

Pituitary radiotherapy for Cushing's disease

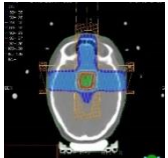
G Minniti

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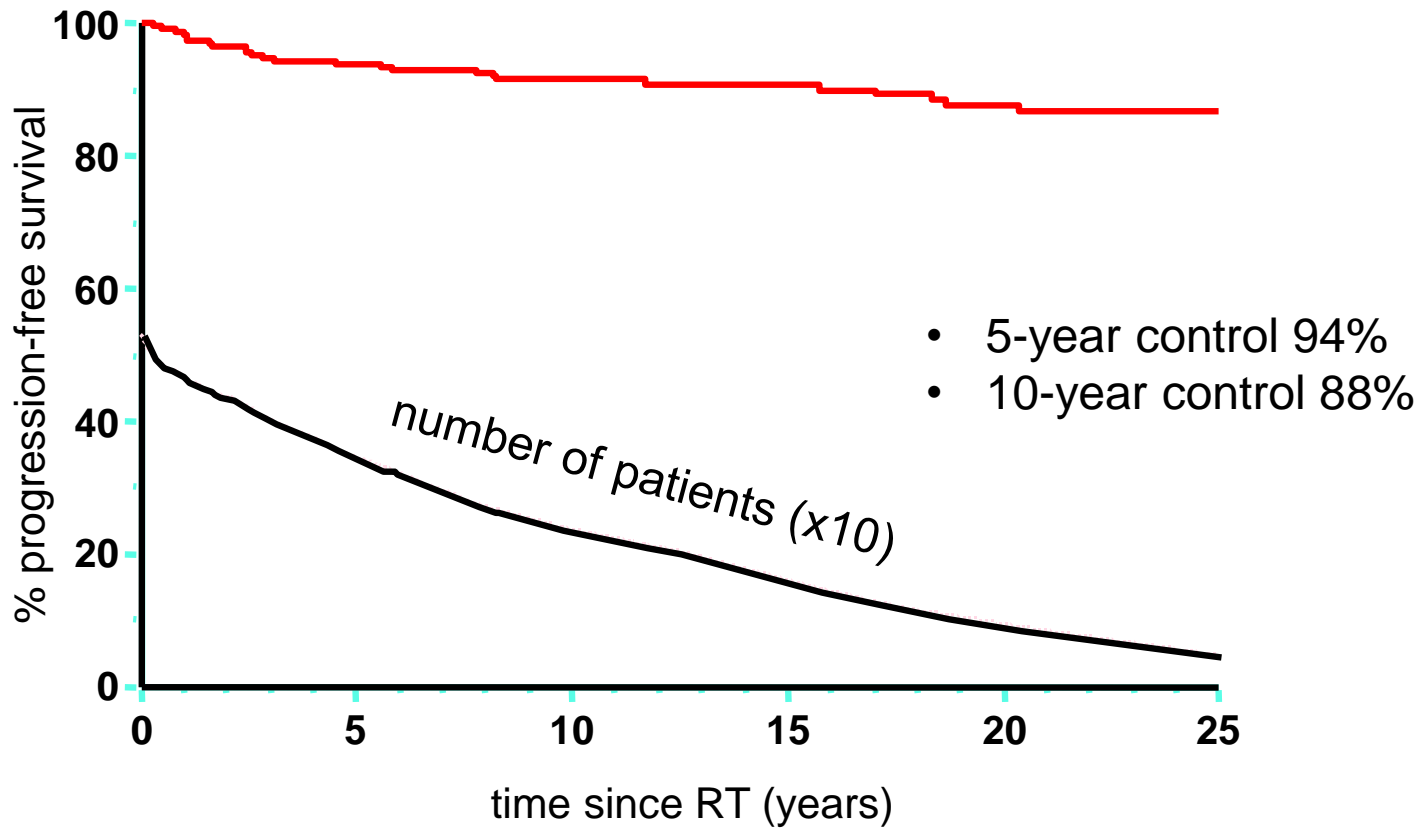
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➤ *Radiotherapy for pituitary adenoma*

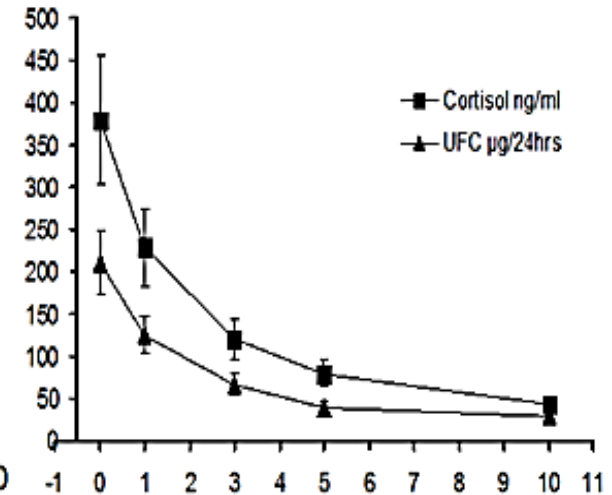
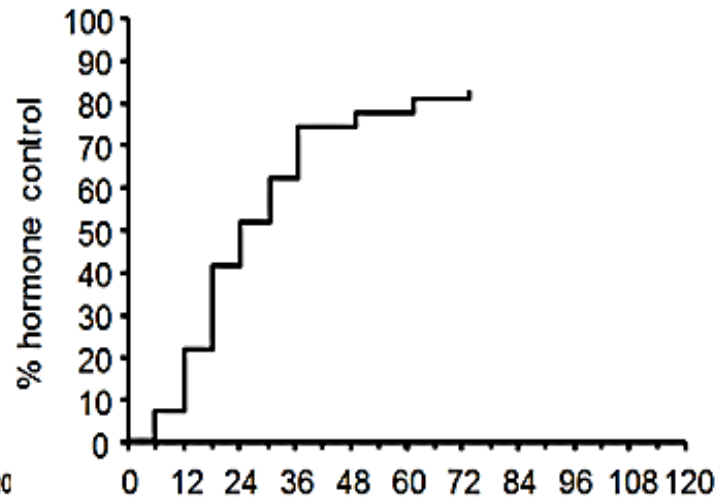
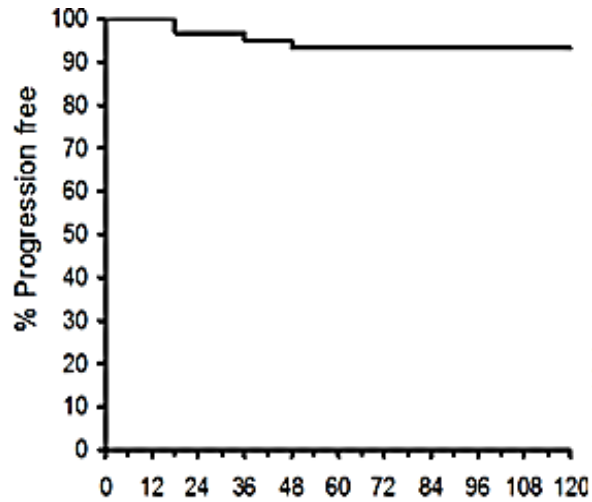
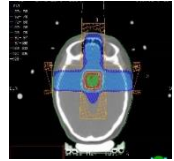
- *tumor control*



✓ *Main published series on conventional RT for Cushing's disease*

<i>Authors</i>	<i>Patients</i>	<i>follow-up</i>	<i>tumor control</i>
<i>Howlett et al., 1989</i>	21	7.9	57
<i>Littley et al., 1990</i>	24	9.5	46
<i>Murayama et al., 1992</i>	24	12.4	55
<i>Tsang et al., 1996</i>	20*	7.3	56
<i>Estrada et al., 1997</i>	29	3.5	83
<i>Storr et al., 2003</i>	30	6.9	100
<i>Minniti et al., 2007</i>	40	8	73 /78 at 3 /5 yrs

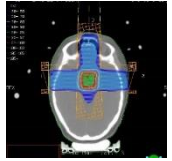
✓ *Progression free survival and hormone control in 40 patients with Cushing's disease after CRT*



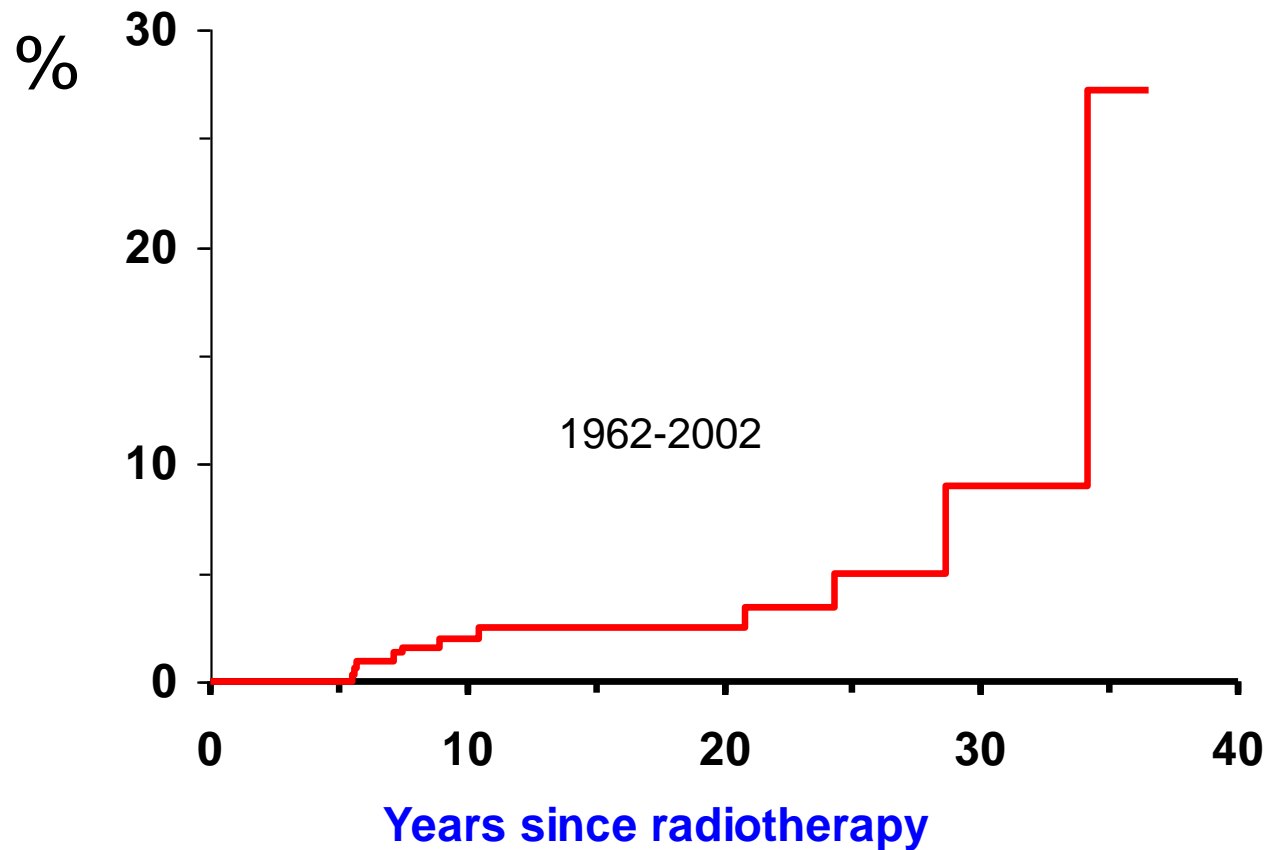
- ✓ *Late toxicity of conventional radiotherapy*
- ✓ *Hypopituitarism (40%-75% at 5 and 10 yrs)*
- ✓ *Radionecrosis (0%-3%)*
- ✓ *Optic neuropathy (0%-8%)*
- ✓ *Cranial nerves deficits (0-5%)*
- ✓ *Neurocognitive effects (0%- ?%)*
- ✓ *Radiation induced tumors (2% at 20-30 yrs)*
- ✓ *Increased CVA (?)*



