Radiation Therapy for Pituitary Tumors

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Disclosure

UAB has research contracts with Varian

Goals of Pituitary Radiation

- Control of tumor growth
  - Improve neurologic dysfunction
- Control of endocrine secretion

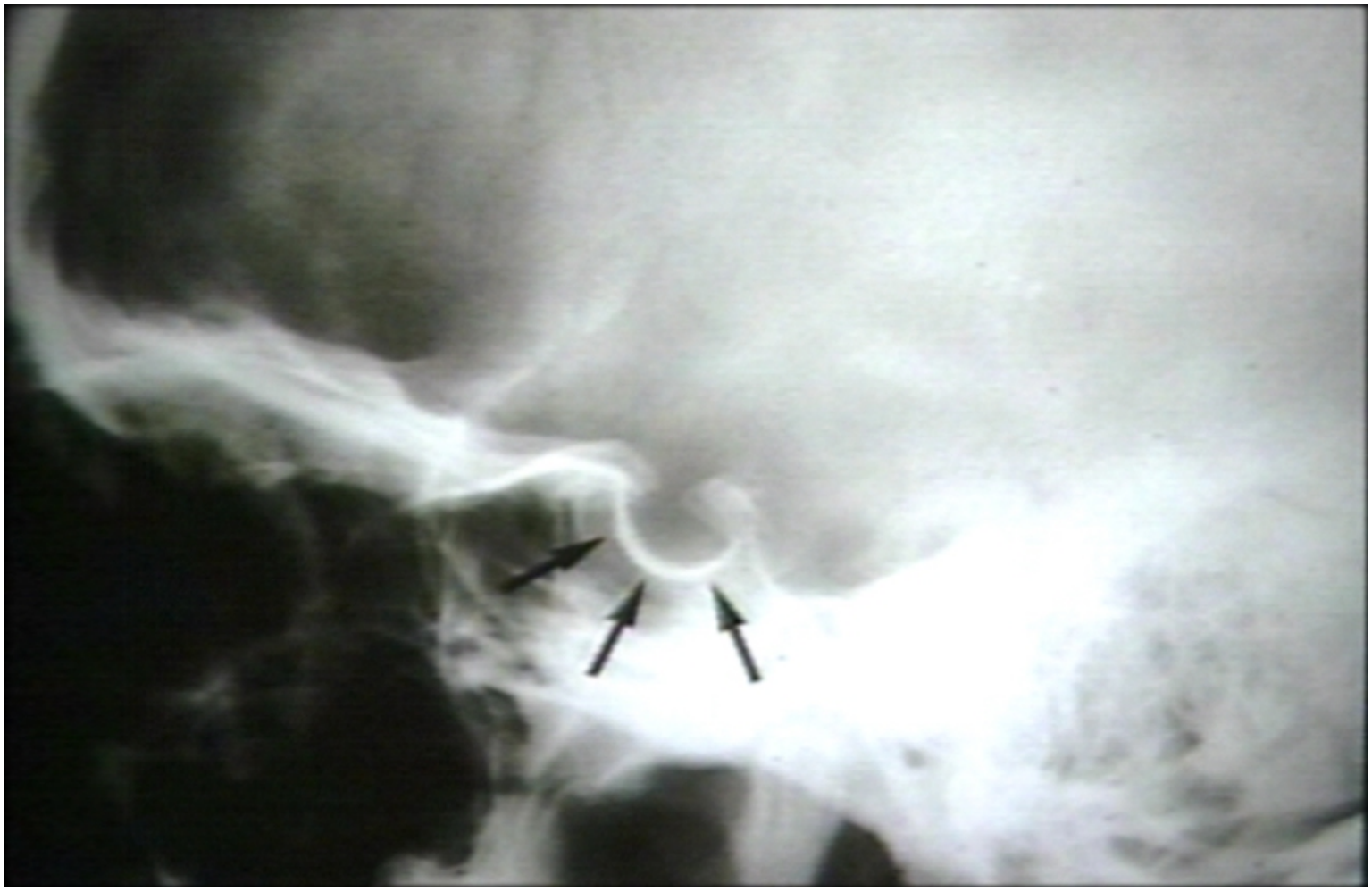
Radiation Dose Schedules

- Radiosurgery = one fraction
  - Gamma Knife is a machine that only performs radiosurgery
  - 12-14 Gy for non-secreting tumor
  - 20-24 Gy for control of secretion
- Fractionated radiation therapy
  - ~50 Gy in 25 fractions (M-F, 5 weeks)

