Invasive ACTH-Producing Pituitary Macroadenoma

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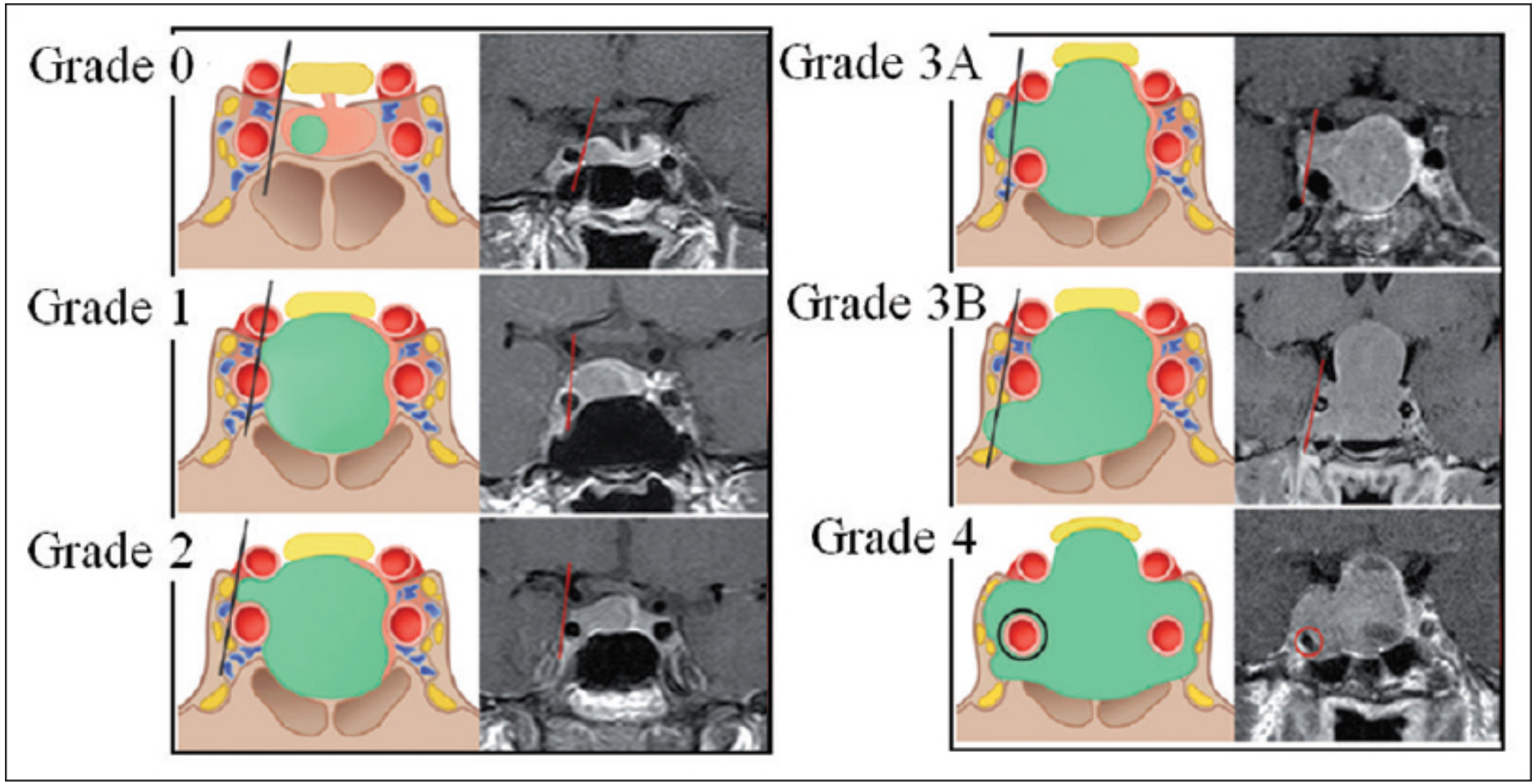
KNOSP CLASSIFICATION



SILENT CORTICOTROPH ADENOMA

TABLE 1. Characteristics of Silent Corticotroph Adenomas

Lack of clinical symptoms of Cushing's syndrome
No or only minor increases in serum adrenocorticotropic hormone levels
Normal serum cortisol concentrations
High frequency of symptoms attributable to mass effects, particularly visual field defects and hypopituitarism
Large tumor size (all macroadenomas)
Frequent hemorrhagic infarctions, with subsequent cystic changes
Sphenoid or cavernous sinus invasion
Frequent need for postoperative radiation therapy and/or reoperations to treat residual tumor or major tumor regrowth

Translational or post-translational abnormalities of ACTH

- Functionally inactive ACTH
- Abnormal processing of POMC
- Lower expressions of proconvertase 1/3

Endocrinol Diabetes Metab Case Rep. 2019; 2019: 19-0046.

Clinically silent corticotroph tumors of the pituitary gland. *Neurosurgery* 2000. 723–729

SILENT CORTICOTROPH ADENOMA

TABLE 3. Clinical and Endocrinological Comparison of Adrenocorticotropic Hormone-producing Pituitary Adenoma Variants

	Cushing's Adenoma	Silent Corticotroph Adenomas (Overall)
Age	Adolescence to young adulthood	11–79 yr (mean, 48 yr)
M/F	1:3	2:1
Symptoms	Cushing's syndrome	Mass effects (visual symptoms)
Recurrence/persistence	10%	57%
Apoplexy	No	9%
Serum adrenocorticotropic hormone levels	Normal to moderately elevated	Low to mildly elevated
Serum/urinary cortisol levels	Elevated	Low to normal
Preoperative pituitary insufficiency	Very rare	35%
Tumor size	85% microadenoma, 15% macroadenoma	100% macroadenoma
Invasion (dura/bone)	10% microadenoma, 60% macroadenoma	50%
Hemorrhage, necrosis, or cyst formation	No	60%

More aggressive

Clinically silent corticotroph tumors of the pituitary gland. *Neurosurgery* 2000. 723–729