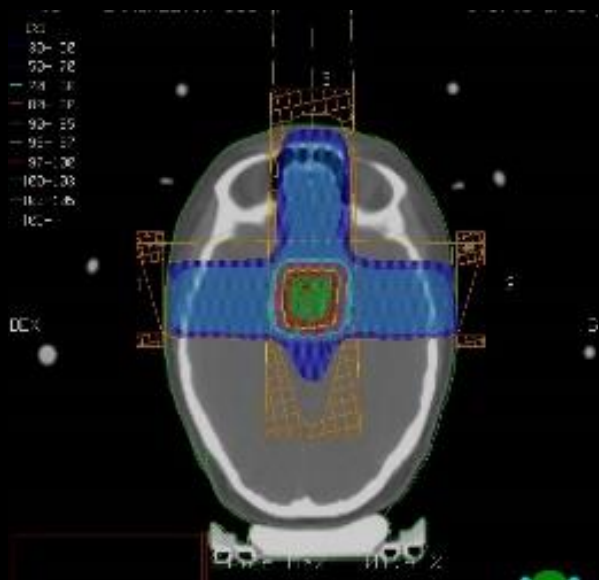
✓ *Second brain tumor in pituitary adenomas*



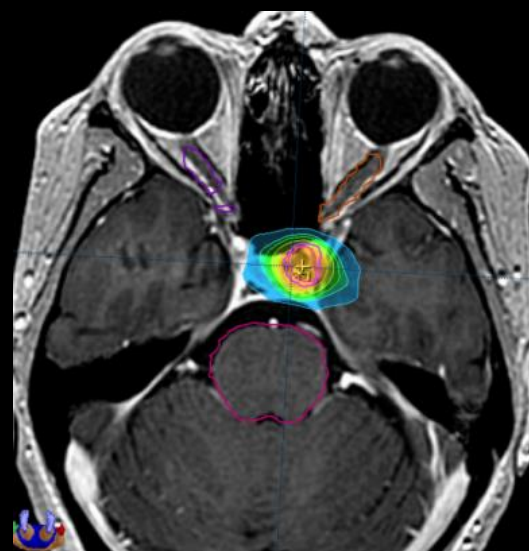
✓ *Cumulative risk of second brain tumor*



What has changed between the early 80s and now?



1980

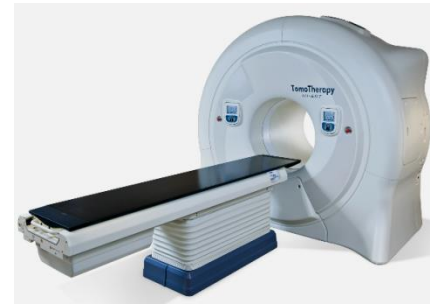


2015



✓ *The modern radiotherapy*

- *Stereotactic conformal radiotherapy (SRT)*
- *Stereotactic radiosurgery (SRS)*
- *Intensity modulated radiotherapy (IMRT)*
- *Tomotherapy*
- *Particle radiotherapy*

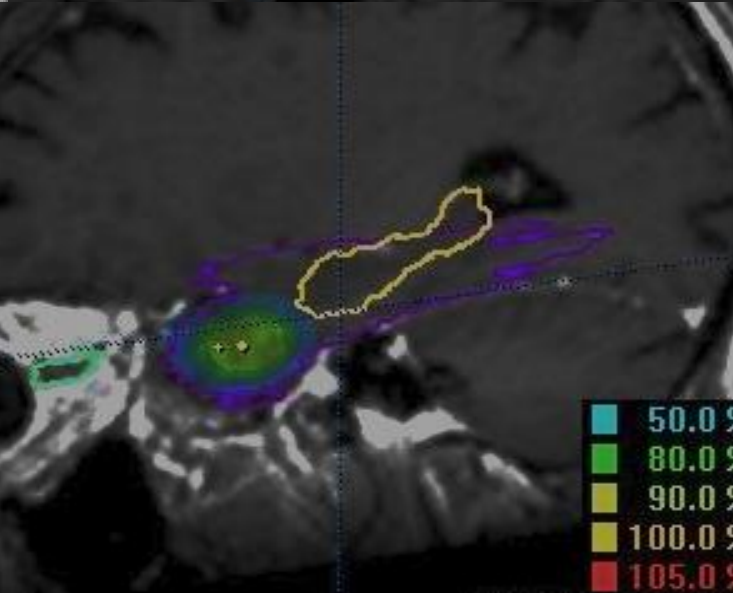
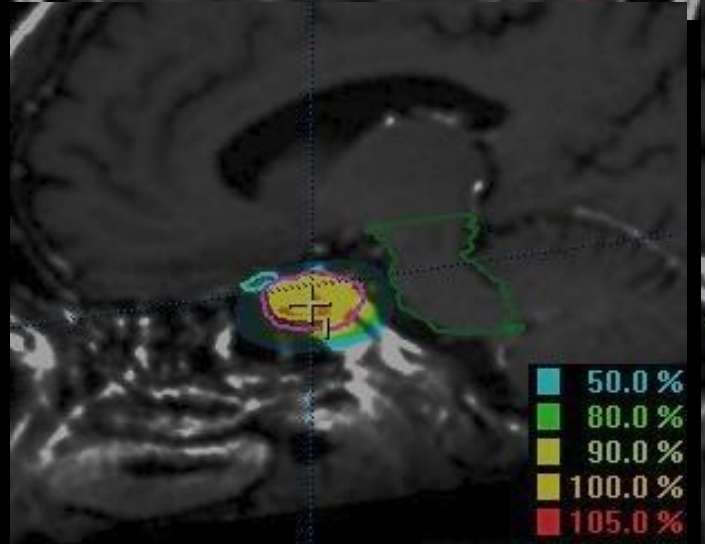
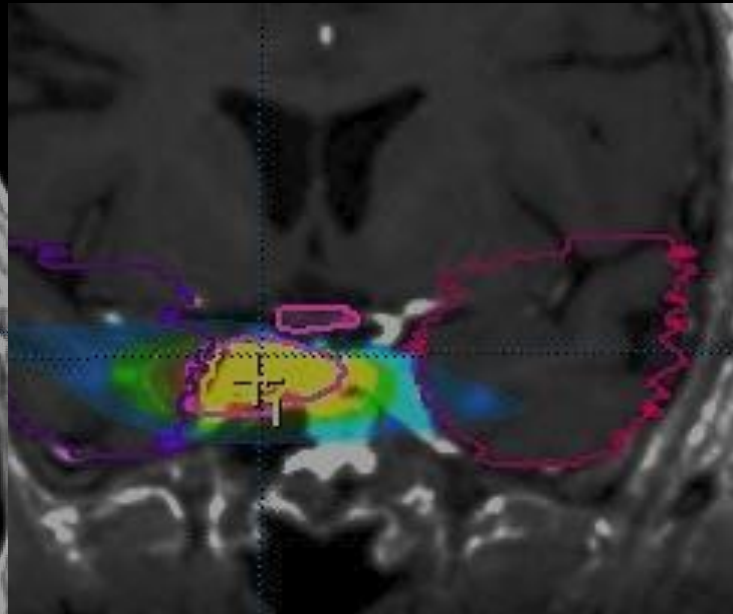
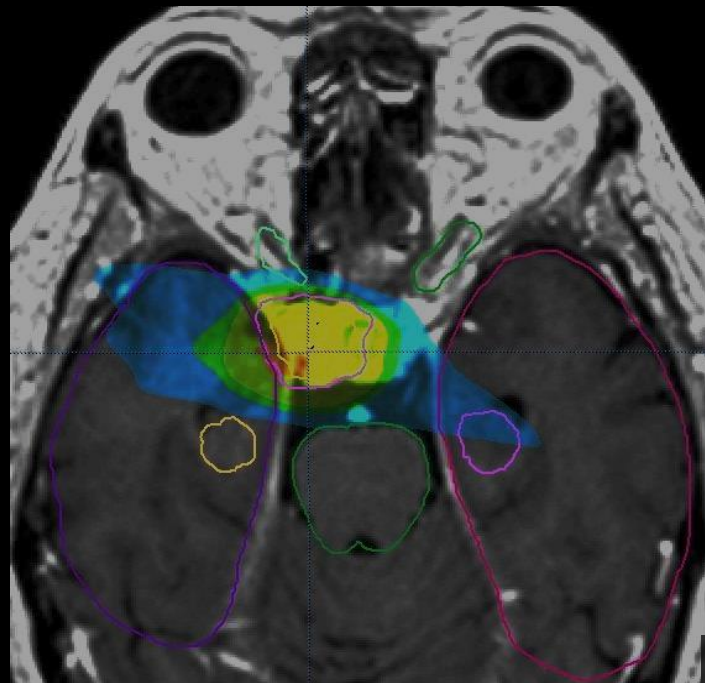