Potential for Iatrogenic Harm

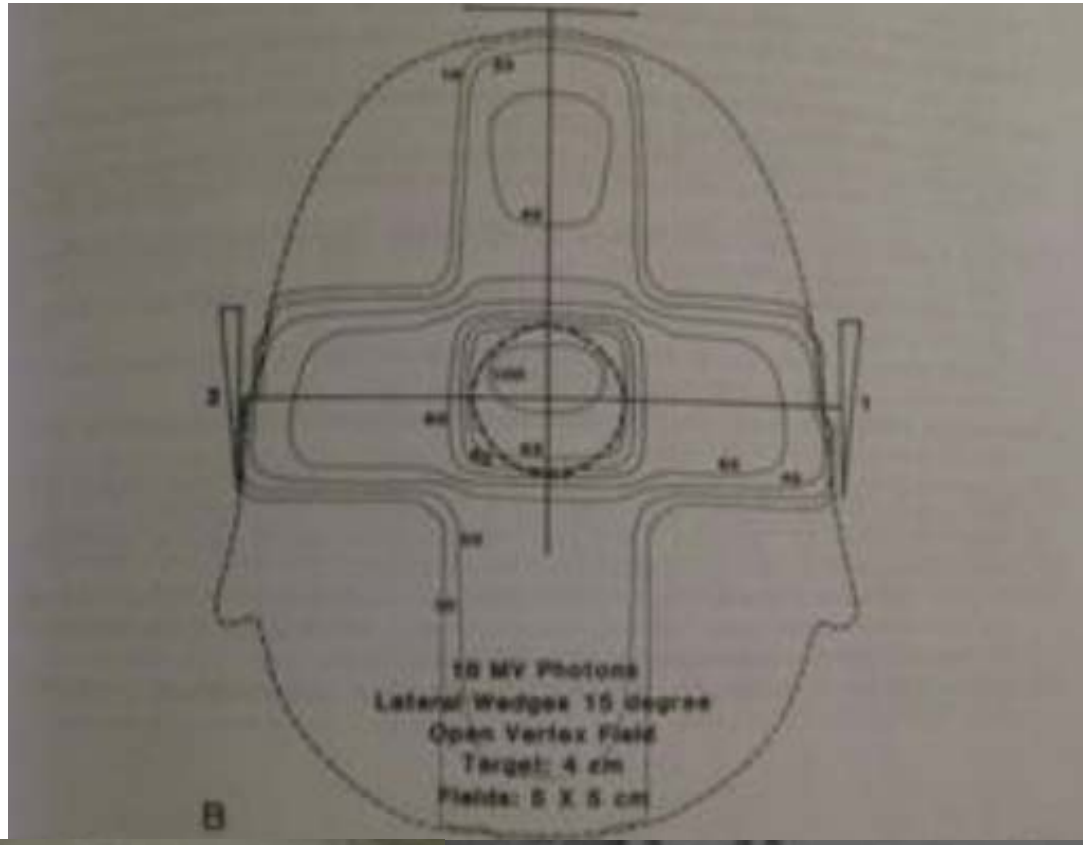
- Optic nerves and chiasm (1%)
- Cavernous sinus nerves (<1%)
- Carotid
- Temporal lobe injury
- Secondary tumors
- Endocrine dysfunction (8-50%)