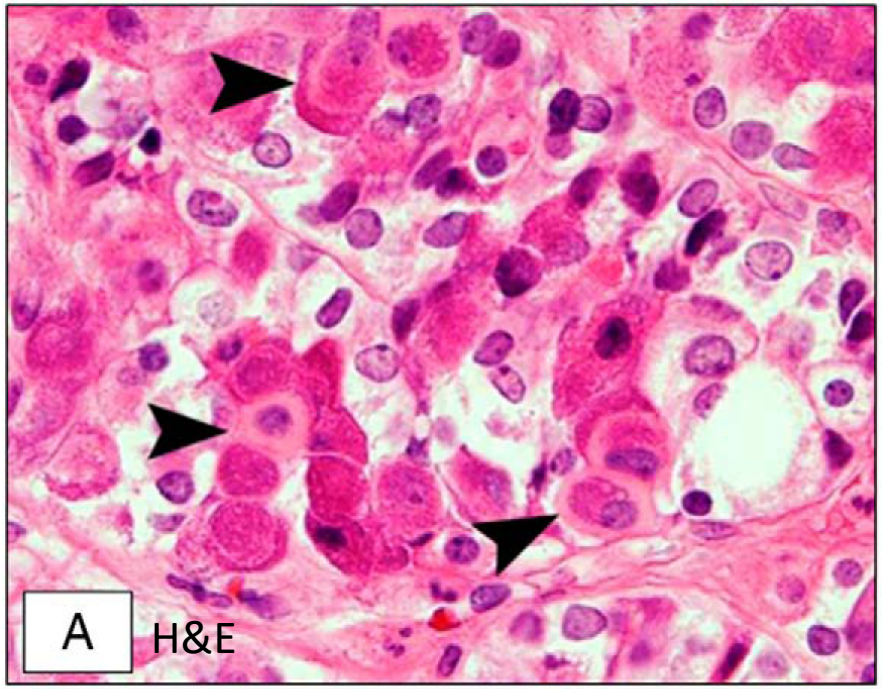
SILENT CORTICOTROPH ADENOMA

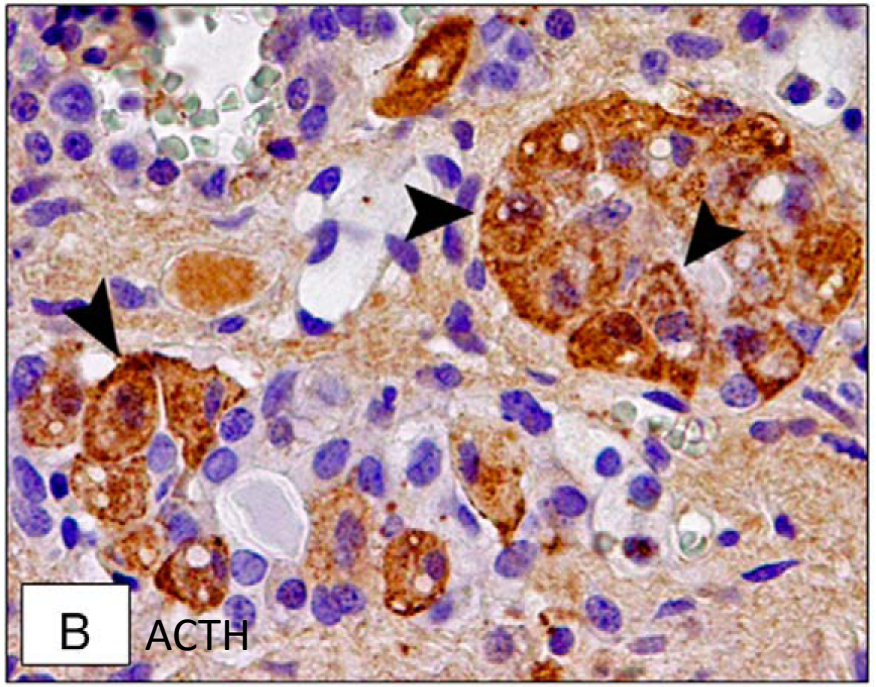
2 subtypes

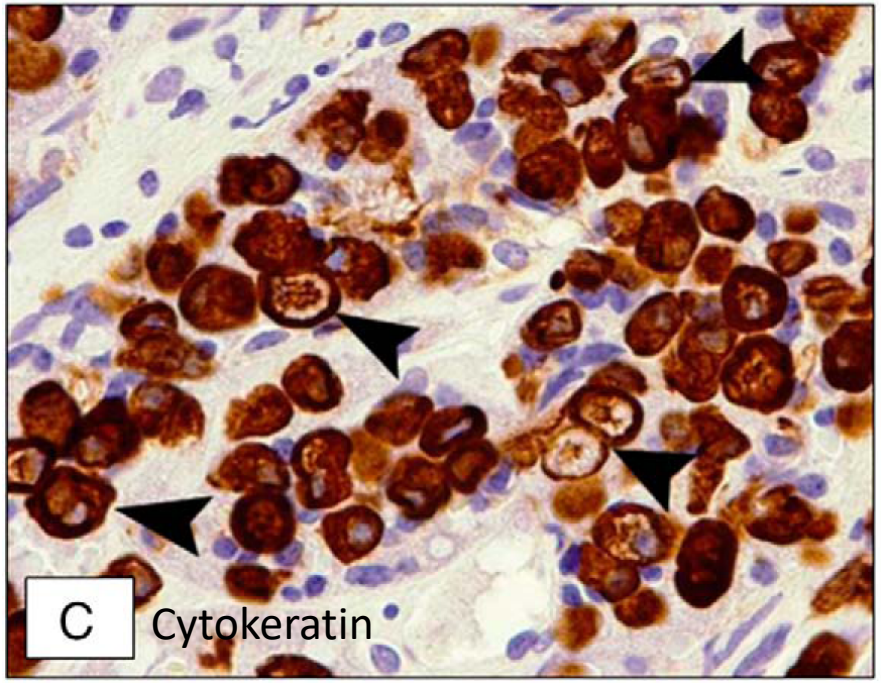
Type I SCA – 68%
Histologically indistinguishable from classical Cushing adenoma
Crooke's hyaline changes
Strong ACTH expression

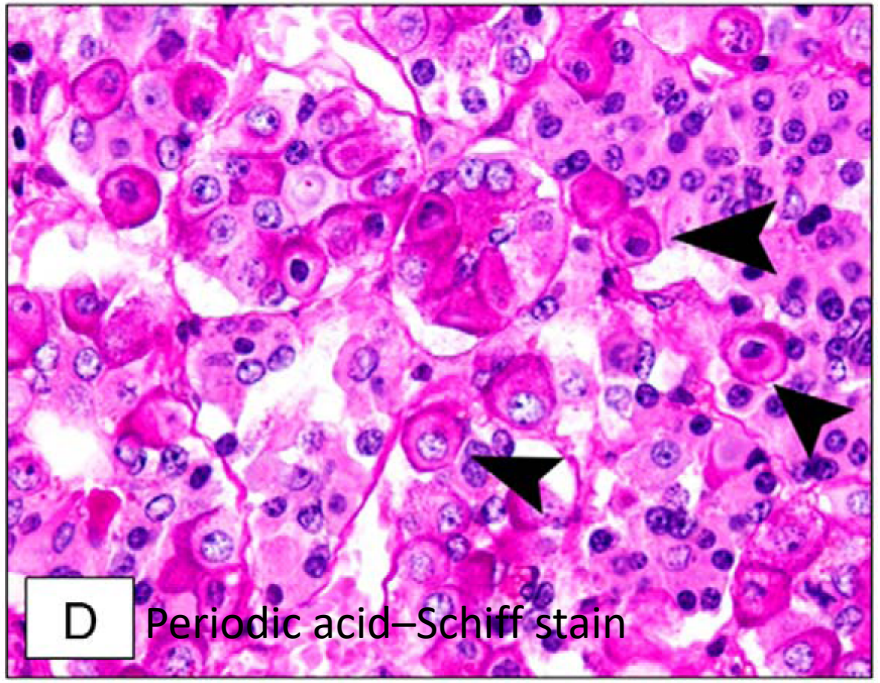
Type II SCA
Patchy or faint ACTH positivity by immunohistochemistry

Clinically silent corticotroph tumors of the pituitary gland. *Neurosurgery* 2000. 723–729









Crooke's hyaline change

The Journal of Clinical Endocrinology & Metabolism, Volume 100, Issue 8, 1 August 2015, Pages 3

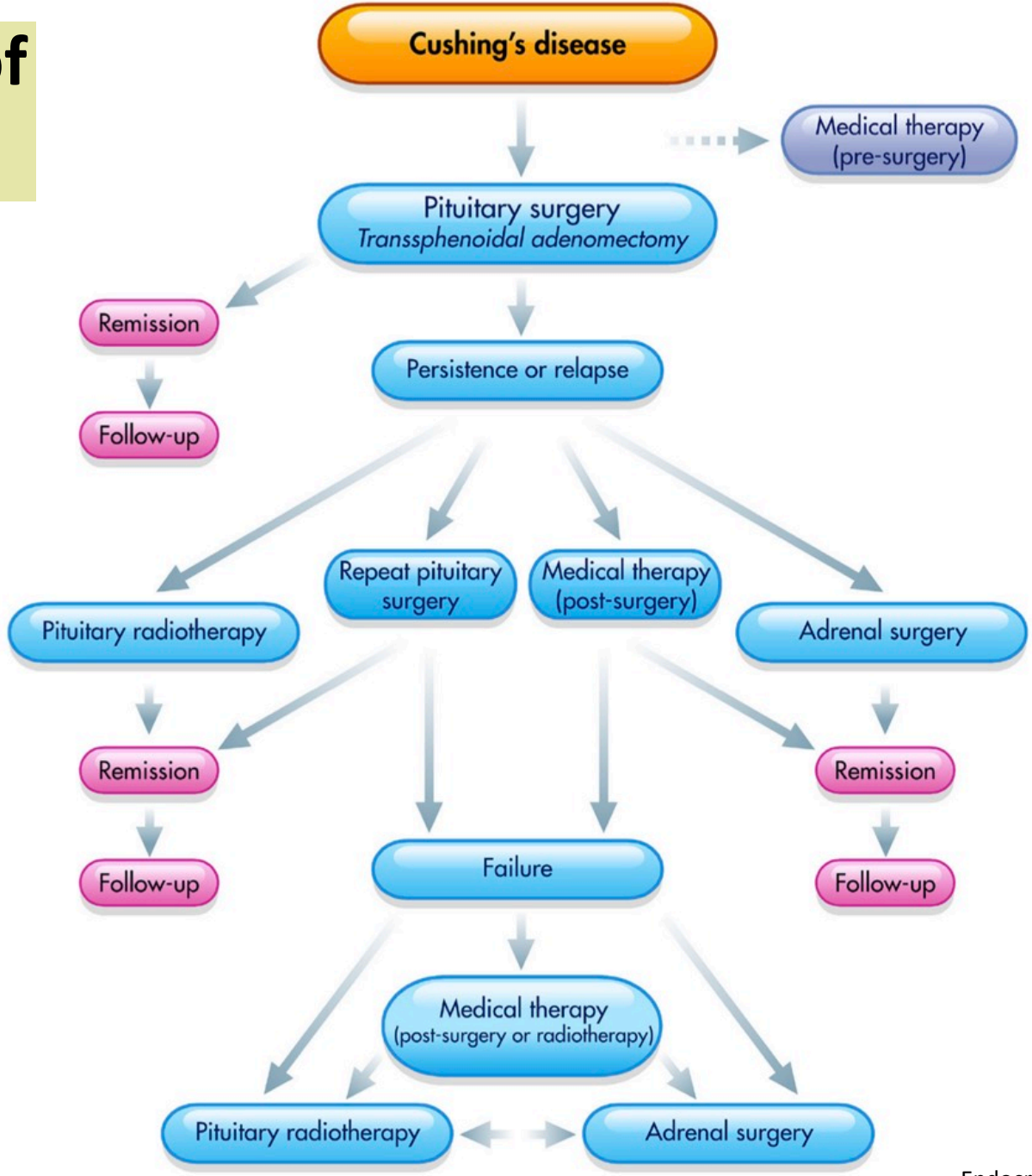
TRANSFORMATION FROM SCA INTO BIOCHEMICALLY CUSHING'S DISEASE

- Rare
- Case report
- Role of the PC1/3 expression in the transformation of phenotype from SCA to CD

Postoperative expression of Cushing disease in a young male: metamorphosis of silent corticotroph adenoma?

Endocrinol Diabetes Metab Case Rep. 2019; 2019: 19-0046.