➤ *Stereotactic techniques*

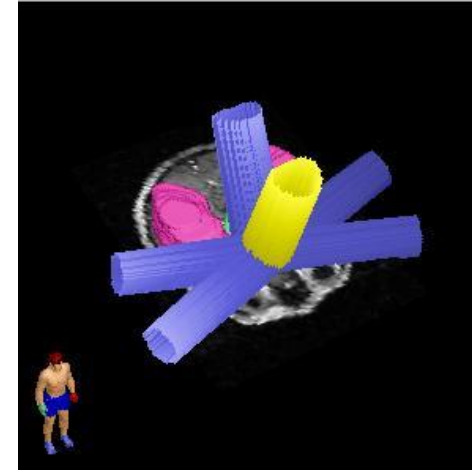
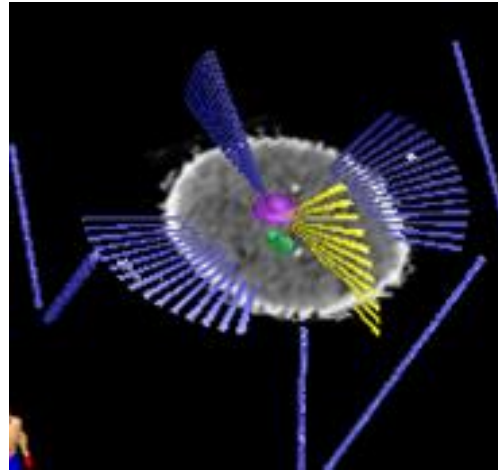
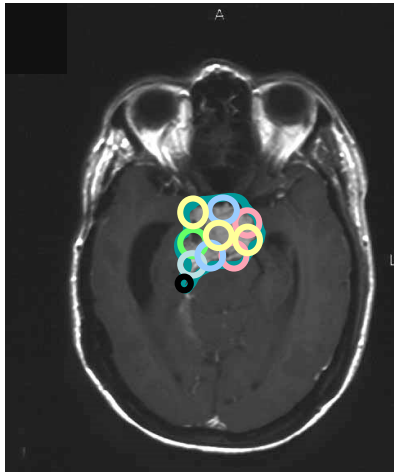
- ✓ *Radiosurgery (SRS) either Gamma Knife (GK), Cyberknife, or a linear accelerator (LINAC), delivered as a single treatment;*
- ✓ *Stereotactic fractionated radiotherapy (FSRT) delivered as a fractionated treatment.*

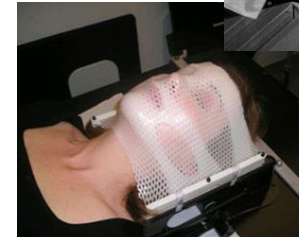
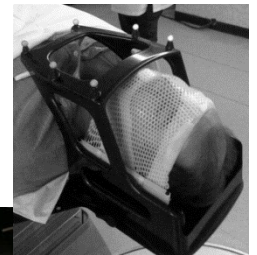
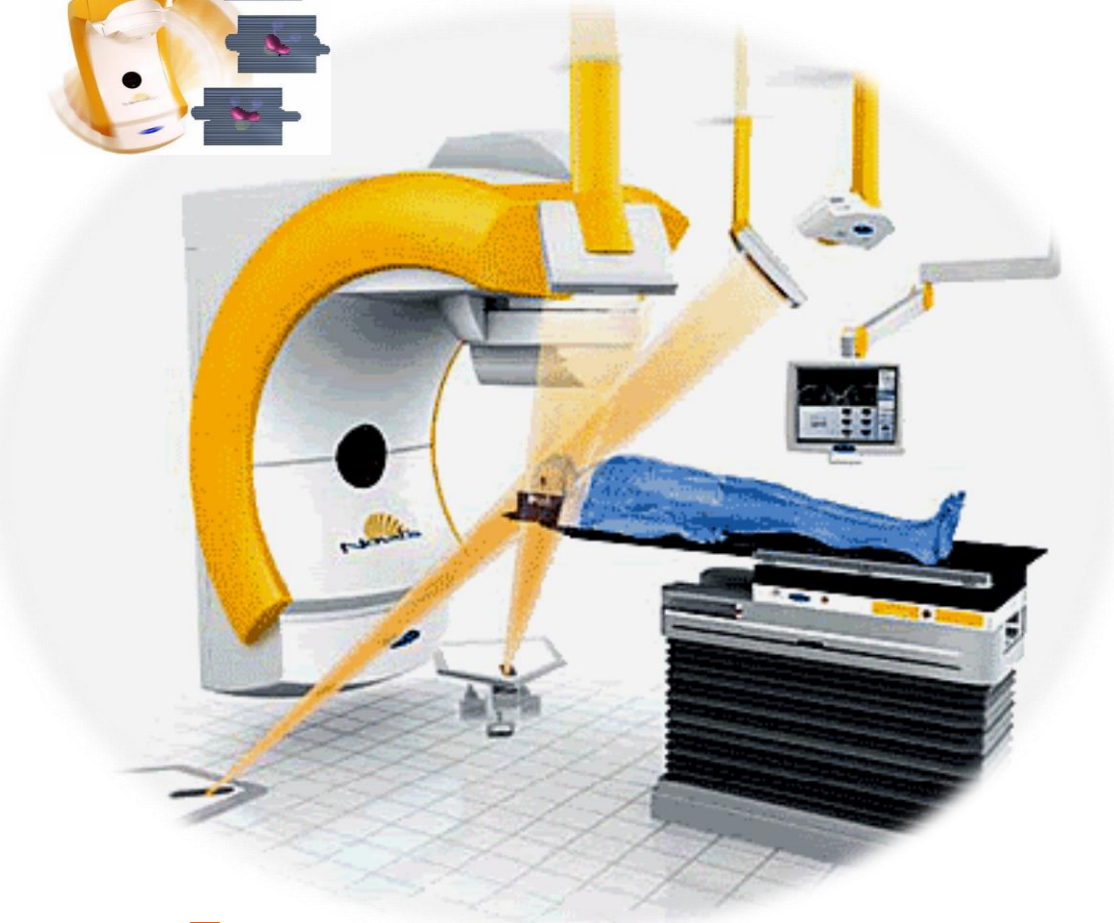
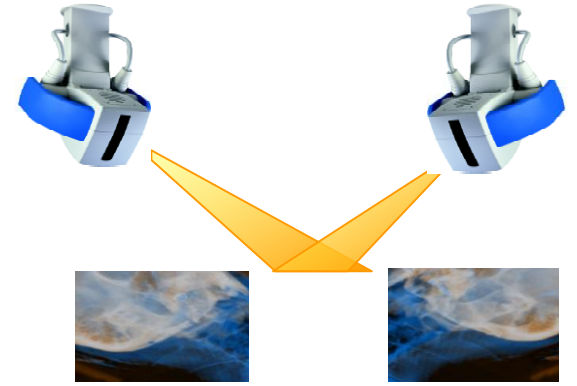
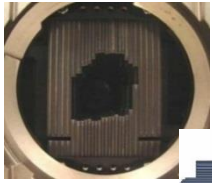


Treatment planning



✓ *Treatment delivery*





✓ *Results of SRT and SRS for ACTH-secreting pituitary adenomas*

✓ *Efficacy*

- *Tumor control*
- *Endocrine control*

✓ *Toxicity*

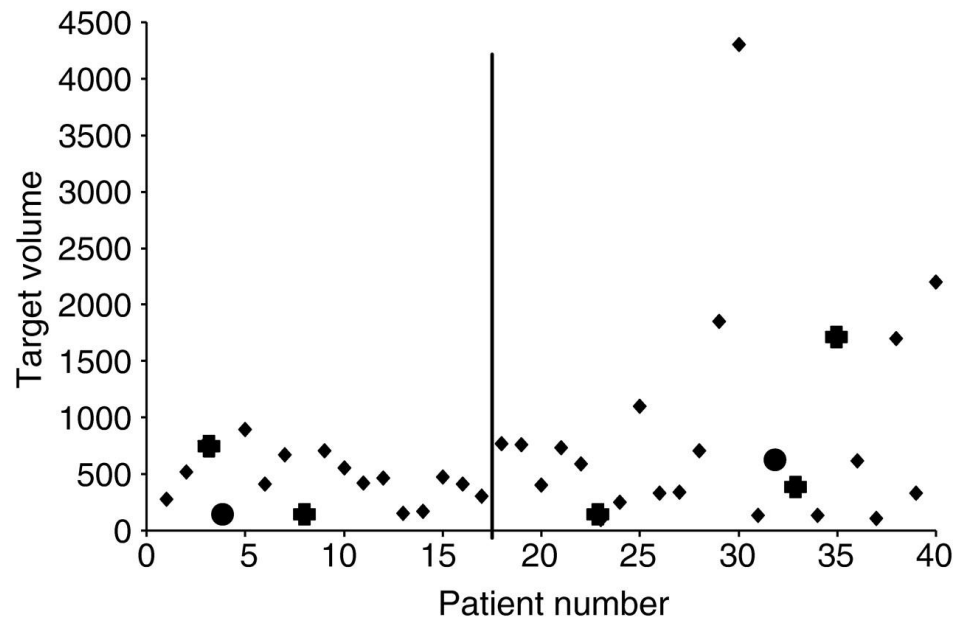
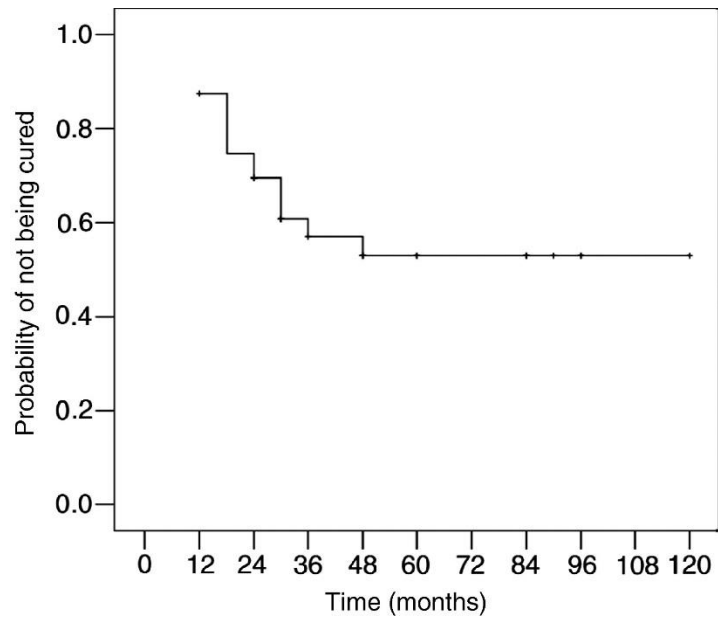


