 transkranial
- 1991 ve 2012 yıllarında eksternal RT
- 1991 yılından beri panhipopitüitarizm tedavisi alıyor
- Sağ göz görme kaybı
  - 2005 yılından sonra başlamış, 2006 operasyondan sonra hızlanmış, 2008 operasyonundan fayda görmemiş, 2013 Ocak sağ göz total görme kaybı
- Mart- Ağustos 2013 tarihleri arasında 6 kür temozolomid tedavisi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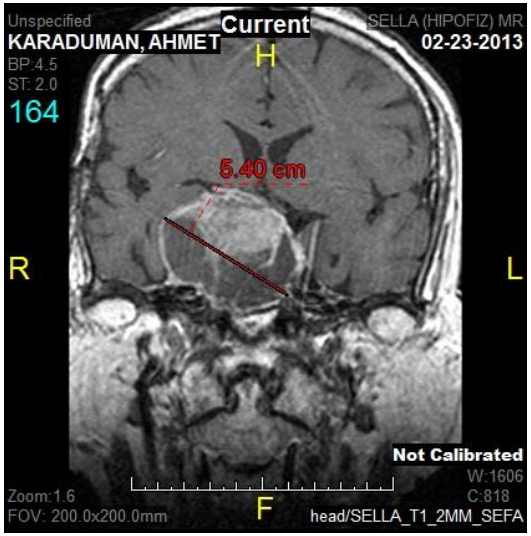
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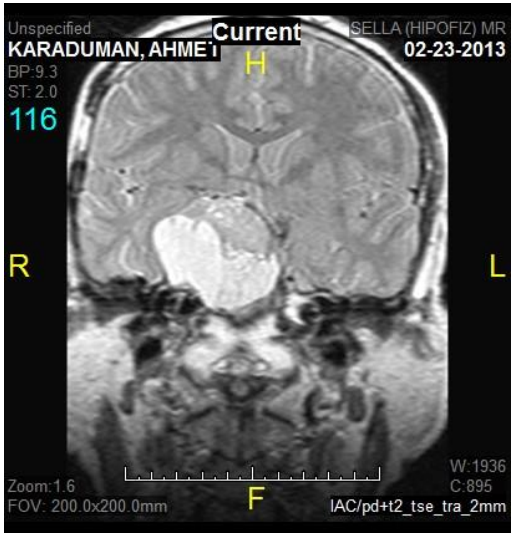
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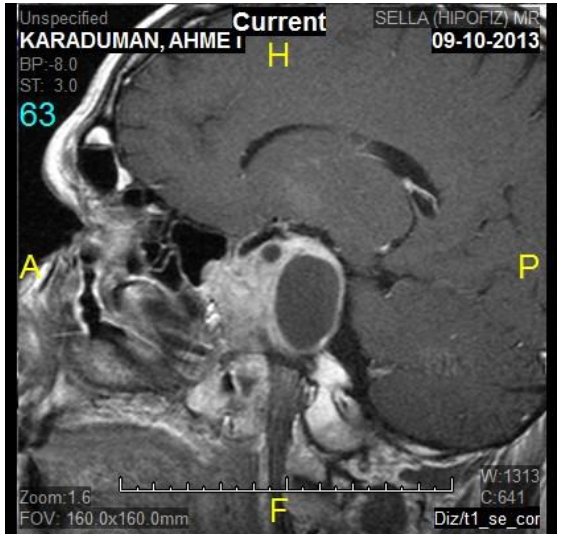
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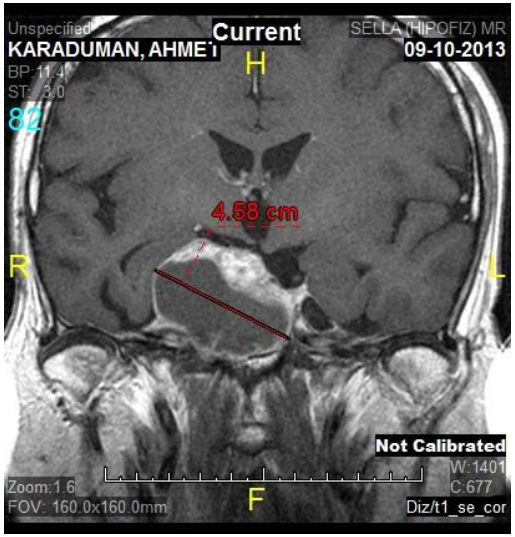
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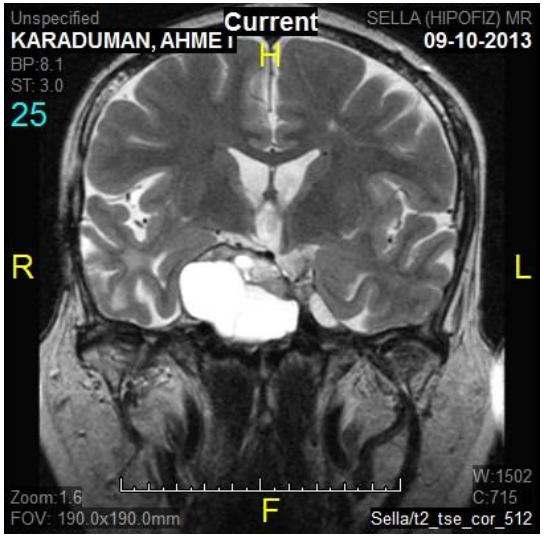
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PROLAKTİNOMA
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Prof. Dr. Erdinç ERTÜRK
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