Treatment strategy of Cushing disease



Endocrine Reviews, August 2015, 36(4):385–486

PREOPERATIVE MANAGEMENT

- Control Hypercortisolism
- Antihypertensive drug
- Thromboembolism prophylaxis

HYPERTENSION IN PATIENTS WITH CUSHING'S SYNDROME

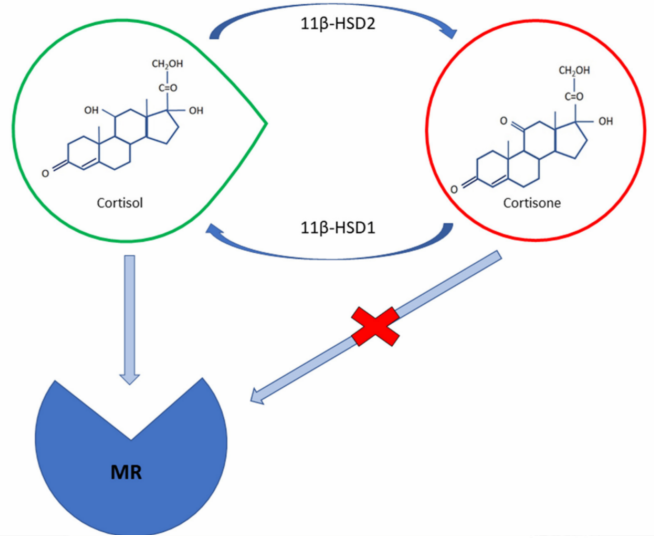
TABLE 1. Mechanisms involved in the pathogenesis of hypertension induced by glucocorticoid excess in human studies

	Human studies	Reference
Renin–angiotensin system (RAS)	↑ Angiotensinogen	[29,30,33]
	↑ DBP in response to peripheral administration of Ang II	[29,33]
	↑ AT-II 1A receptor in blood cells	[32]
Mineralcorticoid activity	↑ 11β-HSD 2 saturation	
	↑ Plasma volume	
Sympathetic nervous system	↑ Sensitivity to β receptor agonists	
Vasoregulatory system	↑ Endothelin 1 (ET-1)	
	↑ Erythropoietin (EPO) in GC-treated patients	
	↑ Circulating ANP	
	↓ ANP activity	
	↓ Nitric oxide pathway	
	↓ Urinary PGE2	
	↓ of PGI_2 production	
	↓ Urinary kallikrein	
	↑ Urinary kininase I, II, NEP	

Overall increased throughout in the RAS

Esp. in Pt with severely edema and hypokalemia

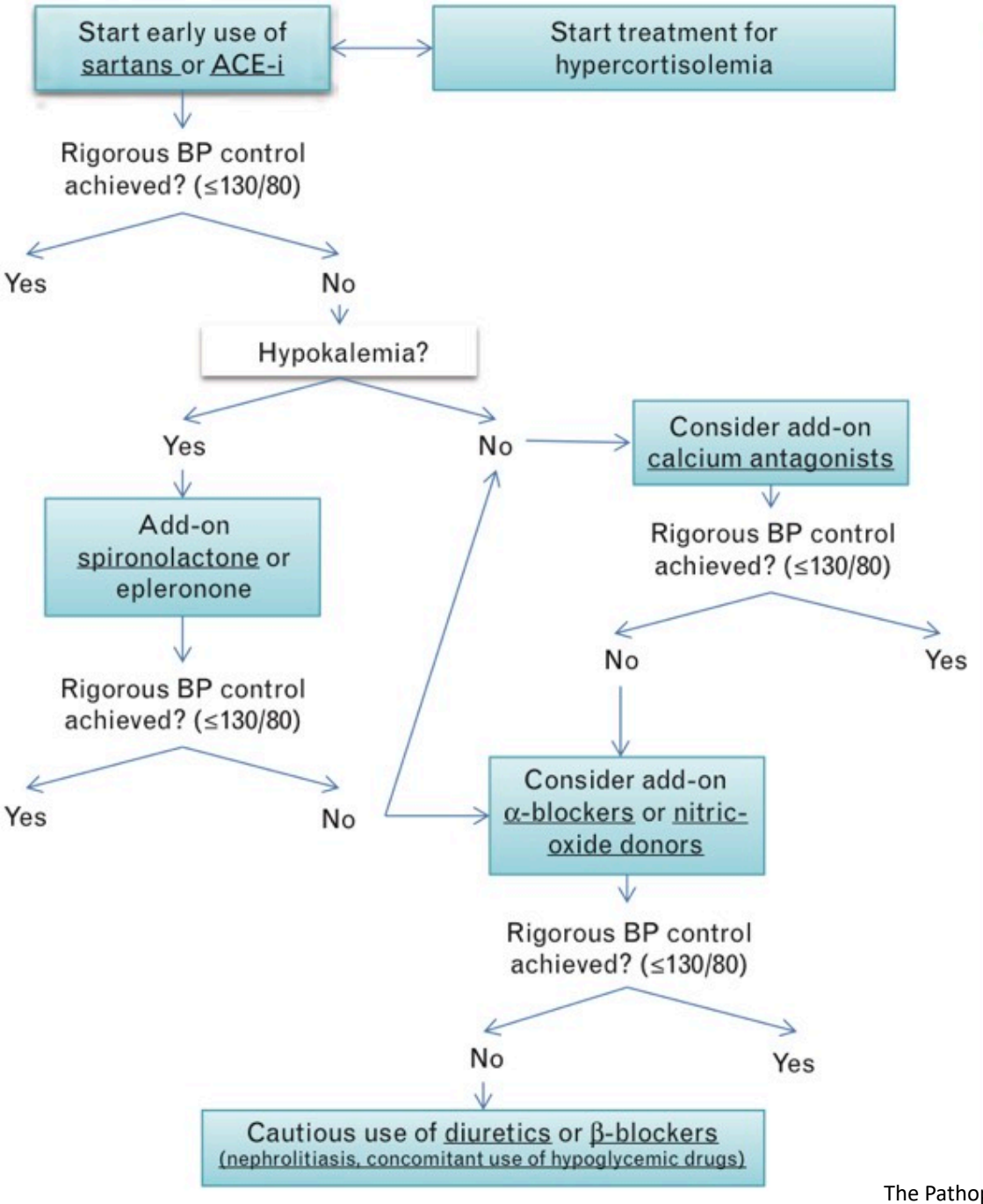
↑Sensitivity of angiotensin receptor



11β-HSD 2,11β-Hydroxysteroid dehydrogenase type 2; Ang II, angiotensin II; ANP, atrial natriuretic peptide; AT 1A, angiotensin type 1A receptor; CS, Cushing's syndrome; MR, mineralcorticoid receptor; NEP, neutral endopepeptidase; PGE2, prostaglandin E2; PGI_2 prostacyclin; VEGF, vascular endothelial growth factor.

Journal of Hypertension 2015, 33:44–60

The Pathophysiology and Treatment of Hypertension in Patients With Cushing's Syndrome. Front. Endocrinol. 10:321.



ACEi/ARB

⬇

CCB or MRA (favor if hypokalemia)

Journal of Hypertension 2015, 33:44–60

The Pathophysiology and Treatment of Hypertension in Patients With Cushing's Syndrome. Front. Endocrinol. 10:321.

TABLE 1 | Cortisol lowering medications, their effectiveness and effects on hypertension in CS patients.

	Drug	Mechanism of action	Dose used	Hormonal control	Effects on BP	Overall effect on BP
Pituitary directed drugs	Cabergoline	Acts through D2R receptors express on adenocorticotroph	0.5–7 mg/week, oral	25–40%	↓cortisol levels ↑vasodilatation through D1 receptors	⇩
	Pasireotide	Somatostatin multi-ligand with particularly high SSTR5	300–1,800 μg/day Twice a day, sc	20–62%	↓cortisol levels	⇩
	Retinoic Acid	Reduces ACTH production through inhibition of AP-I and Nur77/Nurrl transcriptional activities	10–80 mg/day 1–3 times/day, oral	20–50%	↓cortisol levels	⇩
Steroidogenesis inhibitors	Metyrapone	11β-hydroxylase inhibitor	0.5–6 g/day 3–4 times/day, oral	45–100%	↓cortisol levels ↑11-deoxycorticosterone	=
	Ketoconazole	Cholesterol side-chain cleavage complex, 17,20-lyase, 11β-hydroxylase and 17α-hydroxylase inhibitor	200–1,200 mg/day 2–3 times/day, oral	~50%	↓cortisol levels	⇩
	Osilodrostat	11β-hydroxylase and aldosterone synthase inhibitor	4–60 mg/day 2 times/day, oral	~90%	↓cortisol levels ↑11-deoxycorticosterone	=
	Mitotane	Inhibition of steroid synthesis (inhibition of SOAT1, intracellular toxic lipid accumulation) + adrenolytic action	2–5 g/day 2–3 times/day, oral	~70%	↓cortisol levels ↓aldosterone levels	⇩
GR antagonist	Mifepristone	Glucocorticoid receptor antagonist	300–1,200 mg/day Once daily, oral	NA	↓cortisol action on GR ↑cortisol levels and its action on MR	⇧ ⇩

↑ *means increase;* ↓ *decrease;* = *neutral effect.*

The Pathophysiology and Treatment of Hypertension in Patients With Cushing's Syndrome. Front. Endocrinol. 10:321.