✓ Summary of recent published results of SRS for Cushing disease

Series	Year	Number of patients	Mean/median follow-up (months)	Radiosurgery type	Mean/median margin dose (Gy)	Endocrine remission (%)	Post-radiosurgery hypopituitarism (%)
Izawa et al.	2000	12	26.4	Gamma Knife	23.8	16.7	0
Sheehan et al.	2000	43	39.1	Gamma Knife	20	63	16
Shin et al.	2000	6	88.2	Gamma Knife	32.3	50	16.7
Hoybye et al.	2001	18	16.8	Gamma Knife	NR	44	68.8
Feigl et al.	2002	4	55.2	Gamma Knife	15	60*	40*
Kobayashi et al.	2002	20	64	Gamma Knife	28.7	23.3	NR
Laws et al.	2002	40	NR	Gamma Knife	20	74	24
Pollock et al.	2002	9	42.4	Gamma Knife	20	78	16
Choi et al.	2003	7	42.5	Gamma Knife	28.5	55.6	0
Petrovich et al.	2003	4	34	Gamma Knife	15	NR	NR
Witt et al.	2003	8	24	Gamma Knife	24	0	NR
Wong et al.	2003	5	38	LINAC	NR	100	20
Devin et al.	2004	35	42	LINAC	14.7	49	40
Kajiwara et al.	2005	2	38.5	CyberKnife	26	50	50
Voges et al.	2006	17	58.7	LINAC	16.4	52.9	12.3
Castinetti et al.	2007	40	54.7	Gamma Knife	29.5	42.5	15
Jagannathan et al.	2007	90	45	Gamma Knife	23	54	22
Petit et al.	2008	33	62	Proton Beam	20	52	52
Pollock et al.	2008	8	73	Gamma Knife	20	87	36
Tinnel et al.	2008	12	37	Gamma Knife	25	50	50
Castinetti et al.	2009	18	94	Gamma Knife	28	50	21
Kobayashi et al.	2009	30	64.1	Gamma Knife	28.7	35	NR
Wan et al.	2009	68	67.3	Gamma Knife	23	27.9	1.7
Hayashi et al.	2010	13	36	Gamma Knife	25.2	38	0
Sheehan et al.	2011	82	31	Gamma Knife	24	54	22
Wein et al.	2012	17	23	LINAC	18	58.8	11.8
Grant et al.	2013	15	40.2	Gamma Knife	35	73	40

NR not reported, LINAC linear accelerator

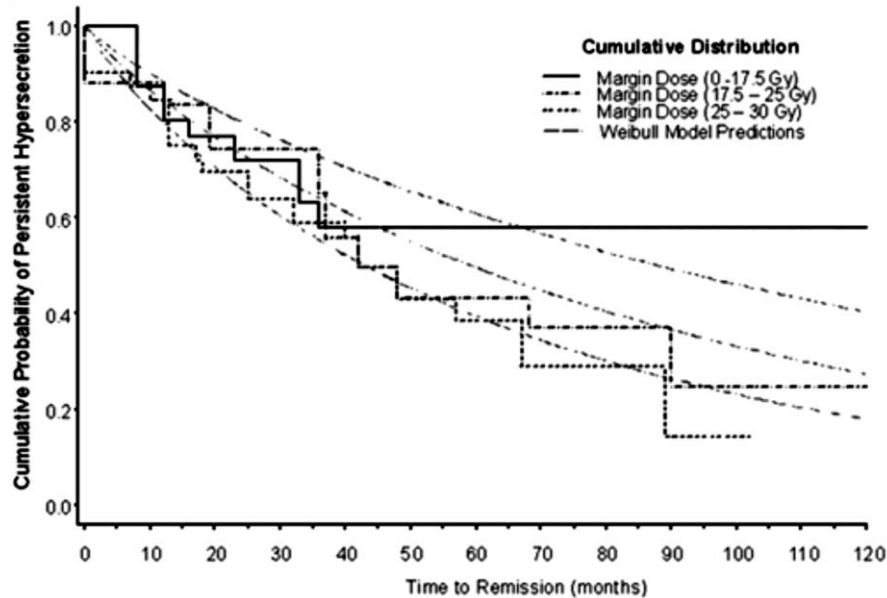
Long-term effects of GK in Cushing's disease evaluated by Kaplan–Meier analysis: probability of being uncured as a function of time.



Gamma Knife surgery for pituitary adenomas: factors related to radiological and endocrine outcomes

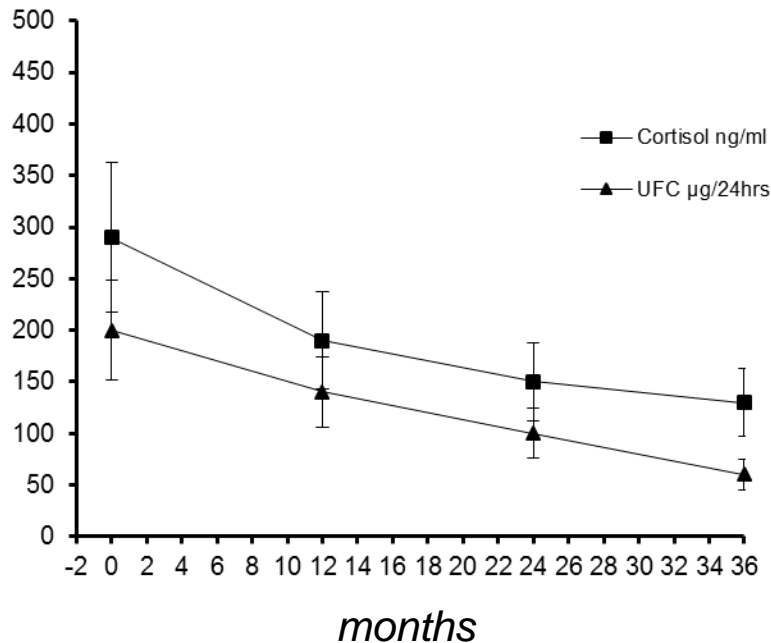
JASON P. SHEEHAN, M.D., Ph.D.,¹ NADER POURATIAN, M.D., Ph.D.,¹
 LADISLAV STEINER, M.D., Ph.D.,¹ EDWARD R. LAWS, M.D.,² AND MARY LEE VANCE, M.D.³

Departments of ¹Neurological Surgery and ³Medicine, University of Virginia Health System, Charlottesville, Virginia; and ²Department of Neurological Surgery, Brigham and Women's Hospital, Boston, Massachusetts



Adenoma Type	No. of Patients	Remission (%)	Median Time to Remission (mos)	New Pituitary Deficiency (%)
acromegaly	130	53	29.8	34
CD	82	54	13.0	22
prolactinoma	32	26	24.5	38
Nelson's syndrome	22	20	50.0	28

✓ *Effect of SRS on plasma cortisol and urinary free cortisol (UFC) secretion in patients with Cushing's disease treated with SRS*



*hormone normalization
23% at 12 months, 50%
at 24 months, 62% at 36
months**

* 18 patients treated with SRS

Hypopituitarism After Stereotactic Radiosurgery for Pituitary Adenomas

Zhiyuan Xu, MD*

Mary Lee Vance, MD‡

David Schlesinger, PhD§

Jason P. Sheehan, MD, PhD*

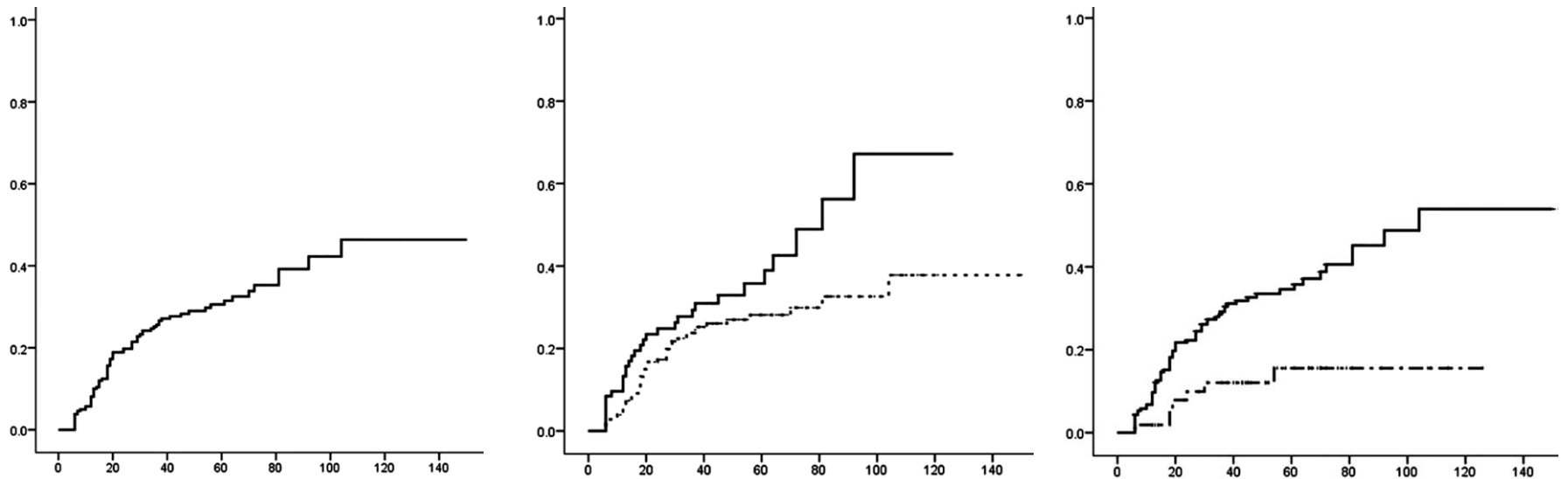


FIGURE. **A,** Kaplan-Meier plot for new-onset hypopituitarism after stereotactic radiosurgery (SRS). **B,** Kaplan-Meier plot for new-onset hypopituitarism in relation to suprasellar tumor extension. **C,** Kaplan-Meier plot for new-onset hypopituitarism in relation to a radiation dose of 16 Gy to the tumor margin.