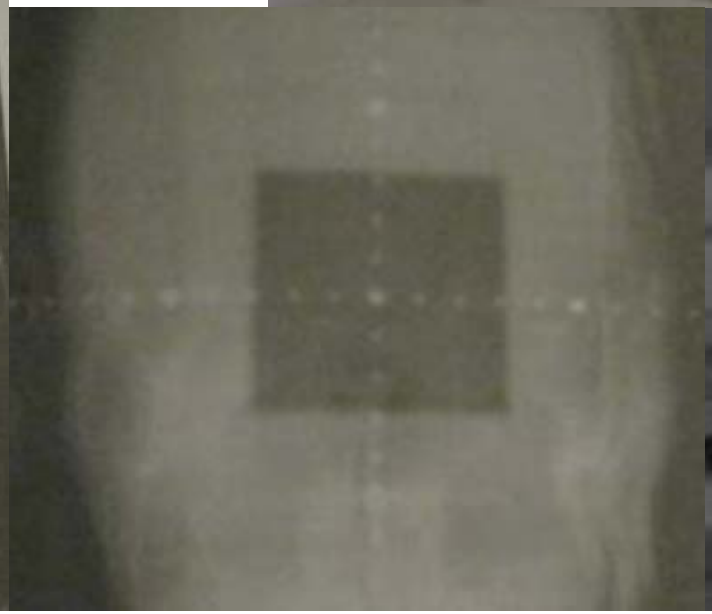
Radiosurgery Prior to CT/MR Imaging

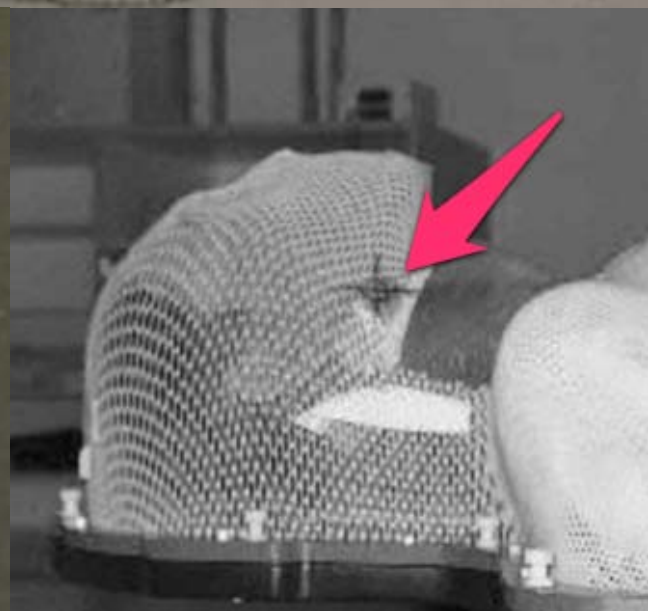


Boney anatomy correlated to target but no 3D information spread outside sella

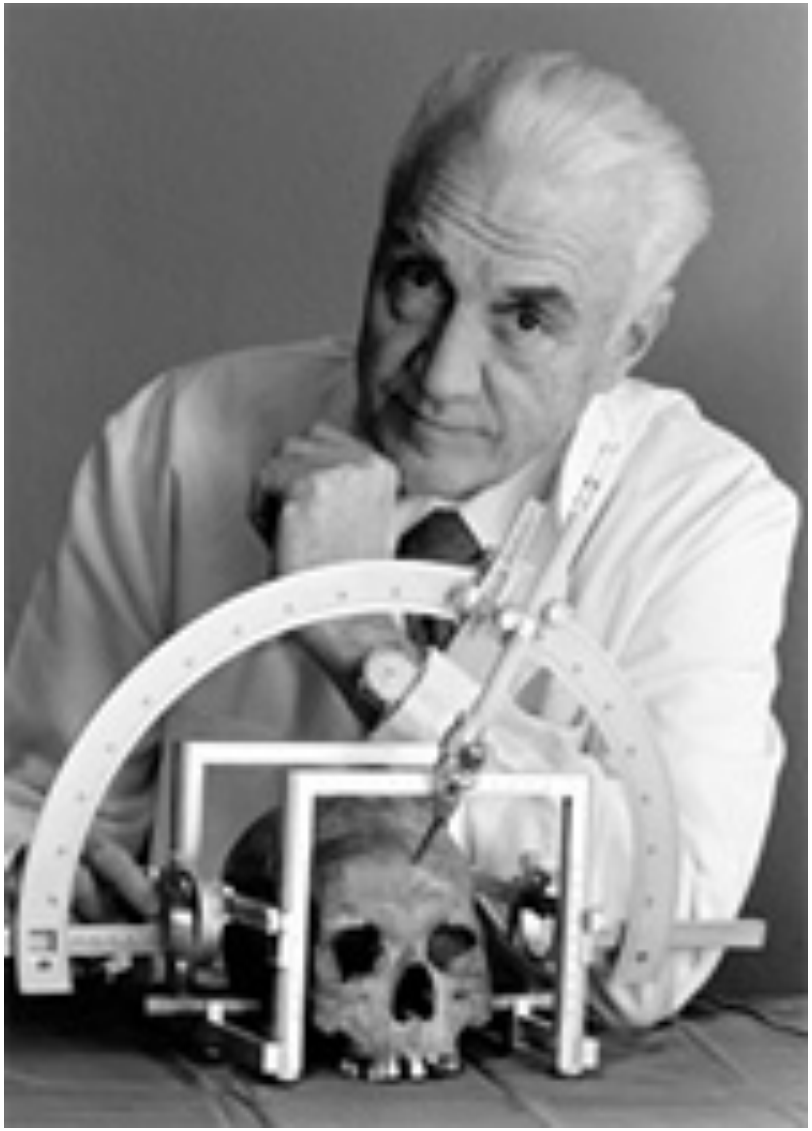
Fractionated RT Prior to Image Guidance and 3D Planning







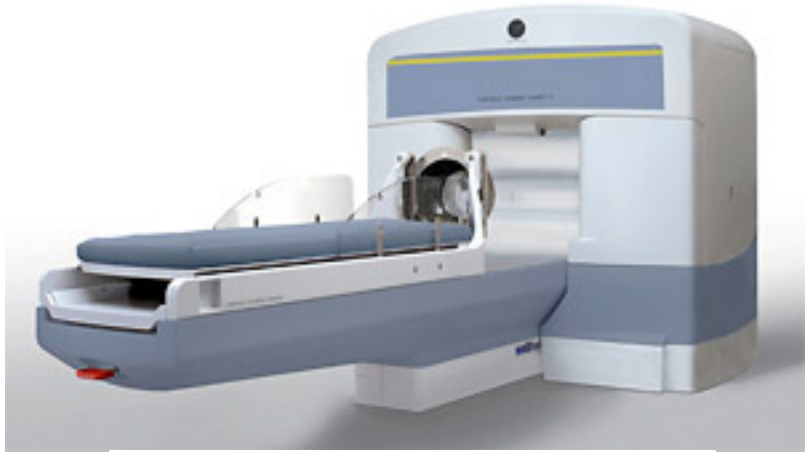