THROMBOEMBOLISM PROPHYLAXIS

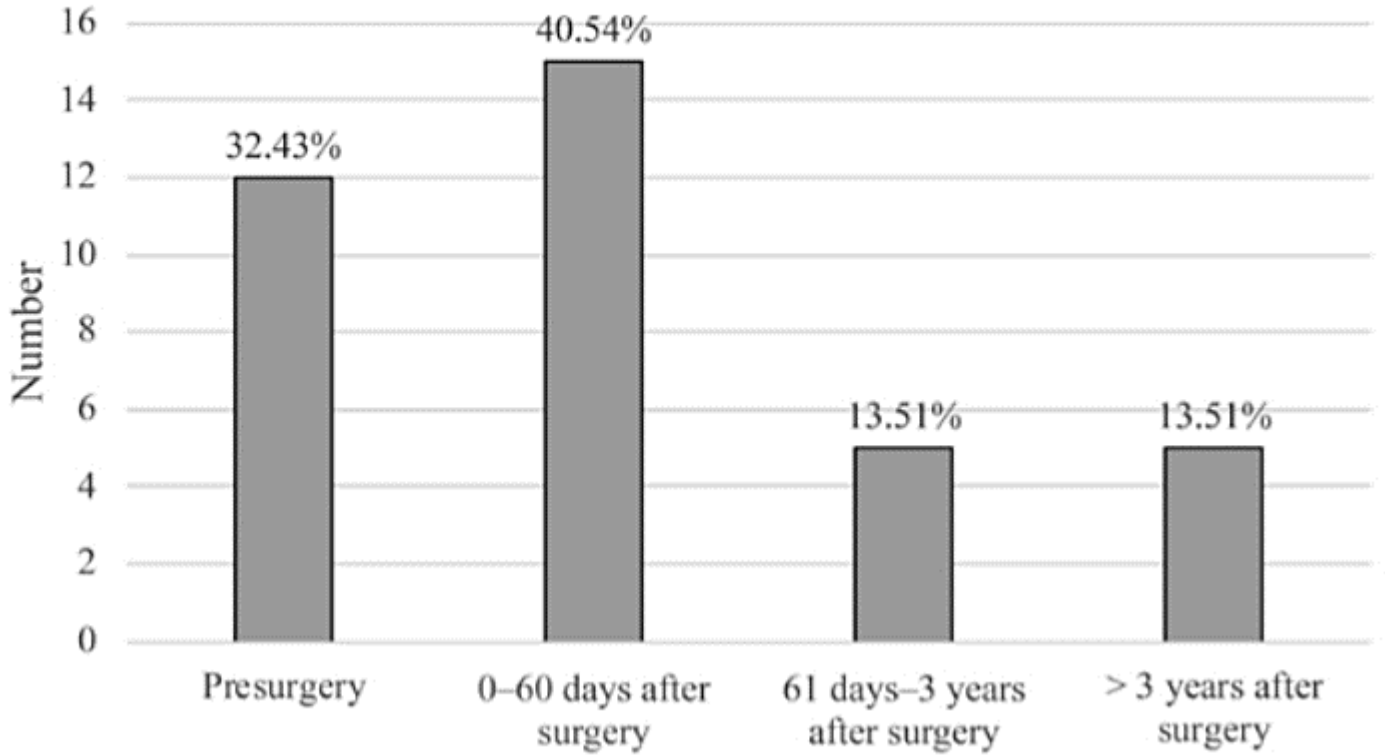
Increase thrombosis risk

- Cortisol excess stimulate synthesis of several clotting factors e.g., fibrinogen, factor VIII, von Willebrand factor and plasminogen activator inhibitor
- Increased homocysteine and taurine
- Consequence of metabolic syndrome
  - Increase risk especially within 4 week after surgery and alter coagulation profile upto 1 year after surgical cure

Perioperative prophylaxis for VTE is suggested

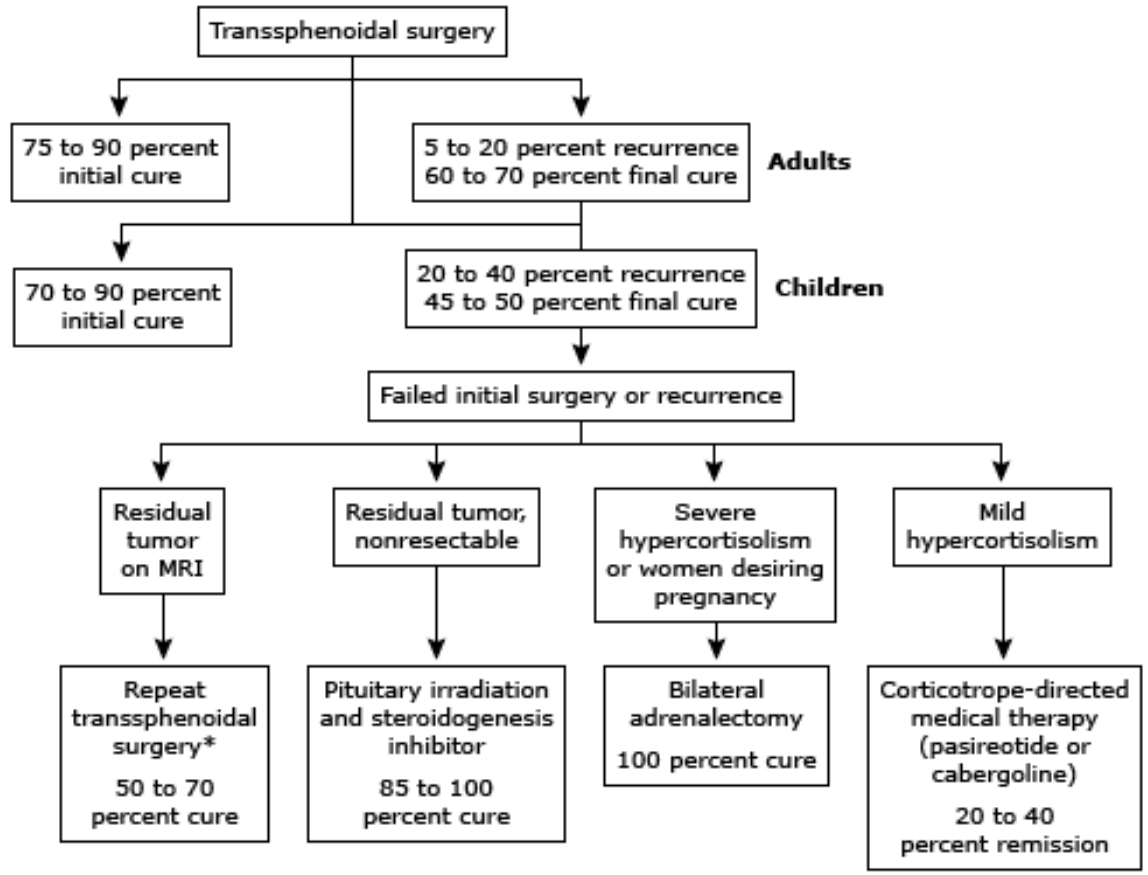
- The optimal prophylactic anticoagulation duration is unknown.

INTERVAL FROM SURGERY TO THROMBOTIC EVENT



Journal of the Endocrine Society | doi: 10.1210/jendso/bvz033

Treatment of Cushing's disease



MRI: magnetic resonance imaging.

* The choice of treatment after failed transsphenoidal surgery should be individualized for each patient based upon the presence of dural or cavernous sinus invasion, the presence of a surgical target on MRI, the location of tumor in relationship to optic nerves, the need for prompt resolution of hypercortisolism, contraindication to specific medical therapy, and the patient's values and preferences.

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PITUITARY SURGERY: TRANSSPHENOIDAL ADENOMECTOMY

Remission rate

- Microadenoma 73-76%
- Macroadenama 43%

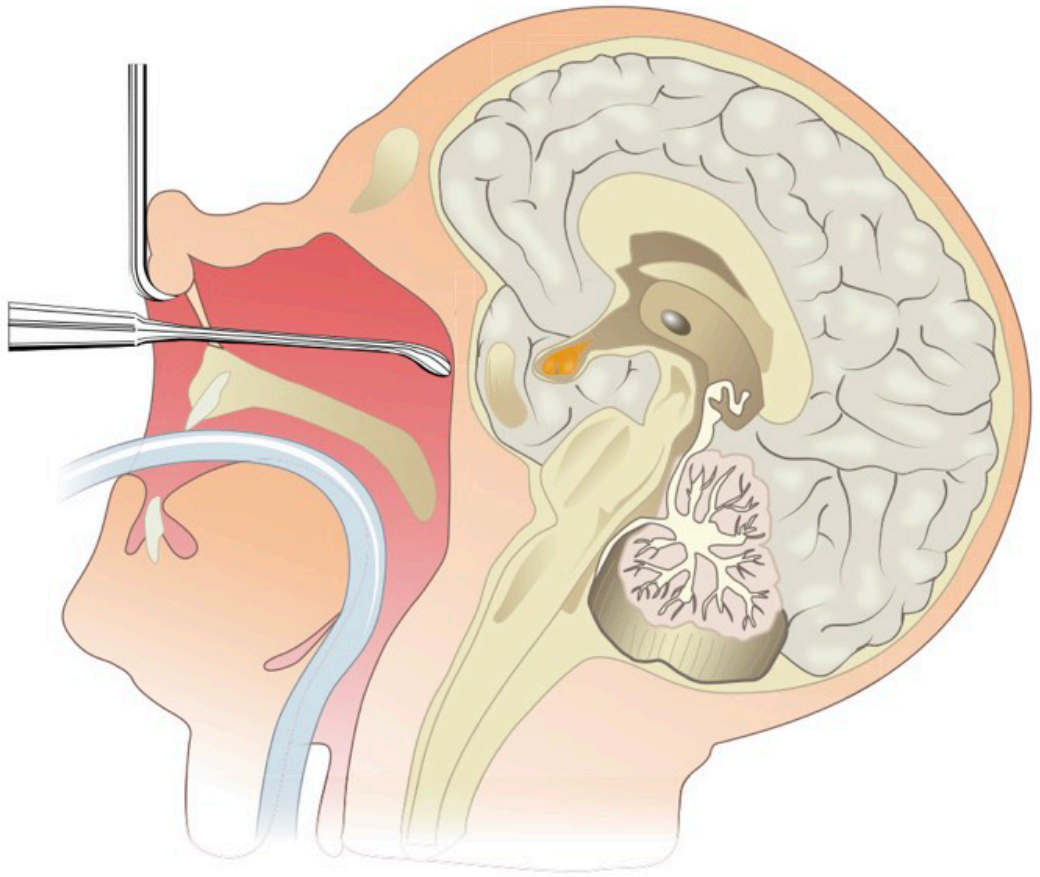
15-66% relapse within 5-10 year

Initial remission:
morning serum cortisol < 5µg/dL or UFC < 10-20 µg/d within 7 day of tumor resection

J Clin Endocrinol Metab. 2015 Aug; 100(8): 2807–2831.