✓ Summary of recent published series of SRT for pituitary adenomas

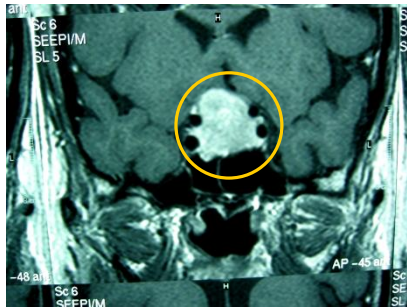
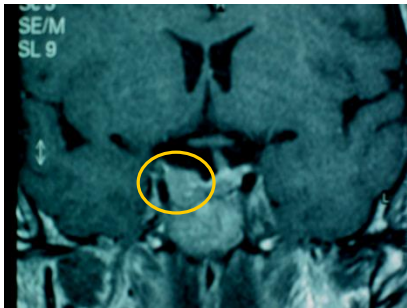
Authors	type of adenoma	Patients	mean dose (Gy)	follow-up (months)	tumor control (%)	late toxicity (%)	
						visual	hypopituitarism
Milker-Zabel et al., 2001	NFA, SA	68	50.4	38	93 at 5 years	7,5	5
Milker-Zabel et al., 2004	GH	20	52.2	26	100 (92**)	0	3
Paek et al., 2005	NFA, SA	68	50	30	98 at 5 years	3	6
Colin et al., 2005	NFA, SA	110	50.4	48	99 at 5 years	1,8	29 at 4 years
Minniti et al., 2006	NFA, SA	92	45	32	98 at 5 years	1	22
Kong et al., 2007	NFA, SA	66	50.4	36.7	97	0	27.3 at 5 years
Roug et al., 2010	GH	34	54	34	91 (30**)	0	29 at 4 years
Schalin-Jantti et al., 2010	NFA, SA	30	45	64	100	0	40
Wilson et al., 2012	NFA	67	50	60.1	93 at 5 years	1,5	7
Kopp et al., 2013	NFA, SA	37	49.4	57	91,9	5	5
Kim et al., 2013	NFA, SA	76	50.4	80	97,1 at 7 years	0	48

NFA, nonfunctioning adenoma; SA, secreting adenoma; **biochemical remission of disease

✓ SRT vs SRS

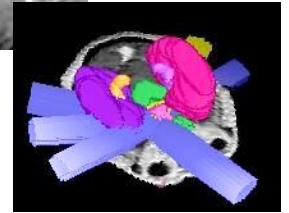
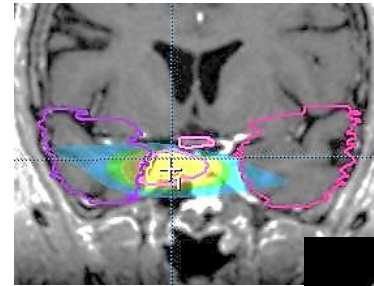


✓ *Limitation of radiosurgery*



- Size of adenoma (more than 2.5-3.0 cm)
- Proximity to the optic chiasm (< 2-3 mm)