Localization and Immobilization

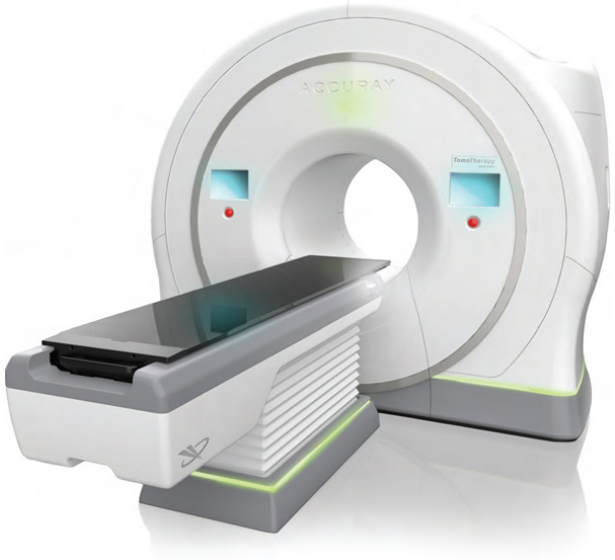


- Frame coordinate system (stereotaxis)
- Imaging coordinate system
  - Orthogonal KV
  - Cone beam CT
  - IR diodes
  - Surface tracking cameras
  - GPS beacons

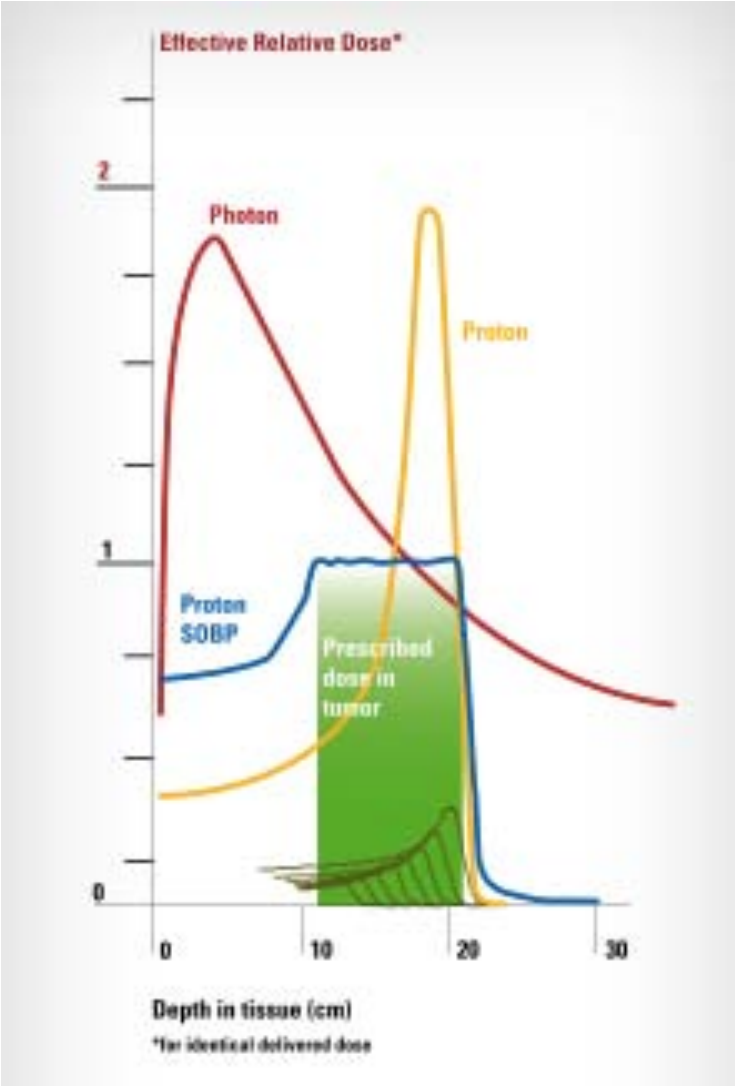
Lars Leksell treated the first pituitary patient with radiosurgery in 1968