Factors predicted Sx unfavorable outcome

- Male gender
- Macroadenoma with diameter >2 cm
- Tumor with suprasellar extension
- Tumor with cavernous sinus invasion
- No tumor identification at pre-surgical imaging evaluation
- No tumor identification at surgical intervention
- No tumor identification at post-surgical pathological examination
- Surgeon inexperience



Endocrine Reviews, August 2015, 36(4):385–486

Literature review: clinical outcomes after initial surgery for Knosp grades 3 and 4 adrenocorticotropic hormone-secreting pituitary adenomas.

Authors, year	Patient characteristics		Surgery approach	Remission rate	Initial remission criteria (cited from the original articles)
Shin et al. (2017)[23]	CD	N=50	Endoscopic endonasal approach	3/6 for Knosp 3–4	Symptoms of adrenal insufficiency requiring HRT, 36-h PO fasting nadir cortisol level ≤5 μg/dL, and/or 8 AM cortisol level ≤5 μg/dL within 2 wk PO
	Knosp 3–4	N=6			
Witek et al, (2016)[19]	CD	N=59	Transsphenoidal approach	0/4 for Knosp 3 0/6 for Knosp 4	6 AM nadir serum cortisol level ≤2.5 μg/dL within 2 d PO
	Knosp 3	N=4			
	Knosp 4	N=6			
Wagenmakers et al, (2013)[17]	CD	N=86	Transsphenoidal approach with endoscope	3/8 for Knosp 3 1/3 for Knosp 4	Disappearance of clinical symptoms of hypercortisolism, and cortisol levels <1.8 μg/dL (50 nmol/L) within 2 d PO, and/or normal suppressive response to LDDST (<1.8 μg/dL) within 3 mo PO
	Knosp 3	N=8			
	Knosp 4	N=3			
Kuo et al, (2015)[22]	CD	N=40	Endoscopic transsphenoidal approach	2/5 for Knosp 4	Morning serum cortisol <5 mg/dL, or 24-h UFC <20 mg/24 h, or normal 24-h UFC PO.
	Knosp 3	N=0			
	Knosp 3	N=5			
Ceylan et al, (2010)[21]	CD	N=20	Endoscopic endonasal transsphenoidal approach	3/4 for Knosp 3–4	Normal 24-h UFC and circadian rhythm of plasma cortisol levels, and serum cortisol level of 2 μg/dL after 2-mg dexamethasone-suppression overnight
	Knosp 3	N=2			
	Knosp 4	N=2			

Zhuang et al. Medicine (2018) 97:46

RADIATION THERAPY

- Conventional RT
- Stereotactic RT

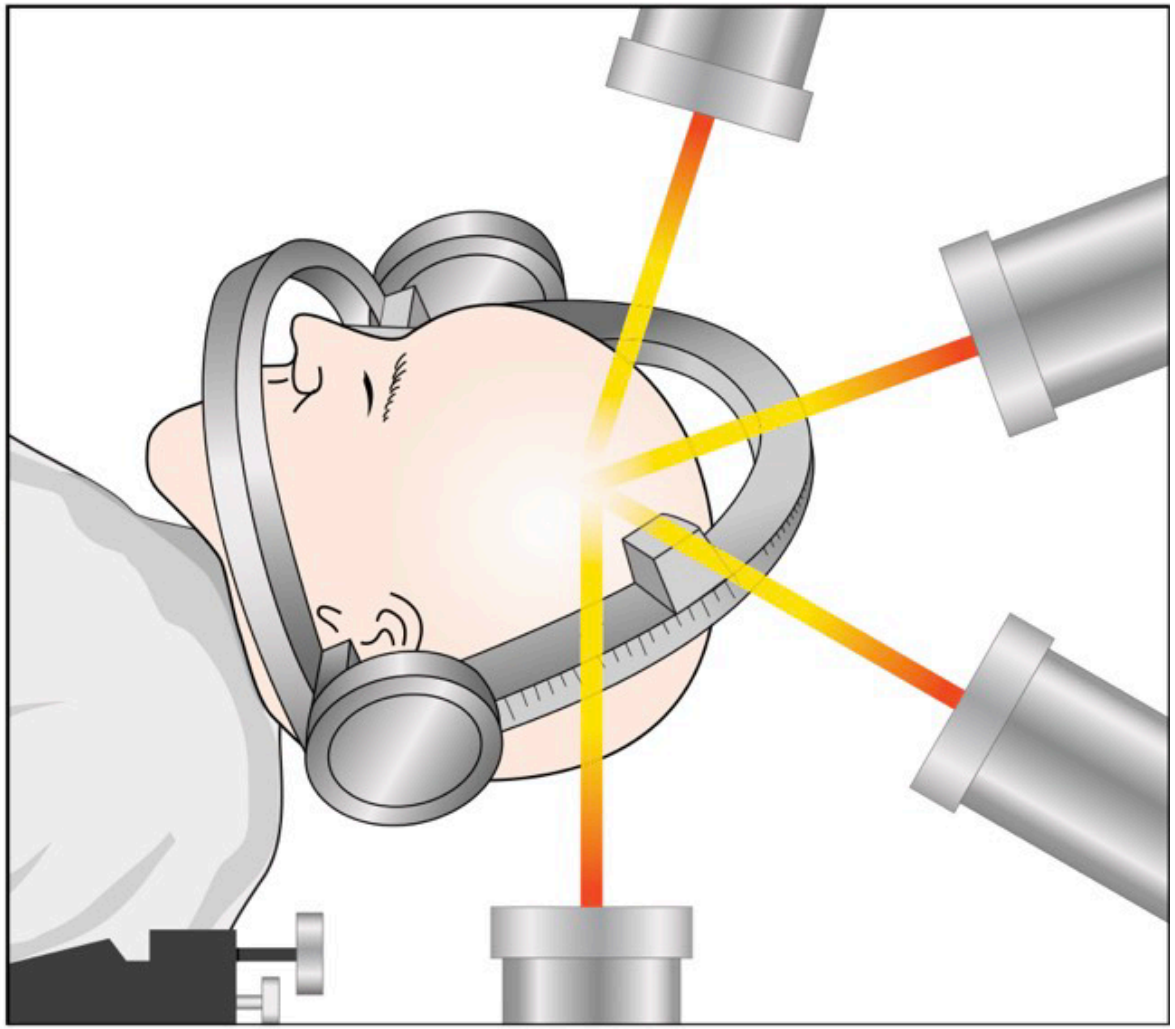
:Control hormonal hypersecretion and tumor growth

PRO	CON
Good rate of antisecretory efficacy • Long term control upto 10 years	Hypopituitarism Secondary brain tumor • Highest risk in who received RT before age of 30 years • Glioma, Meningioma Optic nerve damage and ophthalmoplegia Cerebrovascular disease

European Journal of Endocrinology (2019) 180, D9–D18

Factors predicted SRT unfavorable outcome

- Tumor remnants diameter (>10 mm)
- Distance from optic chiasm (<5 mm)
- Presence of hormone suppressive medication at start of radiotherapy



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Outcome of pituitary conventional radiation therapy

First Author, Year (Ref.)	No. of Patients	Follow-Up, mo	Dose, Gy	Remission Rate, %	Time to Remission, mo	Recurrence Rate, %	Time to Recurrence, mo	Tumor Control Rate, %	Hypopituitarism, %	Optic Nerve Damage, %
Orth, 1971 (298)*	51	R:12–168 M:108	45	19.6	NA	NA	NA	NA	0	0
Edmonds, 1972 (299)*	15	R:48–120	R:35–50	60	R:1–6	11.1	M:18	NA	NA	NA
Ross, 1979 (300)*	13	M:48	46	61.5	NA	62.5	NA	NA	NA	NA
Ahmed, 1984 (301)*	19	R:12–96 M:43.2	20	36.8	R:6–12	0	na	NA	0	NA
Sharpe, 1985 (302)*	8	R:60–144 M:108	43	100	NA	12.5	M:120	NA	100	NA
Howlett, 1989 (303)	30 (21,* 9)	R:69.6–186 M:123.6,* m:114* M:52.2 m:36.2	45	57.1,* 55.6	NA	0	na	100,* 100	28.6,* NA	0
Littley, 1990 (304)*	24	R:13–171 M:99.4 m:93	20	45.8	R:4–36 M:15.9 m:16	45.4	R:18–63 M:50.7 m:50.6	NA	66.7	0
Vicente, 1991 (305)	10	R:18–42 M:29.1 m:27	50	80	R:12–36	0	na	NA	30	NA
Tran 1991 (306)	3 (2,* 1)	R:30–250 M:84	49	100	NA	NA	NA	NA	77.7**	0
Murayama, 1992 (307)*	20	R:24–300 M:148.8 m:114	54	80	R:2–28 M:10.2 m:6.5	25	R:60–84 M:5.7 m:5.5	100	30	0
Zierhut, 1995 (308)	7	R:12–216 M:84	45	57.1	R:16–104	5.3**	R:9–98** M:34.8**	94.1**	58.5**	1.4**
Sonino, 1996 (159)	42 (19,* 23)	R:24–216 m:120	R:45–50	73.7,* 39.1	NA	50,* 0	NA	NA	NA	NA
Tsang, 1996 (309)	29 (8,* 3, 18***)	R:1–223 m:87.6	R:40–52	55.2	NA	NA	NA	96***	13.9–31.1**	0
Estrada, 1997 (310)	30	R:18–114 M:55 m:42	50	83.3	M:18	0	na	100	23.3	0
Minniti, 2007 (311)	40	R:24–180 m:108	44	80	M:24	0	na	92.5	74.9	0
Total	**341**	**R:1–300 M:81.9 m:86.2**	**R:20–54 M:43.5 m:45**	**R:19.6–100 M:63.8 m:60**	**R:1–104 M:17.4 m:6.5**	**R:0–62.5 M:15.9 m:0**	**R:18–84 M:48.6 m:28.1**	**R:53–100 M:98.5 m:100**	**R:0–100 M:39.3 m:30**	**0**