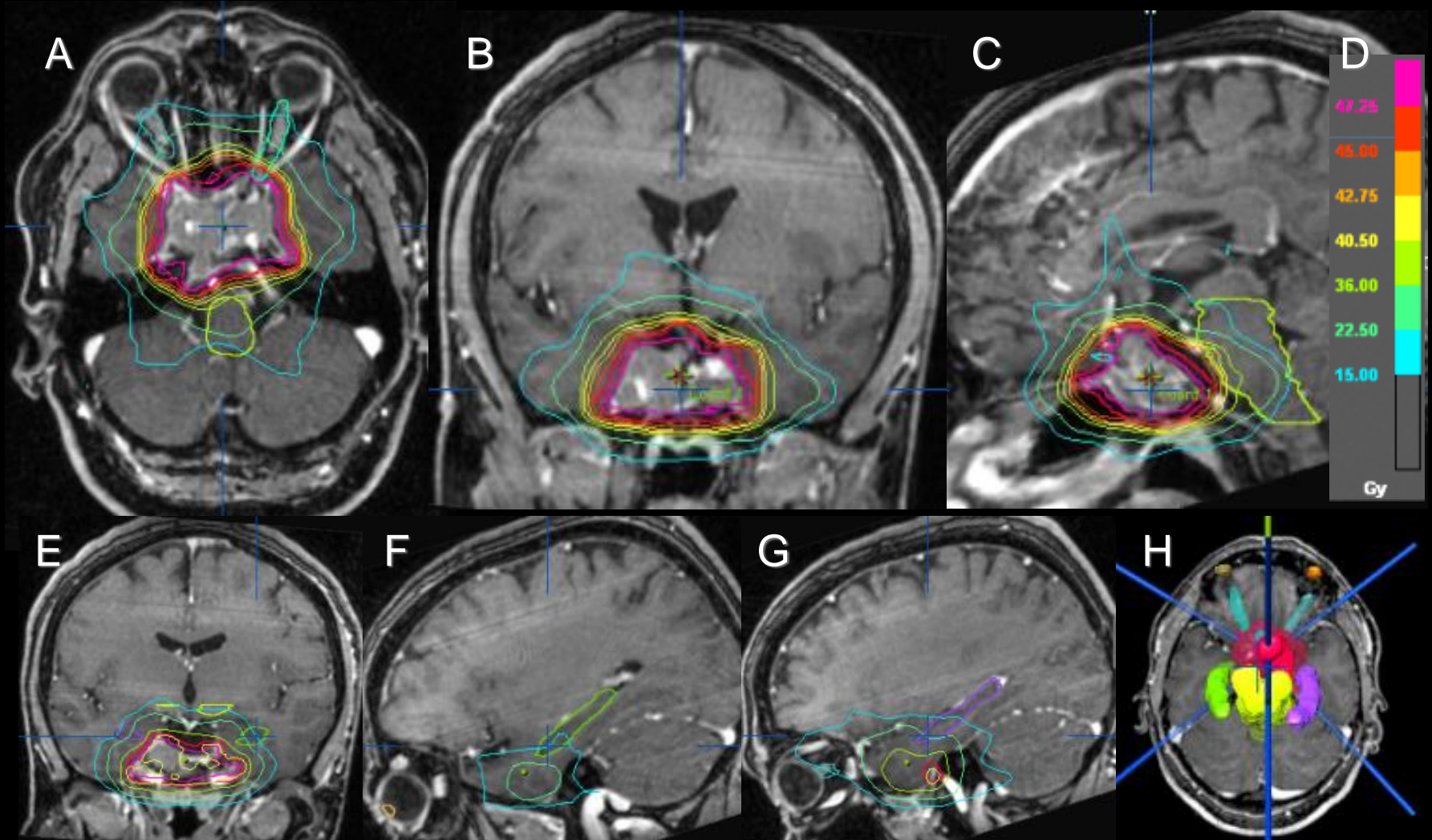
➤ *Radiation tolerance to SRS*



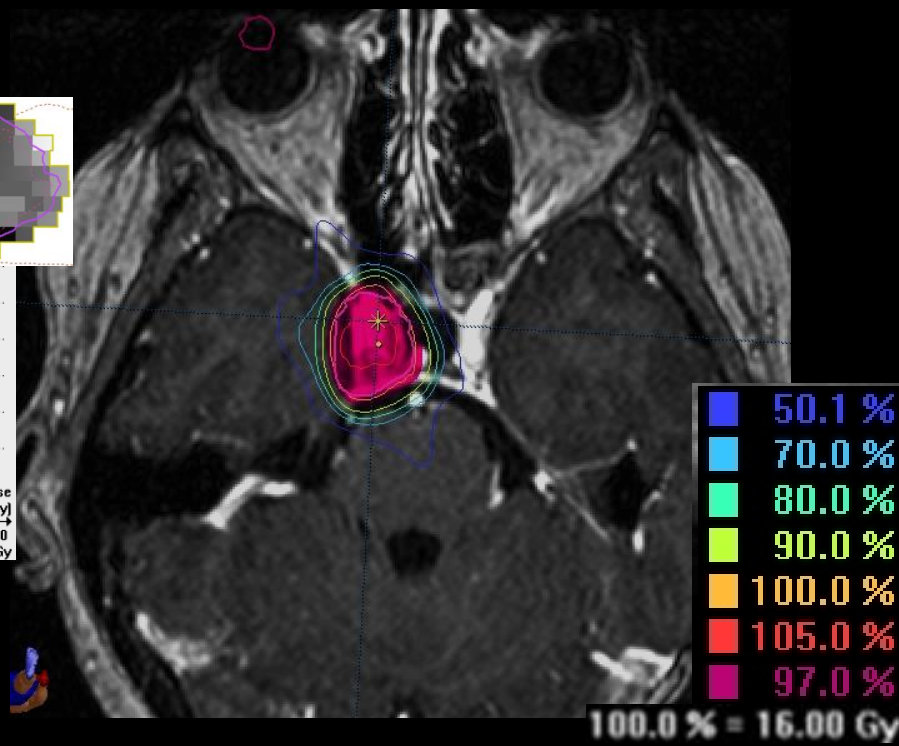
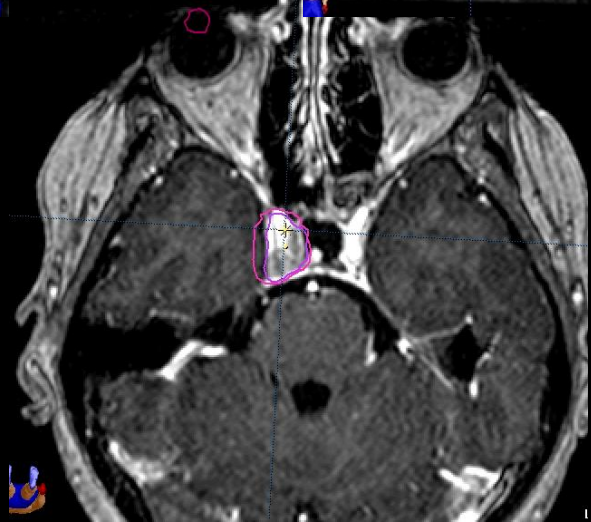
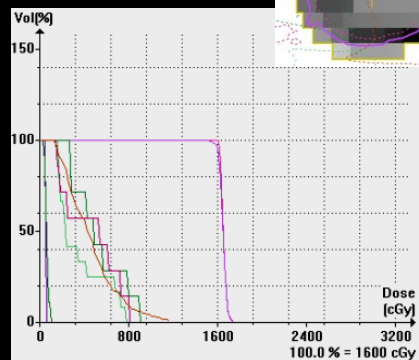
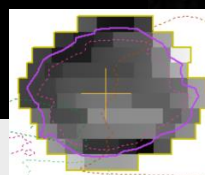
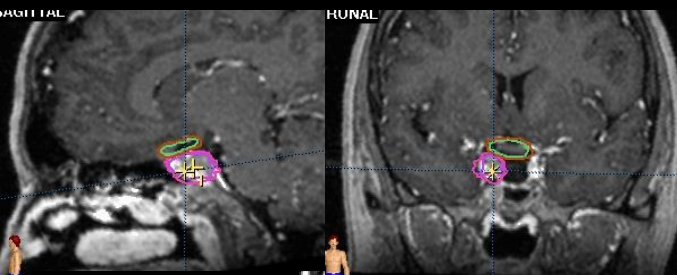
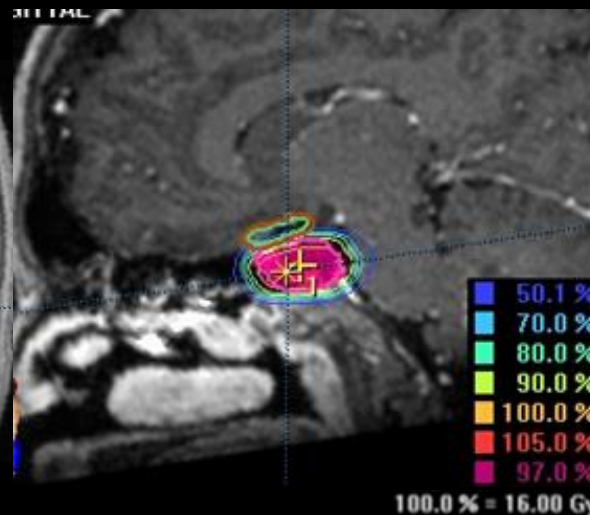
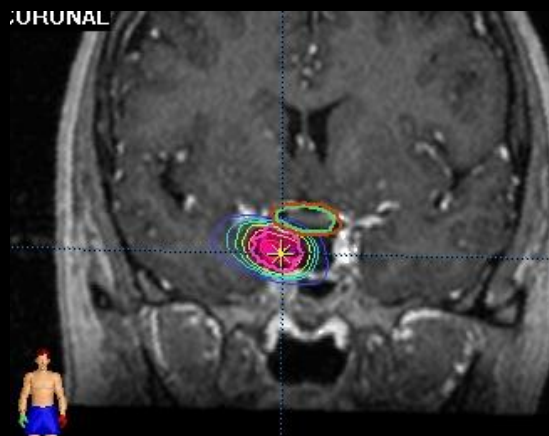
✓ *Radiation induced optic neuropathy (RON)*

<i>dose to optic apparatus</i>	<i>incidence of RON</i>
< 10 Gy	0-3%
10 - 12 Gy	2-5%
> 12 Gy	>10%

NF pituitary adenoma



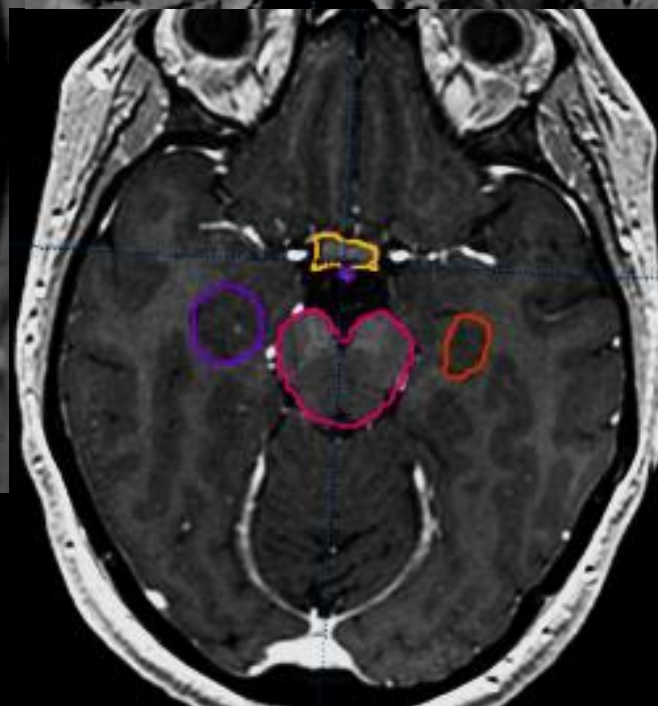
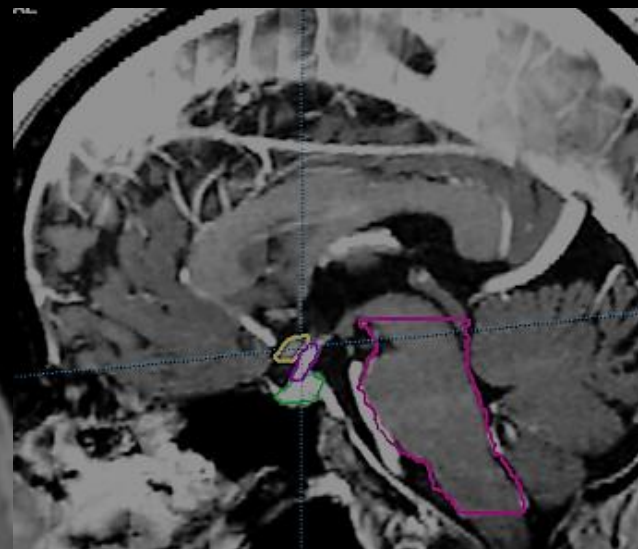
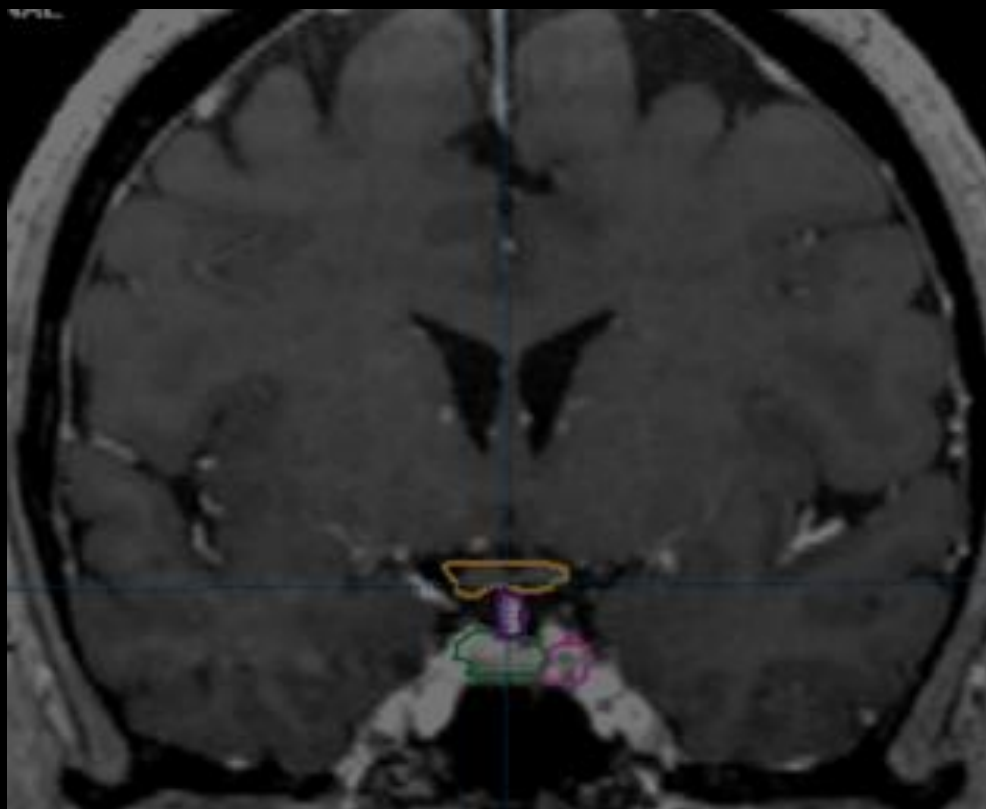
SRS for residual pituitary adenoma