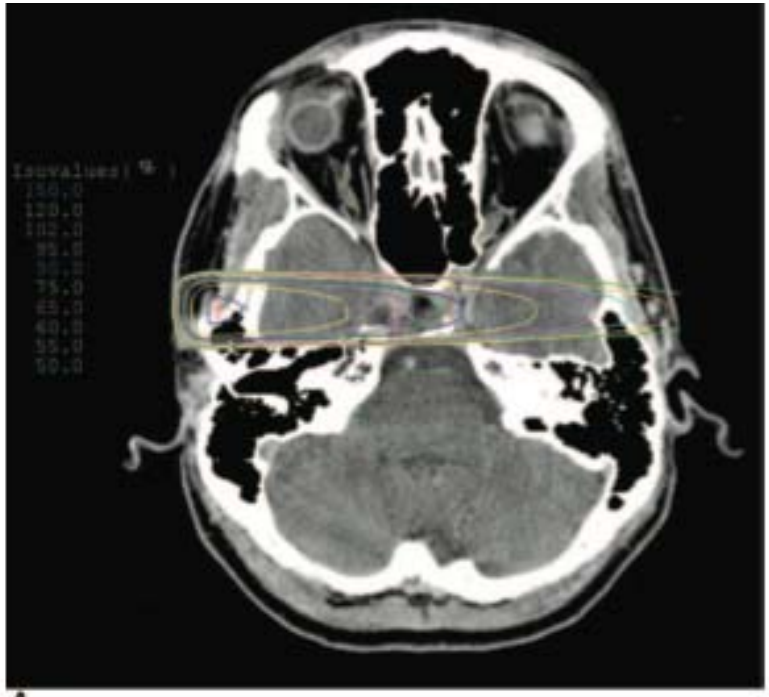
Photon Delivery





Proton Therapy





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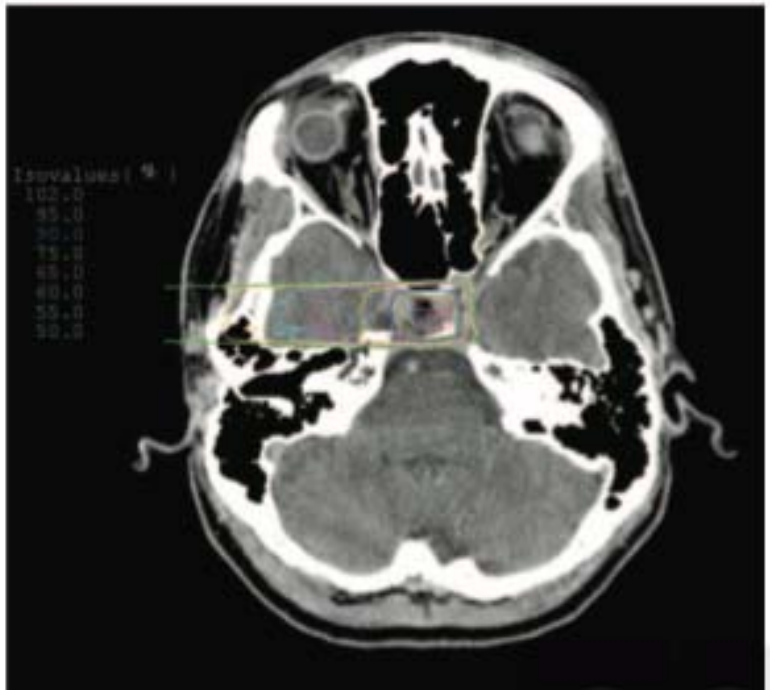
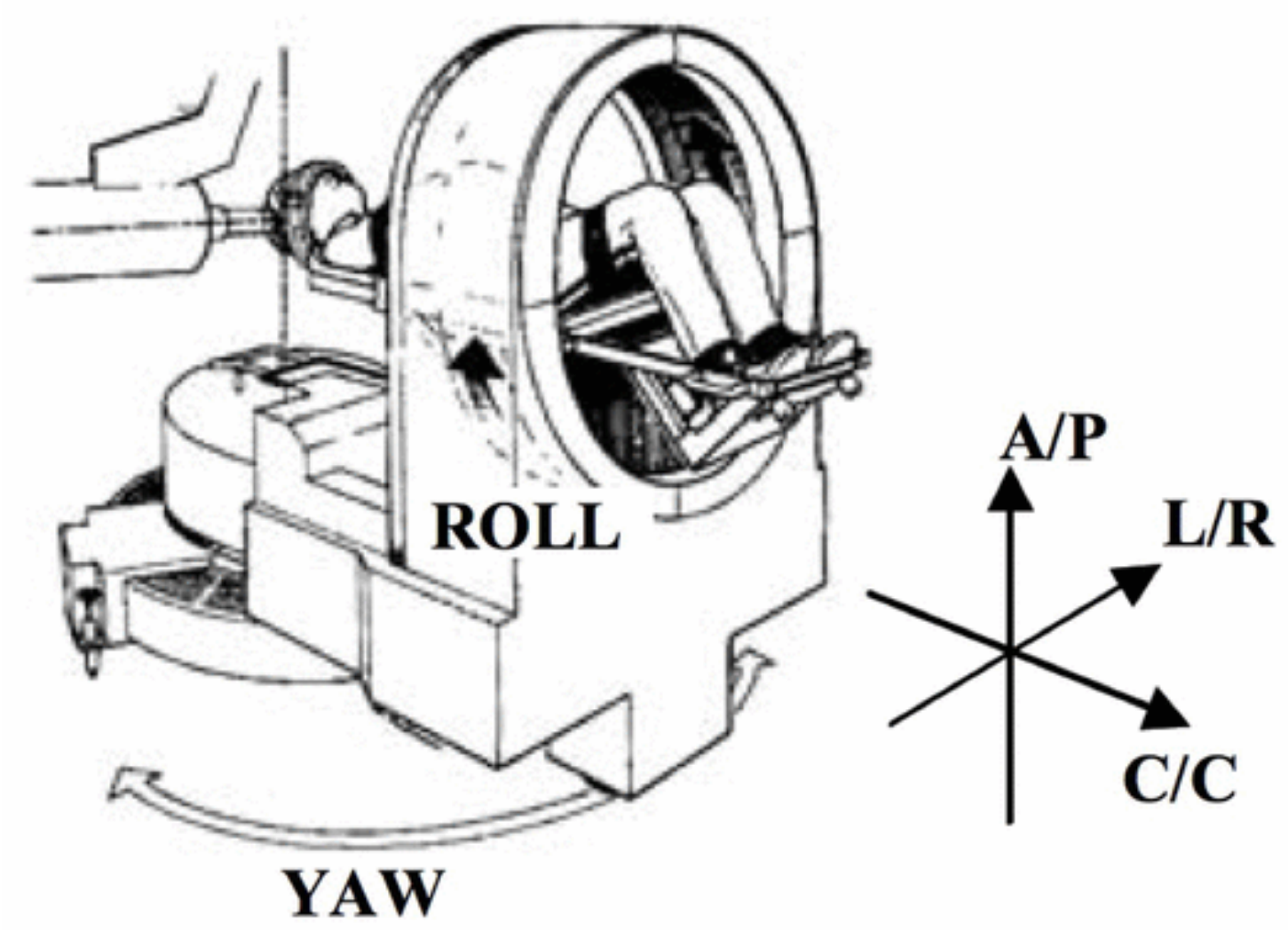