- Remission rate 63.8%
- Time to remission
  Range 1-104 mo
  Mean 17.4 mo
- Recurrence rate 15.9%
- Time to recurrence
  Range 18-84 mo
  Mean 48.6 mo
- Hypopituitarism 39.3%
- Optic nerve damage 0%

Endocrine Reviews, August 2015, 36(4):385–486

Outcome of pituitary stereotactic radiation therapy

First Author, Year (Ref.)	No. of Patients	Radiosurgery Unit	Follow-Up, mo	Mean Margin Dose, Gy	Remission Rate, %	Time to Remission, mo	Recurrence Rate, %	Time to Relapse, mo	Tumor Control Rate, %	Hypopituitarism, %	Optic Nerve Damage, %
Degerblad, 1986 (318)	29	GK	R:36–108 m:72	NA	48.3	R:12–36	0	na	NA	41.1	0
Levy, 1991 (291)	64	PB	NA	NA	92.2	M:12	15.2	NA	NA	0	0
Ganz, 1993 (319)	4	GK	m:18	25	50	NA	NA	NA	100	NA	NA
Martinez, 1998 (320)	3	GK	R:26–45 m:36	24	100	NA	0	na	33.3	33.3	0
Lim, 1998 (321)	4	GK	R:3–54 M:25.5	25.4	25	NA	NA	NA	NA	1.5*	1.5*
Mitsumori, 1998 (322)	5	LINAC	m:36	15	40	M:8.5	NA	NA	100*	77.1*	0
Morange-Ramos, 1998 (323)	6	GK	R:6–36 m:20	28	66.7	M:6	0	na	100	16.7*	0
Hayashy, 1999 (324)	10	GK	M:14.9	23.9	10	NA	NA	NA	100	0	0
Inoue, 1999 (325)	3	GK	M:24 m:24.3	20	100	NA	NA	NA	100	0	0
Mokry, 1999 (326)	5	GK	R:7.1–71 M:56.3	17	20	NA	0	na	98*	40	0
Laws, 1999 (327)	50	GK	M:12	18	58.9	R:3–48 M:13.7	NA	NA	NA	NA	2.5*
Sheehan, 2000 (328)	43	GK	R:18–113 M:39.1 m:44	20	62.8	R:3–48 M:12.1	11	R:19–38 M:31.3 m:37	100	16.3	2.3
Shin, 2000 (329)	6	GK	R:9–112 M:88.2	32.3	50	R:34–96 M:58.3 m:45	33.3	36	100	0	0
Izawa, 2000 (330)	12	GK	M:26.4 m:10	24.2	16.7	NA	NA	NA	83.3	0	0
Zhang, 2000 (331)	18	GK	R:12–46 m:32.1	32.4	83.3	R:6–12	NA	NA	83.3	NA	NA
Hoybye, 2001 (332)	18	GK	R:144–264 M:204 m:198	NA	83	M:3	0	na	NA	66	0
Kobayashi, 2002 (333)	20	GK	M:64.1 m:60	28.7	35	NA	0	na	100	NA	NA
Pollock, 2002 (334)	9	GK	R:12–115 M:42.4 m:36	20	77.8	R:2–44 m:14	0	na	100*	16.3*	11.1
Wong, 2003 (335)	5	LINAC	R:27–49 M:38	17	100	R:6–18 M:8.4	20	12	NA	0	0
Petrovich, 2003 (336)	4	GK	M:41 m:36	15	50	M:22	100	M:30	50	3.8*	3.8*
Choi, 2003 (337)	9	GK	R:6–98 M:42.5 m:43	28.5	55.6	M:21.1	NA	NA	100	0	0
Devin, 2004 (338)	35	LINAC	R:2–137 M:42 m:23	14.7	48.6	R:1–33 M:7.5	23.5	R:17–64 M:35.5	90.9	40	0
Colin, 2005 (339)	10	LINAC	m:80	NA	100	NA	0	na	98*	36.7*	0
Colin, 2005 (339)	40	GK	m:54.7	29.5	42.5	NA	0	na	NA	35.1*	0
Kajiwara, 2005 (340)	2	GK	R:18–59 M:44 m:50	17.5	50	NA	NA	NA	50	50	0
Kong, 2007 (341)	7	GK	M:36.8 m:35	NA	100	m:26	NA	NA	100	11.5*	0
Jagannathan, 2007 (342)	90	GK	R:12–132 M:41.3 m:45	23	54.4	R:2–67 M:13 m:16	20.4	R:7–60 M:27 m:25	95.5	22.2	5.6
Castinetti, 2007 (343)	40	GK	R:12–120 M:54.7 m:48	29.5	42.5	R:12–48 M:22	0	na	100	15	5
Petit, 2008 (292)	33	PB	R:20–108 M:58.5 m:58	20	51.5	R:5–49 M:14	0	na	93.9	51.5	0
Wein, 2012 (344)	17	GK	R:12–59 m:23	18	58.8	R:15–31 M:23	10	14	50	5.8	0
Zeiler, 2013 (345)	8	GK	R:2–79 M:32.8 m:35	23.6	100	NA	0	na	100	12.8*	2.5*
Sheehan, 2013 (346)	96	GK	R:12–209 m:48	22	69.8	R:1–166 m:16.6	22.4	R:5–120 m:38	97.9	36.4	5.2
Grant, 2013 (347)	15	GK	R:12–96 M:40.2	35	73.3	M:11.7	36.4	R:9–24 M:14.2	100	40	3.2*
Budyal, 2014 (348)	20	SCRT	R:12–144 m:37.5	45	75	R:5–84 m:20	0	na	95	40	0
Wilson, 2014 (349)	36	LINAC	R:2–183.6 m:66	20	22.2	m:27.7	NA	NA	83.3	11.1	NA
Wattson, 2014 (293)	74	PB	R:6–247 m:52	20	75.7	m:31	1.8	84	98.5	62*	1.4*
Total	**850**		**R:2–264 M:48.6 m:47.2**	**R:14.7–45 M:23.6**	**R:10–100 M:60.8 m:57.2**	**R:1–166 M:16 m:24.5**	**R:0–100 M:12.3 m:0**	**R:0–120 M:27.6 m:33.5**	**R:50–100 M:90.9 m:100**	**R:0–66 M:23.1 m:19.3**	**R:0–11.1 M:1.1 m:0**

- Remission rate 60.8%
- Time to remission
  - Range 1-166 mo
  - Mean 16 mo
- Recurrence rate 12.3%
- Time to relapse
  - Range 0-120 mo
  - Mean 27.6 mo
- Hypopituitarism 23.1%
- Optic nerve damage 1.1%

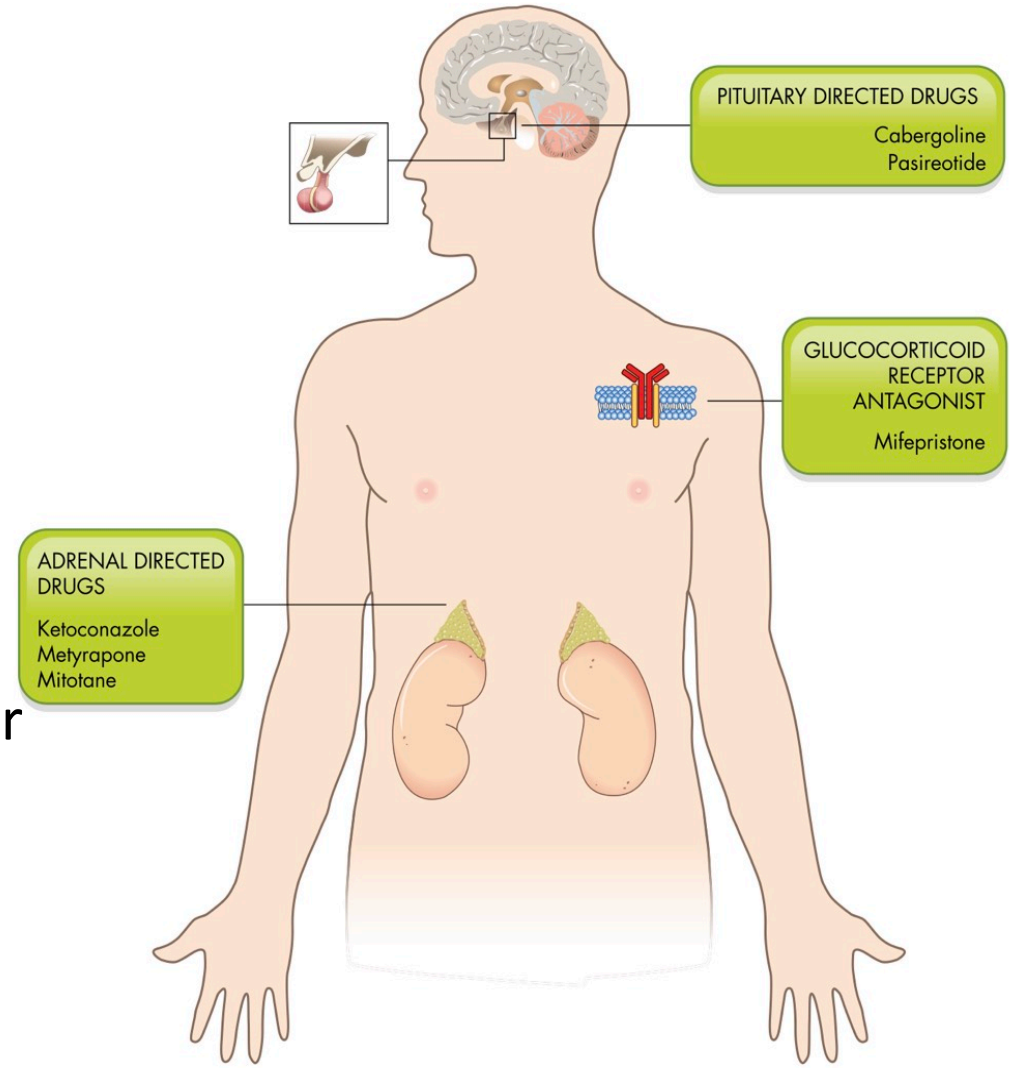
Endocrine Reviews, August 2015, 36(4):385–486