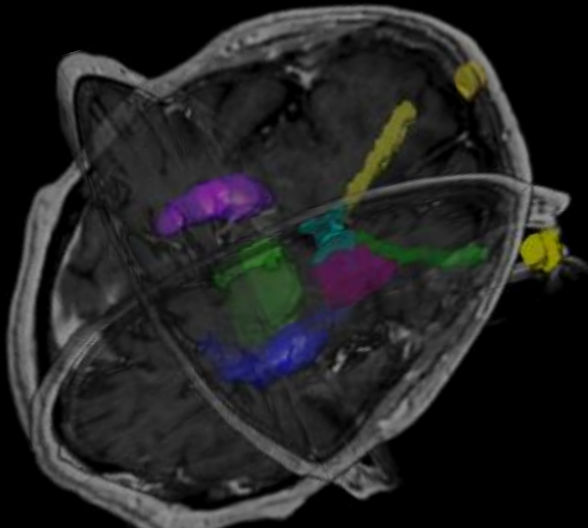
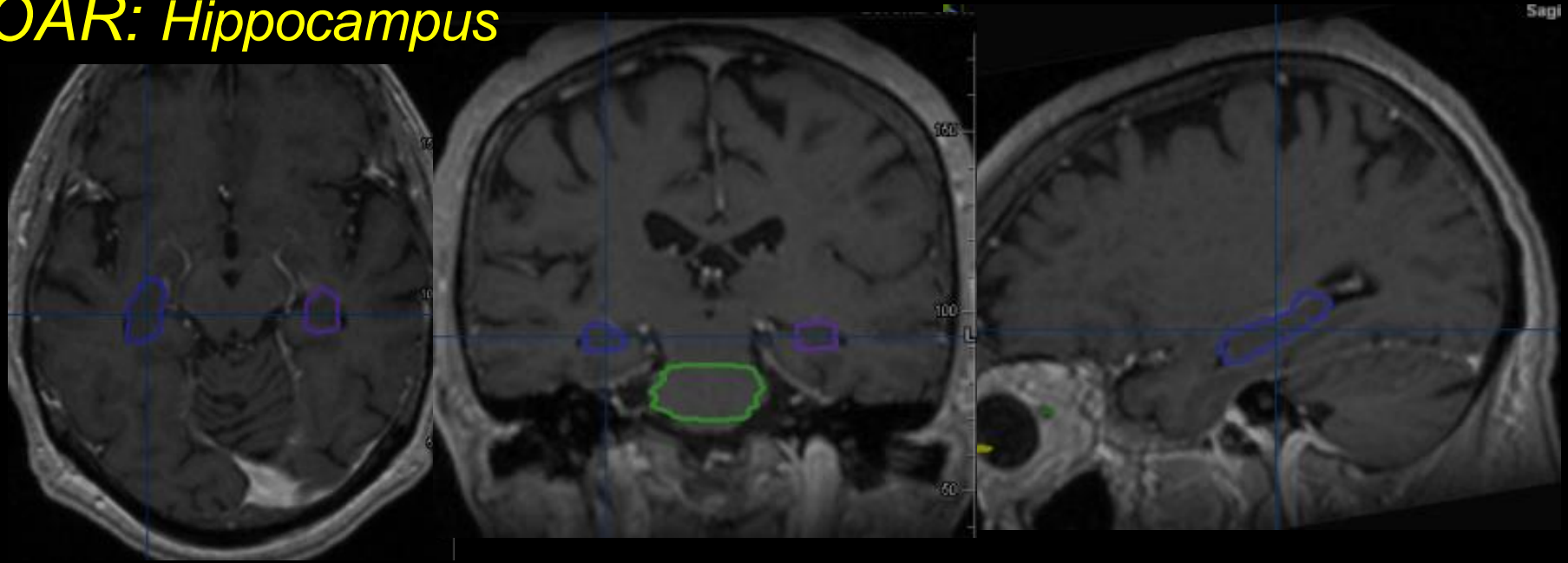
➤ *Can we improve the results of SRS/SRT?*



OAR: pituitary and chiasm

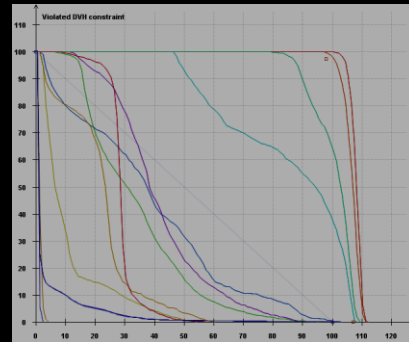
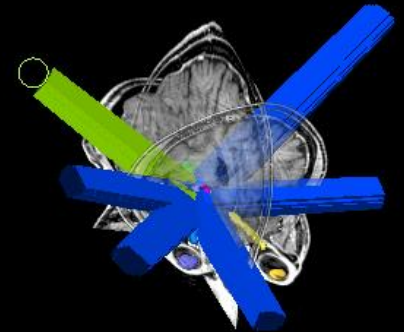
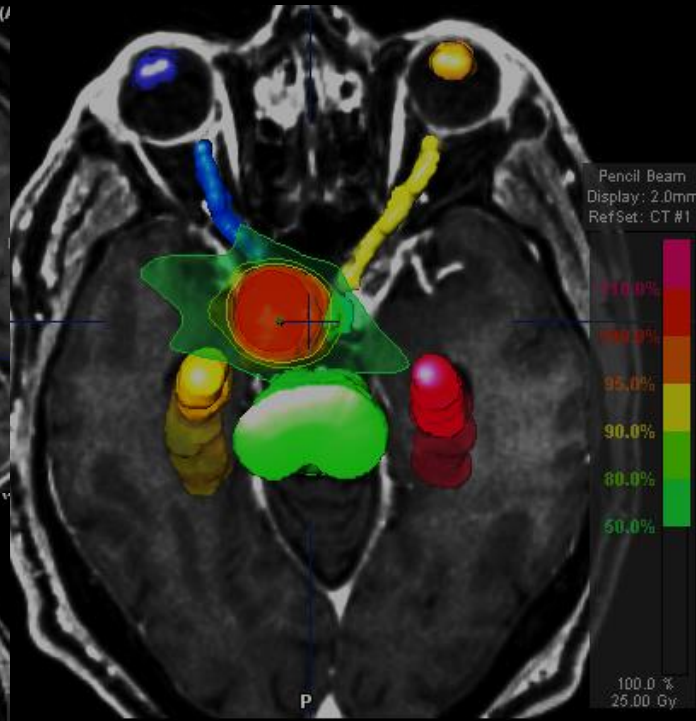
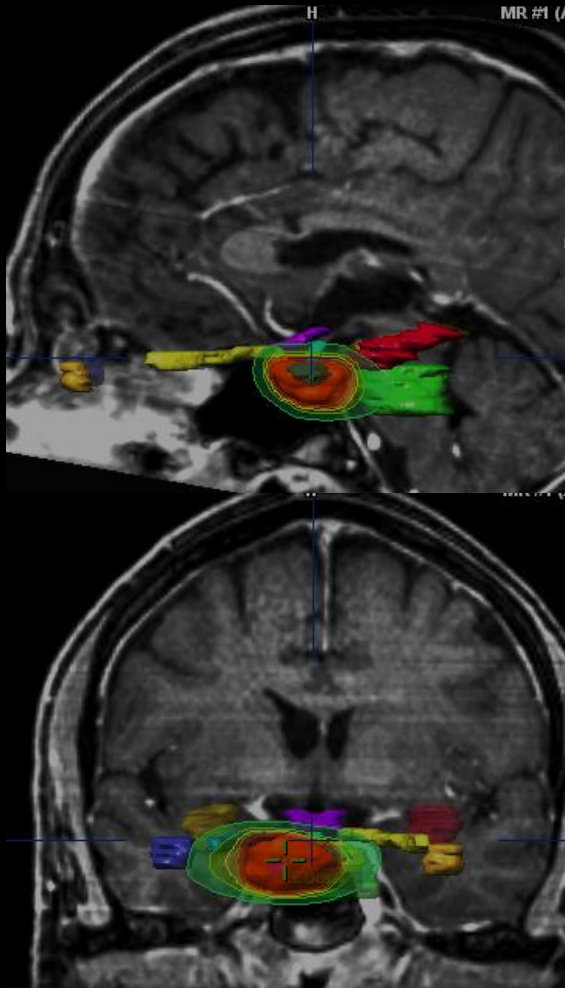