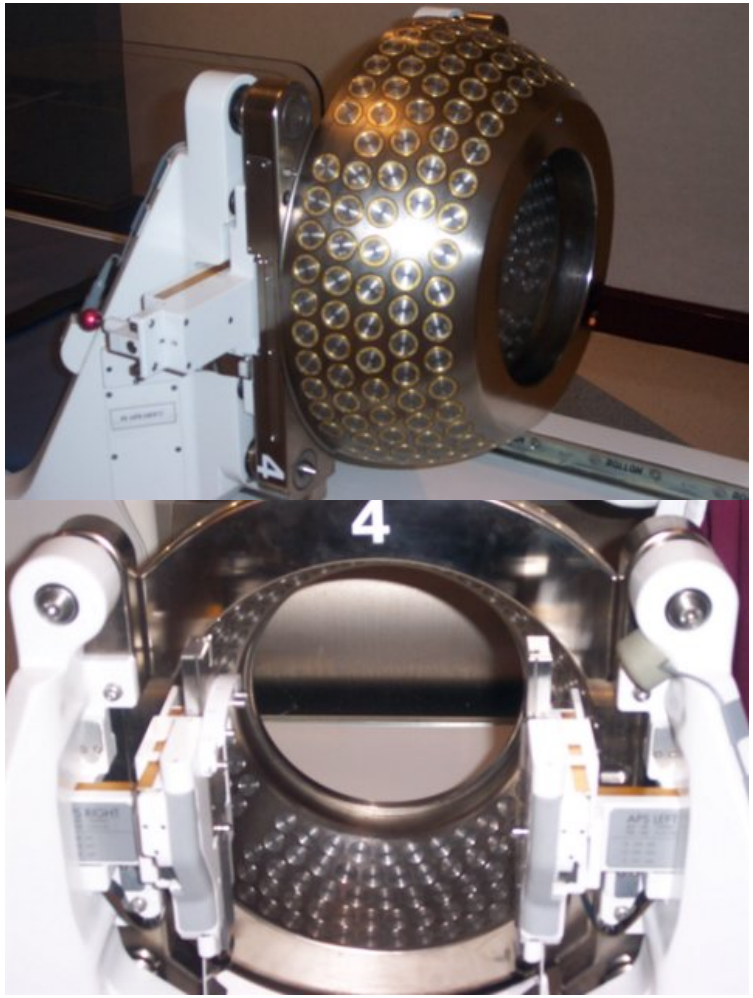
Fixed Gantry

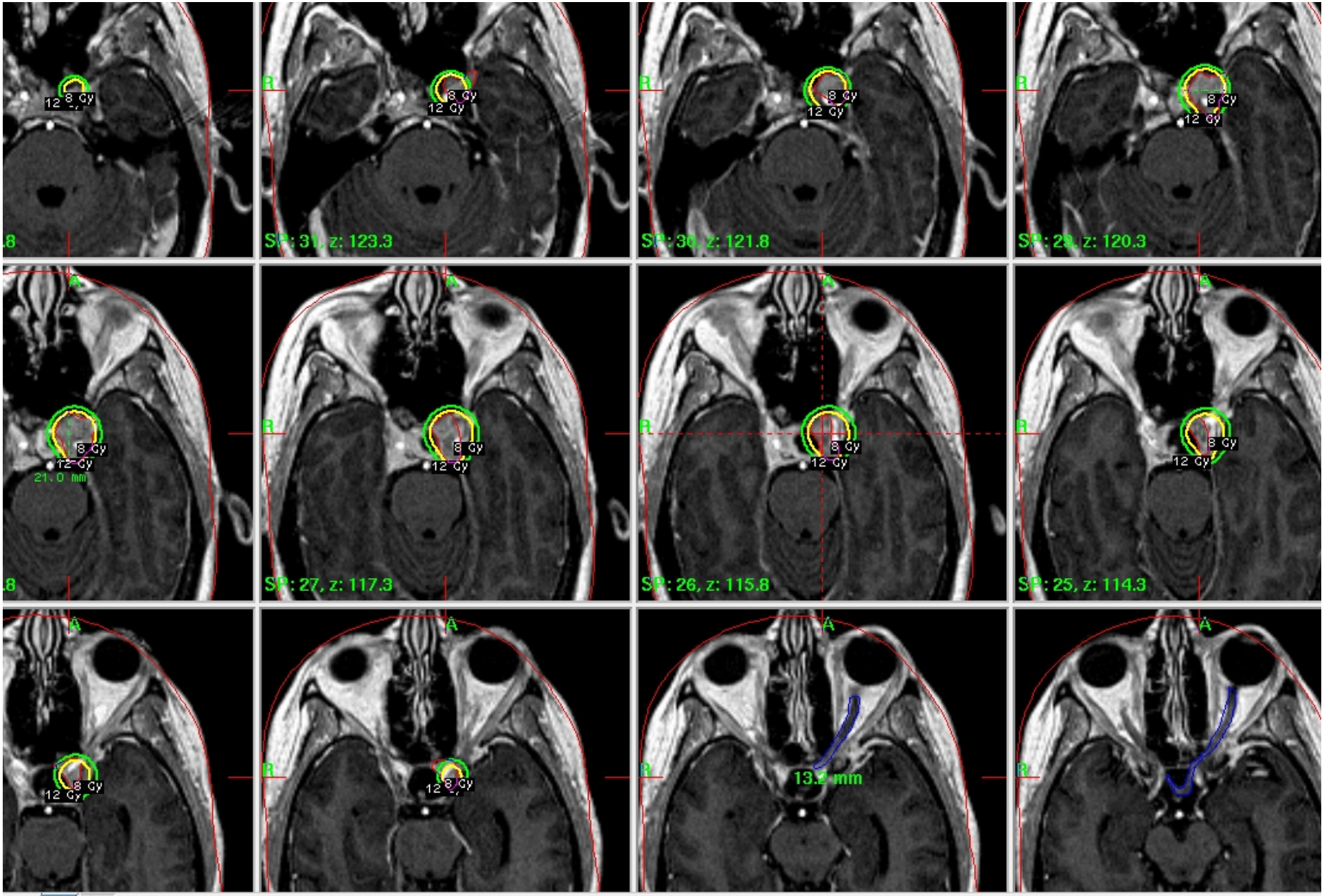


Rotating Gantry

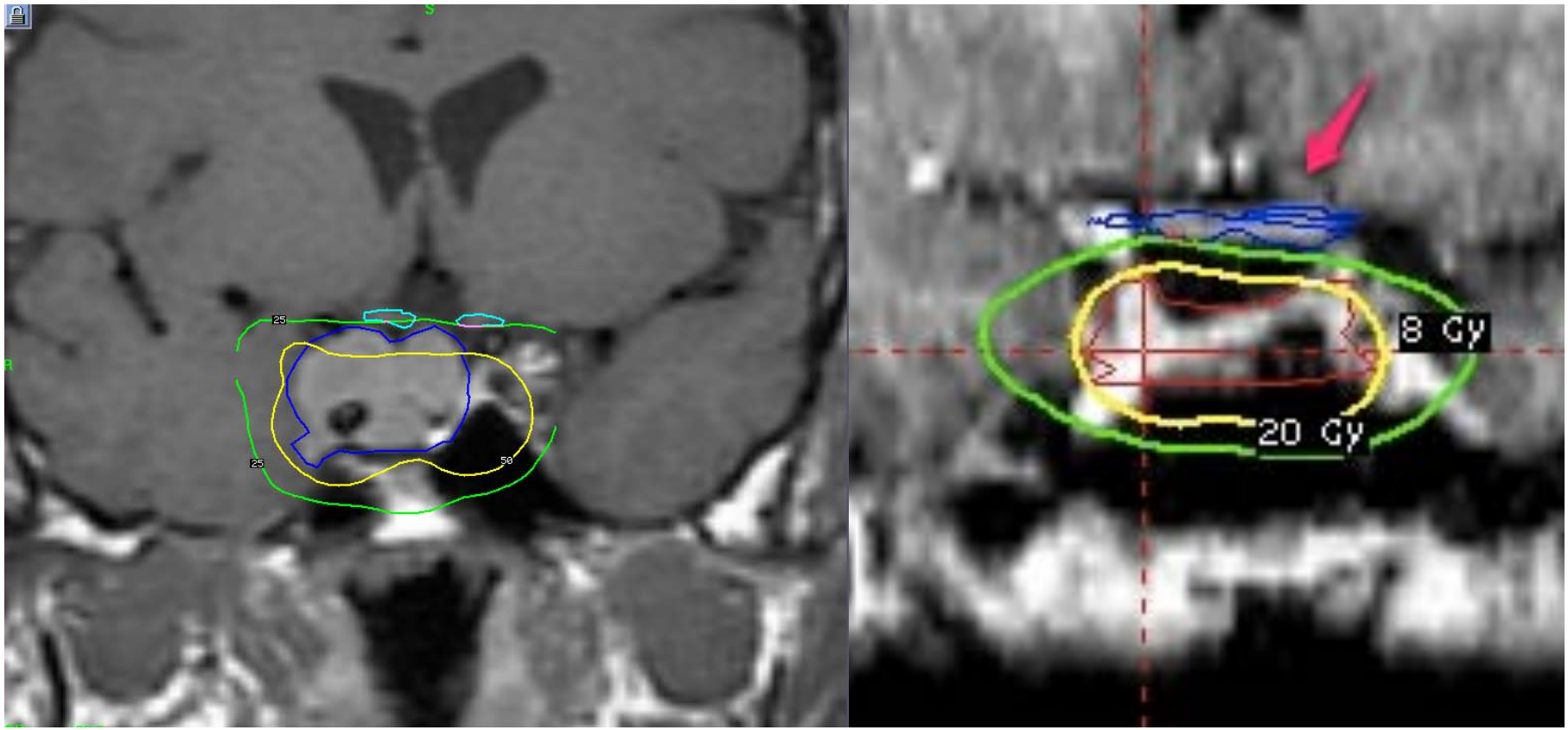
UAB Gamma Knife Procedures

- 1995-2013
- 205 pituitary tumors treated with radiosurgery
  - 92 macroadenomas
  - 113 functional




8 Gy
12 Gy
SP: 31, z: 123.3
SP: 30, z: 121.8
SP: 29, z: 120.3
21.0 mm
SP: 27, z: 117.3
SP: 26, z: 115.8
SP: 25, z: 114.3
13.2 mm
Leksell GammaPlan®

Optic Nerve Proximity



Gamma Knife Radiosurgery Process

- Pituitary clinic
- Radiosurgery conference (every Friday)
- CNS Tumor Board (every Tuesday)
- Treatment day
  - Frame placement
  - MRI with contrast
  - Treatment planning (1-3 hours)
  - Treatment delivery (1-3 hours)

Linac Radiosurgery and RT Process

- Pituitary clinic
- Radiosurgery conference (every Friday)
- CNS Tumor Board (every Tuesday)
- Treatment Planning
  - Treatment planning CT and mask (30-60 minutes)
  - Virtual simulation (offline) and dose calculation
  - Patient specific QA measurements
- Treatment Delivery (20-30 minutes)

Non-functional Tumors