MEDICAL THERAPY

1) Preoperative treatment to control hypercortisolism in patients with severe disease
   - Acutely ill patients e.g., severe infections, recent cardiovascular events (MI or PE), or acute psychosis

2) Adjuvant treatment or Bridging treatment
   - Surgical failure/partial success, while awaiting for definitive treatment
   - Waiting for complete effectiveness of RT

3) Not surgical candidates



Endocrine Reviews, August 2015, 36(4):385–486
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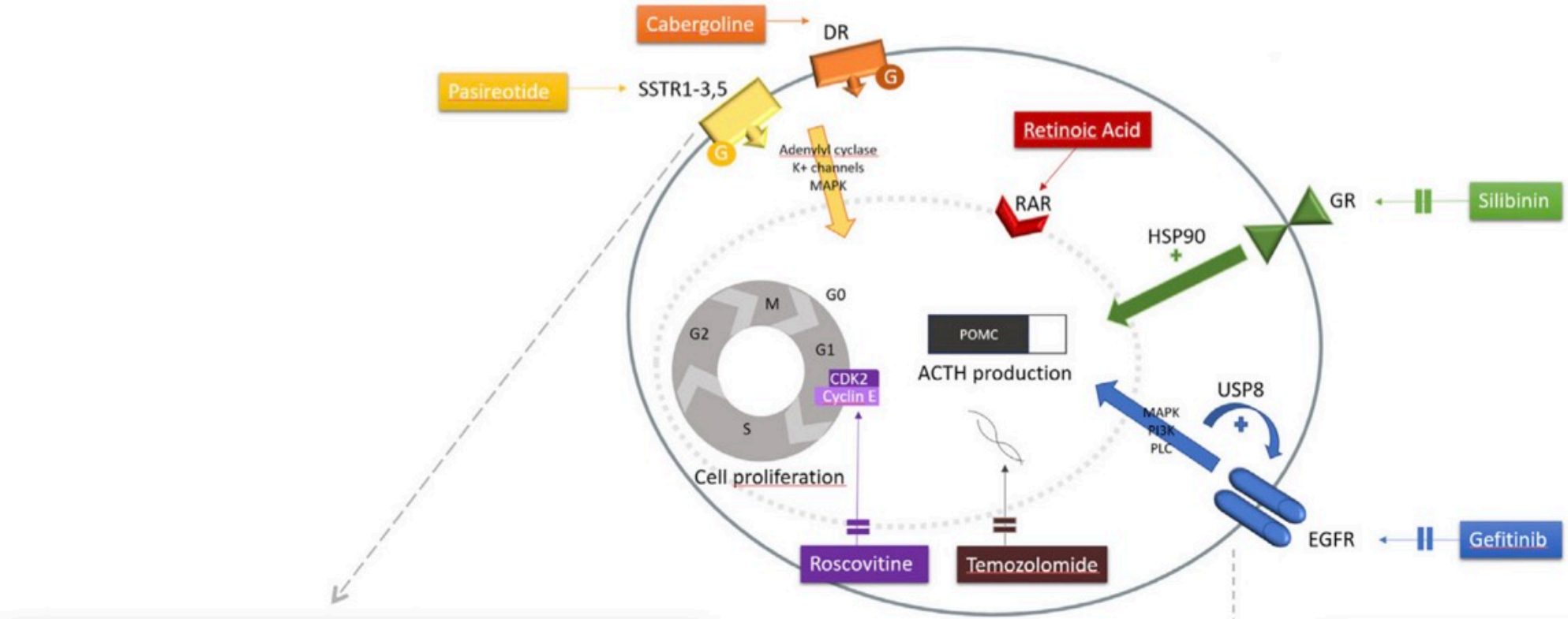
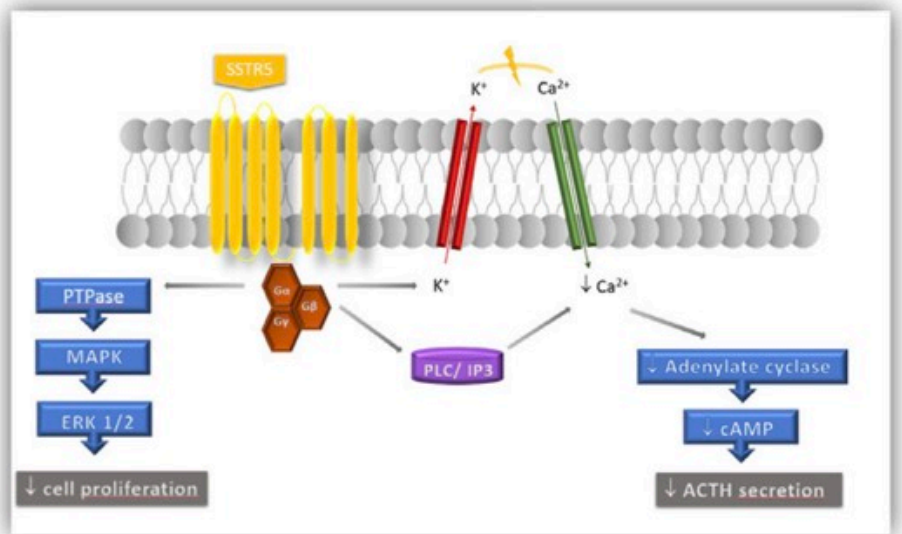
Pituitary directed medical therapy

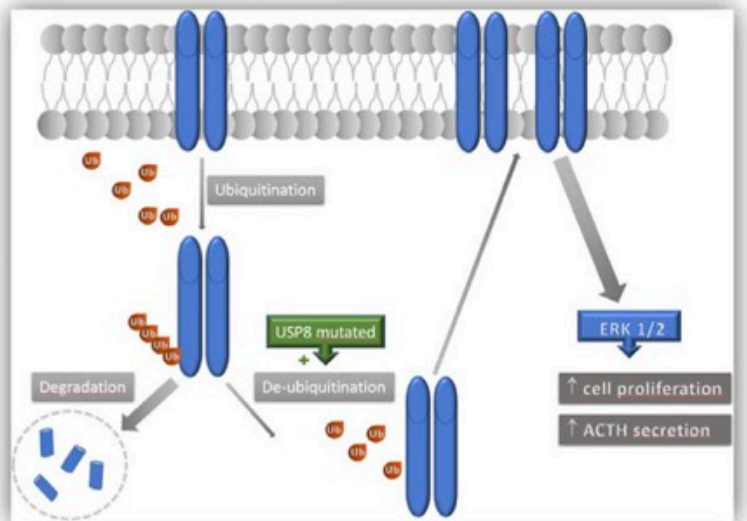
Name	Dose	Route	Mechanism of action	Efficacy to normalize urine free cortisol (%)	Responders characteristics	Tumor size reduction	Side effects	Comments
Pasireotide	600–900 µg twice daily	Subcutaneous	Agonist SSTR5 > 2	30–40	UFC < 5× ULN	25–80%	GI and biliary issues Hyperglycemia QT prolongation	Only drug approved for CD
Pasireotide LAR	10–30 mg monthly	Intramuscular		30–50	UFC < 2× ULN	10–20%		
Cabergoline	0.5–6 mg weekly (in divided doses)	Oral	Dopamine agonist (D2)	25–40	Small subgroup of corticotrophs adenomas expressing D2 receptor	N/A	Hypotension Nausea Headache	Usually short-term response
Temozolomide	150–200 mg/m²/day ×5 days monthly	Oral	Methylation DNA	80	Possibly patients with negative MGMT mutation	0 (stable)–50% for most patients; rarely patients had progressive tumor growth	GI issues Headache Dizziness Hearing loss	Aggressive adenomas or carcinomas
Roscovitine	400 mg twice daily	Oral	Inhibition CDK/cyclin E	N/A	N/A	N/A	Preliminary: Asthenia Nausea Vomiting Hypokaliemia	Phase II study ongoing
Retinoic acid	80 mg once a day	Oral	Agonist RAR	25	Absence of COUP-TF1	N/A	Mucositis Photosensitivity Hypertriglyceridemia	Based on small studies
Gefitinib	250 mg once a day	Oral	Inhibition EGFR	N/A	USP8-mutated adenomas	N/A	Skin reaction Diarrhea Interstitial pneumonitis	Phase II study ongoing
Silibinin	To be determined	To be determined	Inhibition HSP90	N/A	N/A	N/A	Minimal	Animal studies only

In development

Langlois F, Chu J and Fleseriu M (2018) Pituitary-Directed Therapies for Cushing's Disease. Front. Endocrinol. 9:164.