OAR: Hippocampus

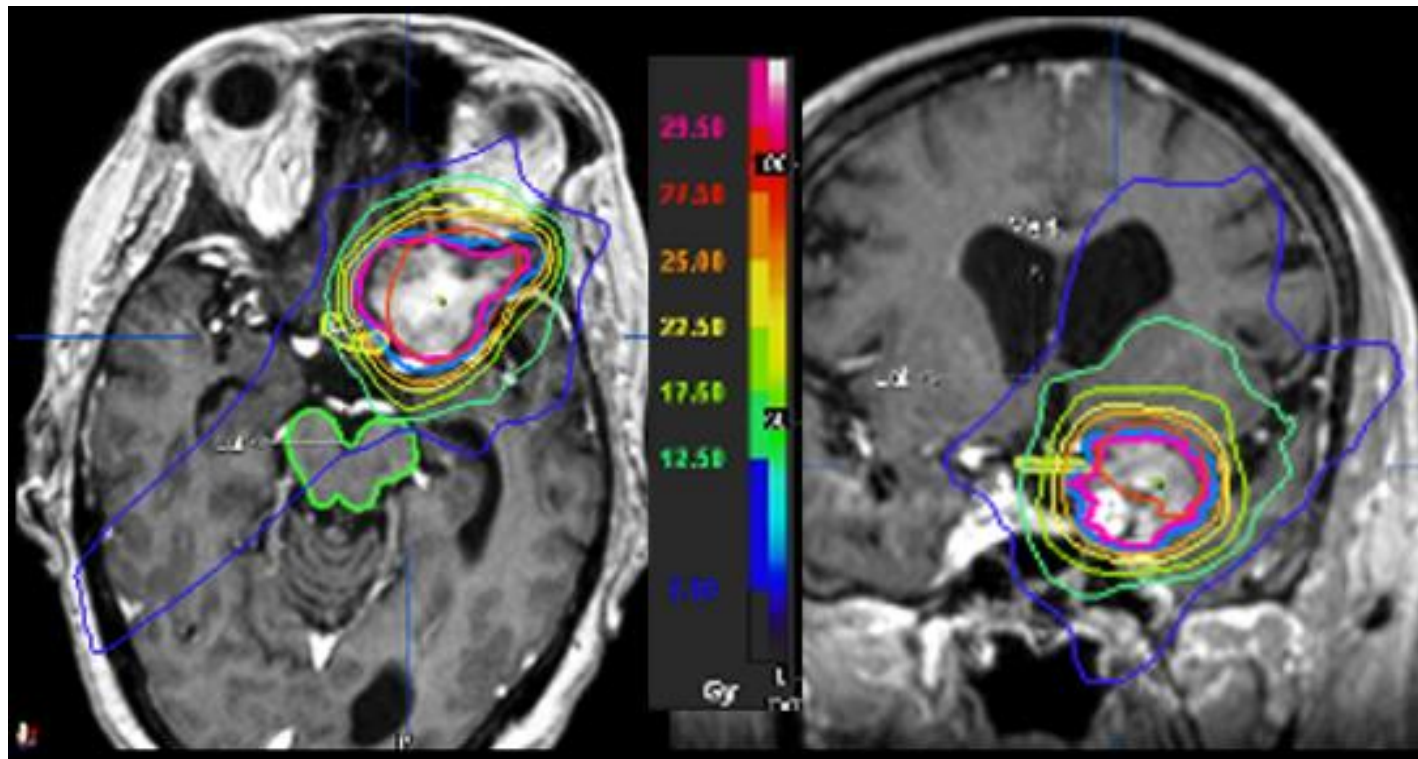


Doses < 7-10 Gy
to bilateral hippocampi

Multi-fraction SRS for an ATCH-secreting pituitary adenoma



- PTV ADEIOMA
- ADEIOMA
- Brainstem
- Chiasm
- Hippocampus, Left
- Hippocampus, Right
- Lens, Left
- Lens, Right
- Optic Nerve, Left
- Optic Nerve, Right
- PITUITARY GLAND
- PITUITARY STALK



✓ Median radiation doses to cavernous sinus, optic nerves and chiasm in patients treated with multi-fraction SRS (5 × 5 Gy)

Site	Median dose (Gy)	Maximum dose (Gy)	Organ at risk volume (cm ³)	Volume (cm ³) receiving a dose > 25.0 Gy	Volume (cm ³) receiving a dose > 27.5 Gy
Cavernous sinus	18.5	29	1.9 (1.44-2.52)	1.7 (1.41-2.4)	0.52 (0.2-1.9)
Optic nerve	13.5	28.5	0.93 (0.71-1.26)	0.08 (0.01-0.5)	0.026 (0.005-0.08)
Optic chiasm	5.5 (12*)	28.5	0.48 (0.33-0.71)	0.13 (0.03-0.28)*	0.022 (0.01-0.06)*

*In 18 patients receiving a total dose to the optic chiasm >25 Gy.

➤ *Conclusions*

- ✓ *New techniques are apparently effective and may reduce the potential long-term toxicity of radiation;*
- ✓ *Both SRT and SRS are feasible options for patients with otherwise uncontrolled ACTH-secreting pituitary adenomas;*
- ✓ *Radiosurgery should be employed for small-to moderate (< 2.5-3 cm) adenomas, 2-4 mm away from the optic chiasm.*



....Grazie per l'attenzione...

Altogether
to Beat
Cushing's
Syndrome

ABCO

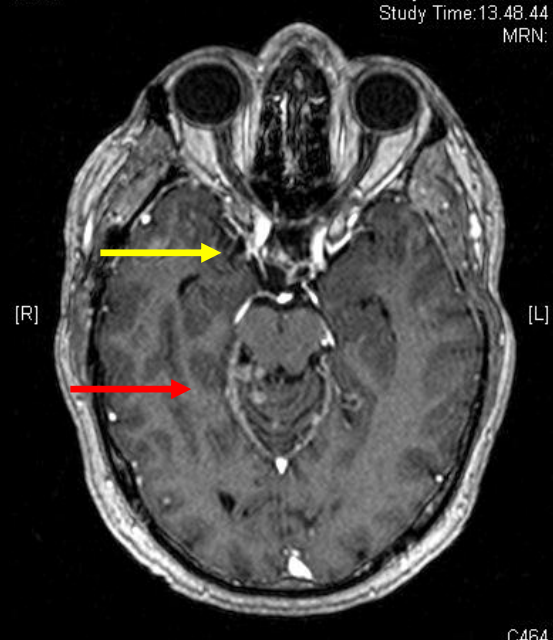
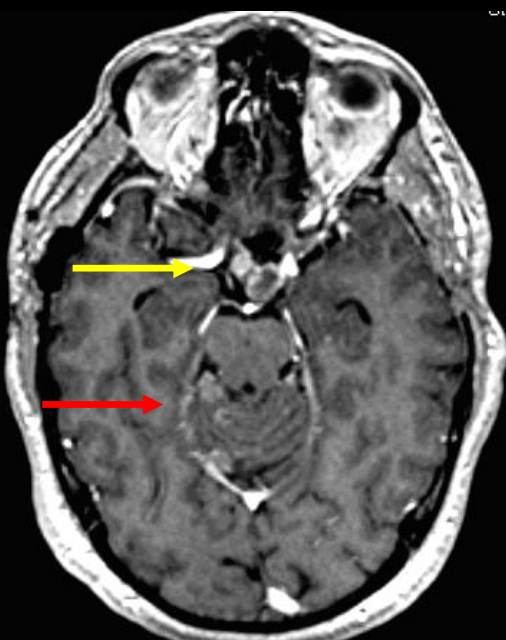
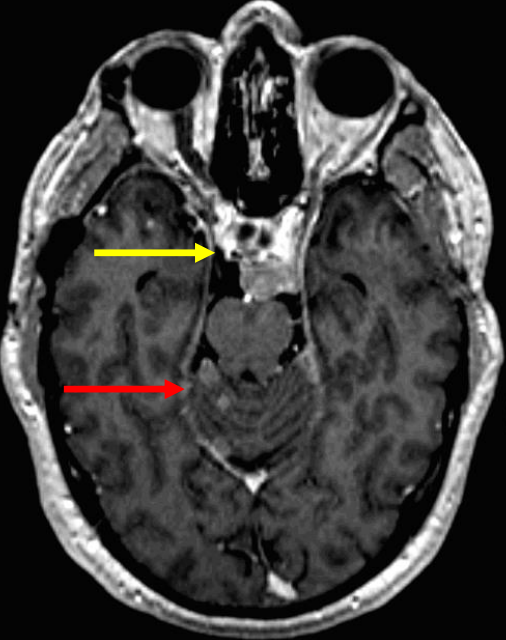
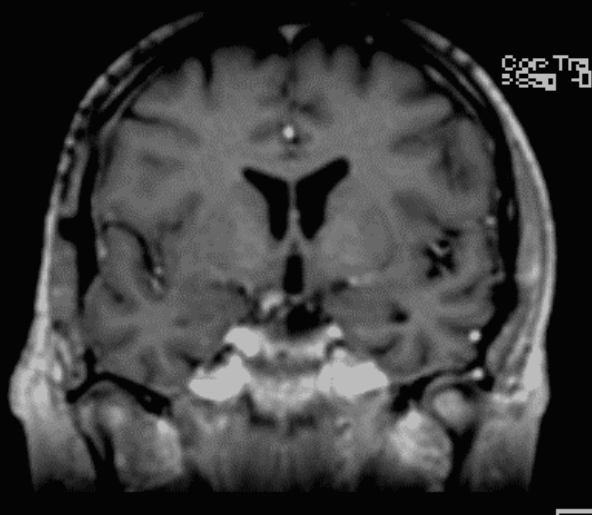
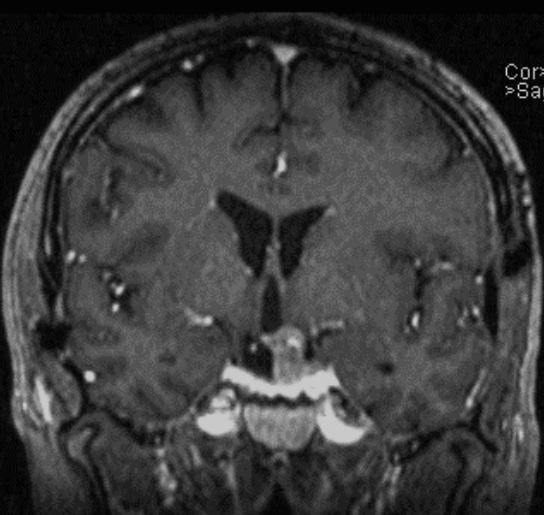
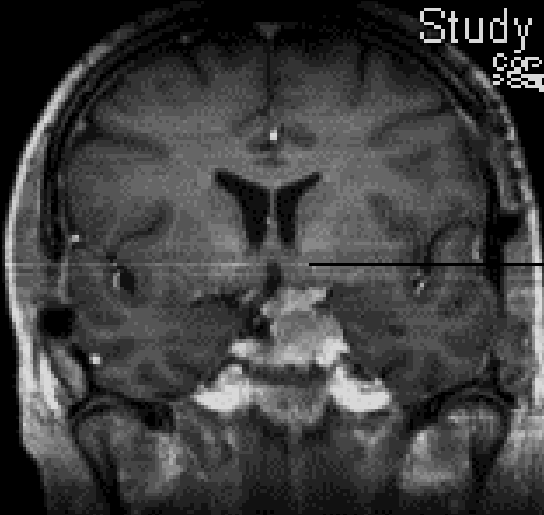
Viaggio alla
(ri)scoperta
della Sindrome
di Cushing 4^a Edizione / 4th Edition
Journey to the (re)discovery of Cushing's Syndrome
Napoli, 5-7 May 2015



➤ Aggressive ACTH adenoma



A case of ACTH-secreting pituitary carcinoma treated with RT plus TMZ



Spine metastases in a patient with ACTH-secreting pituitary carcinoma



6/2007



6/2008



6/2009



1/2010