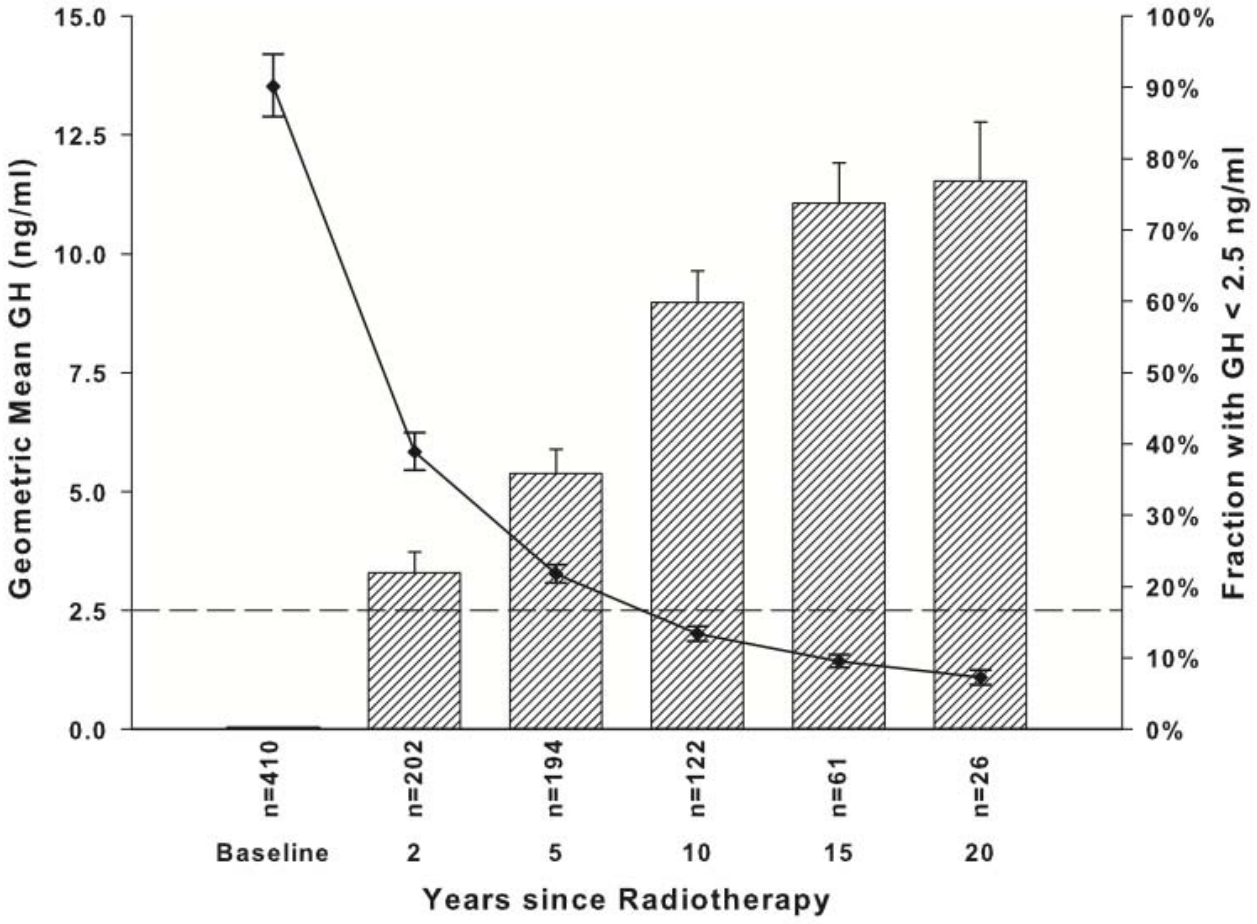
TABLE 1. Radiation therapy for nonfunctioning pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients	Follow-up, median	LC (%)	LC median (yr)
Iwai, 2005 (21)	1994–1999	GK	14	34	5 yr	93	5
Mingione, 2006 (20)	1989–2004	GK	18.5 mean (5–25)	90	3.7 yr	92	
Voges, 2006 (22)	1990–2004	L-SRS	15.3 mean (8–20)	37	6.8 yr, mean	100	
Liscak, 2007 (23)	1993–2003	GK	20 (12–35)	140	5 yr	100	
Pollock, 2008 (9)	1992–2004	GK	16 (11–20)	62	5.3 yr	95	7
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	152	31 months (min, 6 months)	90.3	
Brada, 1993 (24)	1962–1986	Conv	45 (45–50)	252		97	10
						88	20
Tsang, 1994 (25)	1972–1986	Conv	45	128	8.3 yr	91	10
Colin, 2005 (26)	1990–1999	SRT	50.4	63	6.8 yr (mean, 4 yr)	100	6.8
Ronson, 2006 (27)	1991–2001	Protons	54 (50.4–55.94)	24	3.9 yr	100	
Van den Bergh, 2007 (14)	1979–1998	Conv	45 (45–55.8)	76	7.8 yr	95	10
Chang, 2008 (18)	1975–1995	Conv	45 (45–54)	340	8.4 yr	93	5
						87	10
						81	15
						74	20
Snead, 2008 (28)	1983–2003	Conv	45 (43–50.4)	59	6.7 yr	98	10
Erridge, 2009 (29)	1974–2003	Conv	45 (35–60)	189	9.1 yr	95	10