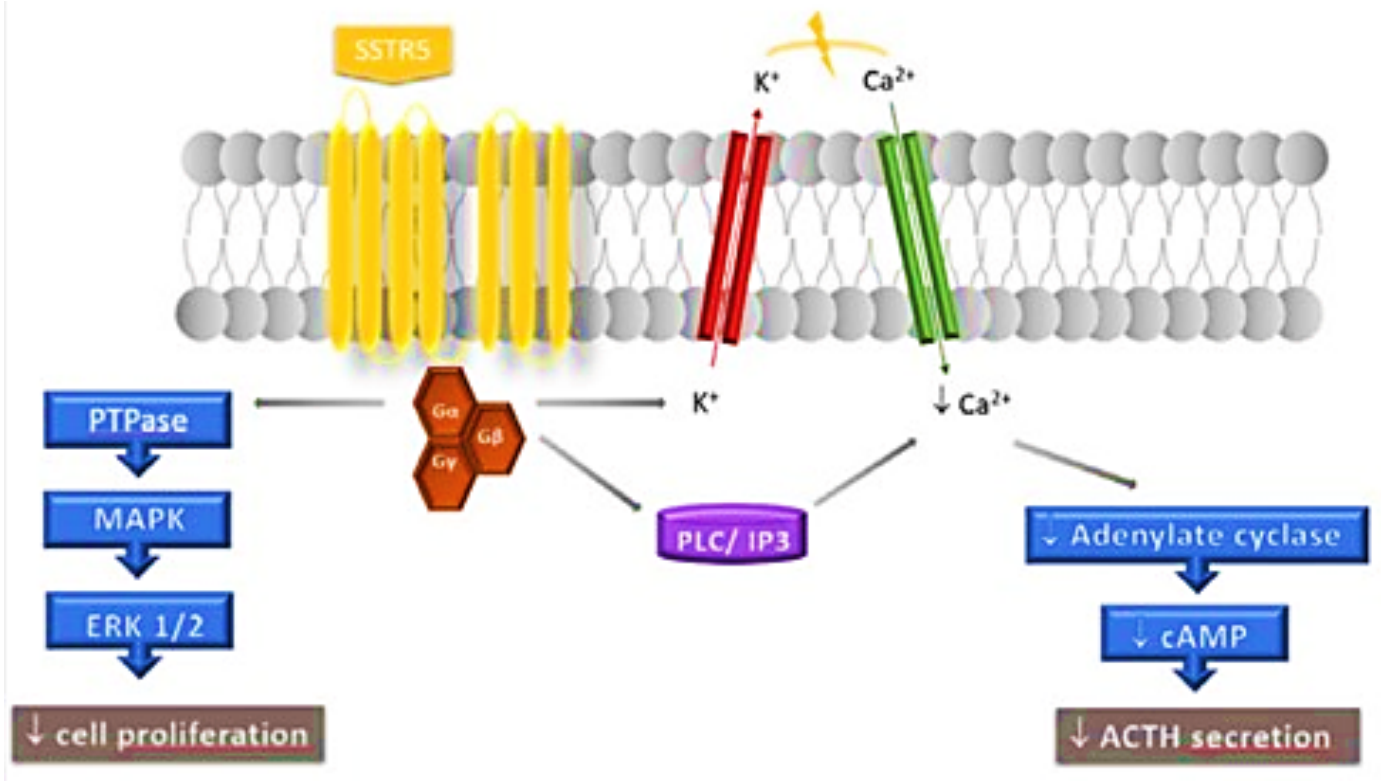




Langlois F, Chu J and Fleseriu M (2018) Pituitary-Directed Therapies for Cushing's Disease. Front. Endocrinol. 9:164.

PASIREOTIDE

- Corticotroph adenomas express mainly SSTR subtypes 5 and 2
- SSTR5 expression is unaffected by high cortisol, whereas SSTR2 is suppressed, but can upregulate with eucortisolemia.
- Pasireotide is a SRL with 40 times the binding affinity to SSTR5 compared with octreotide; it also has high affinity for SSTR1, 2, and 3
  - Restore SSTR2 membrane density thus improving drug efficacy



↓ Tumor size

↓ Hypercortisolism

1. **Short-acting subcutaneous**
- 0.6 or 0.9 mg twice daily
- Titrate ↑↓ 0.3 mg, max UFC reduction observed by 2 mo
- Maintenance: 0.3-0.9 mg sc bid
- Discontinue or combined with other drug if no clinical response to 0.9 mg

2. **Once-monthly IM**
- Pasireotide LAR
- Initial 10 mg IM once a month, increase dose if UFC not normalization within 4 months
- Maximum: 40 mg IM once a month

Side effect:

Hyperglycemia (↓insulin and incretin secretion), gall stone, diarrhea, OT prolonged

Adrenal directed medical therapy

Agent	Mechanism of action	Dose range	Advantages	Limitations
Ketoconazole	Inhibits several adrenal steroidogenic enzymes	200–600 mg orally, 2×/d or 3×/d	Rapid onset of action[a]	Requires gastric acid for absorption; associated with hypogonadism in men; potential for rare but serious hepatotoxicity (regular monitoring advised); potential for drug-drug interactions
Metyrapone	Inhibits 11-β hydroxylase and aldosterone synthase	250-1000 mg orally 3×/d or 4×/d	Rapid onset of action[a]; has been used during pregnancy	Potential for mineralocorticoid and androgenic adverse effects
Osilodrostat	Inhibits 11-β hydroxylase and aldosterone synthase	1-30 mg orally 2×/d	Rapid onset of action[a]	Potential for mineralocorticoid and androgenic adverse effects; potential for drug-drug interactions
Mitotane	Inhibits several adrenal steroidogenic enzymes	0.5-3.0 g orally 3×/d	Cytolytic/cytotoxic[b]; useful activity in adrenocortical carcinoma	Slow onset of action (wks to mos); teratogenic and abortifacient; potential for drug-drug interactions
Etomidate	Inhibits 11-β hydroxylase and cholesterol side-chain cleavage enzyme	5 mg IV bolus, followed by infusion at 0.02-0.3 mg/kg/h	Only agent available for IV use; can control hypercortisolism within hours[c]	Requires careful monitoring for sedation

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COMBINATION THERAPY

Not well-established strategy

Severe hypercortisolism (e.g., ACC, ectopic ACTH secreting tumor, severe ACTH dependent hypercortisolism)

- Ketoconazole, metyrapone, and mitotane
  - Rapid decline in UFC within 48 hr after initiation
- Ketoconazole plus metyrapone therapy

Facilitate disease control and avert the need for urgent bilateral adrenalectomy

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COMBINATION THERAPY

Steroidogenesis inhibitor + 1-2 centrally acting agents

- Ketoconazole plus cabergoline and/or pasireotide

Biochemical control in a higher proportion than single-agent therapy

Need more data: suitable patient characteristic, efficacy and safety

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Adrenal-Directed Rx: Ketoconazole

Benefit

- Rapid action
- Not FDA approved
- Approved in Europe

Risk

- SE: GI disturbances, ↑ liver enzyme, male hypogonadism
- No prospective studies
- Many drug-drug interactions
- Potential escape from Rx response

Fleseriu M. *Endocrinol Metab Clin North Am* 2015;44:51-70.

Adrenal-Directed Rx: Metyrapone

Benefit

- Rapid action
- Not FDA approved
- Approved in Europe

Risk

- SE: GI disturbances, hirsutism, hypertension, hypokalemia
- No prospective studies
- Multiple daily dosing
- Potential escape from Rx response

Fleseriu M. *Endocrinol Metab Clin North Am* 2015;44:51-70.

Adrenal-Directed Rx: Mitotane

Benefit

- Adrenolytic action: approved for adrenal cancer
- Escape unlikely given its adsrenolytic action

Risk

- SE: GI disturbances, neurological disorders, teratogenic actions, adrenal insufficiency (AI)
- No prospective studies
- Slow onset of action

Fleseriu M. *Endocrinol Metab Clin North Am* 2015;44:51-70.

Mifepristone

Benefit

- Approved by FDA to Rx hyperglycemia in adults with endogenous CS
- 50 patients in phase III, doses 300-1,200 mg/d
- Improves glucose and clinical signs & symptoms of CS

Risk

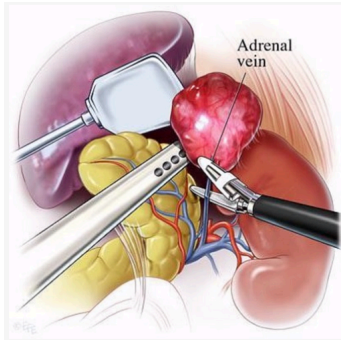
- SE: AI, moderate-to-severe hypokalemia
- Efficacy can only be determined by changes in clinical parameters
  - ACTH & cortisol levels cannot be used to evaluate efficacy
- Thyroid function needs close monitoring
- Does not control tumor volume

Guarda F et al. *Journal of the Endocrine Society* 2019, js. 2019-00188.

Bilateral Adrenalectomy

Benefit

- Involves complete removal of both adrenal glands
- Provides immediate control of hypercortisolism
- Procedure has 84-91% success rate



Risk

- Results in permanent hypoadrenalism requiring lifelong glucocorticoid and mineralocorticoid replacement
- Mortality higher in 1st year post BLA
- Risk of developing Nelson's syndrome
  - Rapid enlargement of corticotrophin adenoma

Biller BMK et al. *BMC Endocr Disord* 2010; 10: 10; Chow JT et al. *Clin Endocrinol (Oxf)* 2008; 68:513-519; Assie G et al. *J Clin Endocrinol Metab* 2007;92:172-179.