RT, Radiation; LC, local control; L-SRS, linear accelerator-based SRS; Conv, conventional fractionated radiation; SRT, fractionated stereotactic radiotherapy; min, minimum.

J Clin Endocrinol Metab, July 2011, 96(7):1992–2003

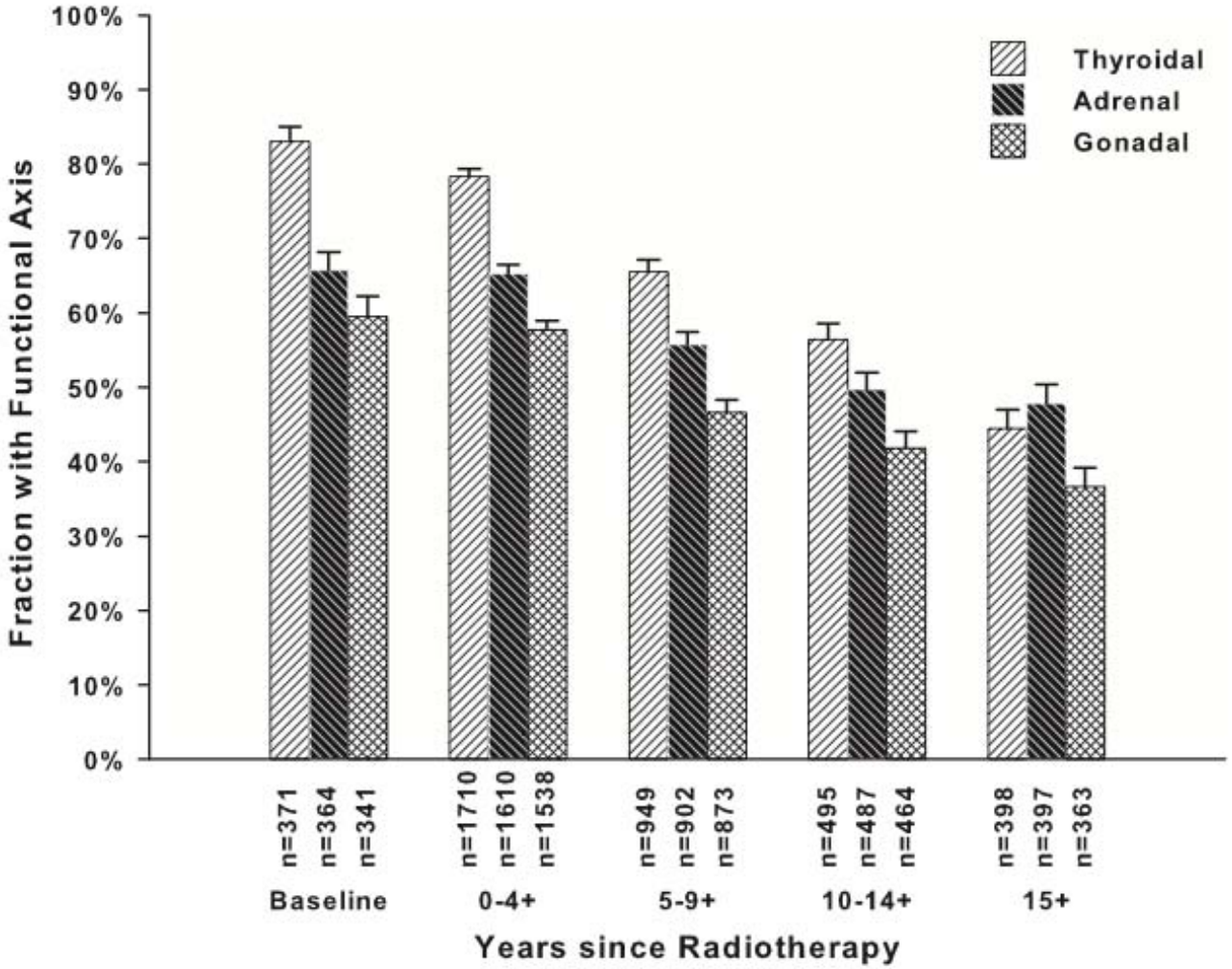
Fractionated RT Growth Hormone



884 patients in 14 UK Centers 1974-2000
45 Gy in 25 fractions most common

J Clin Endocrinol Metab, April 2006, 91(4):1239–1245

Pituitary Function Over Time



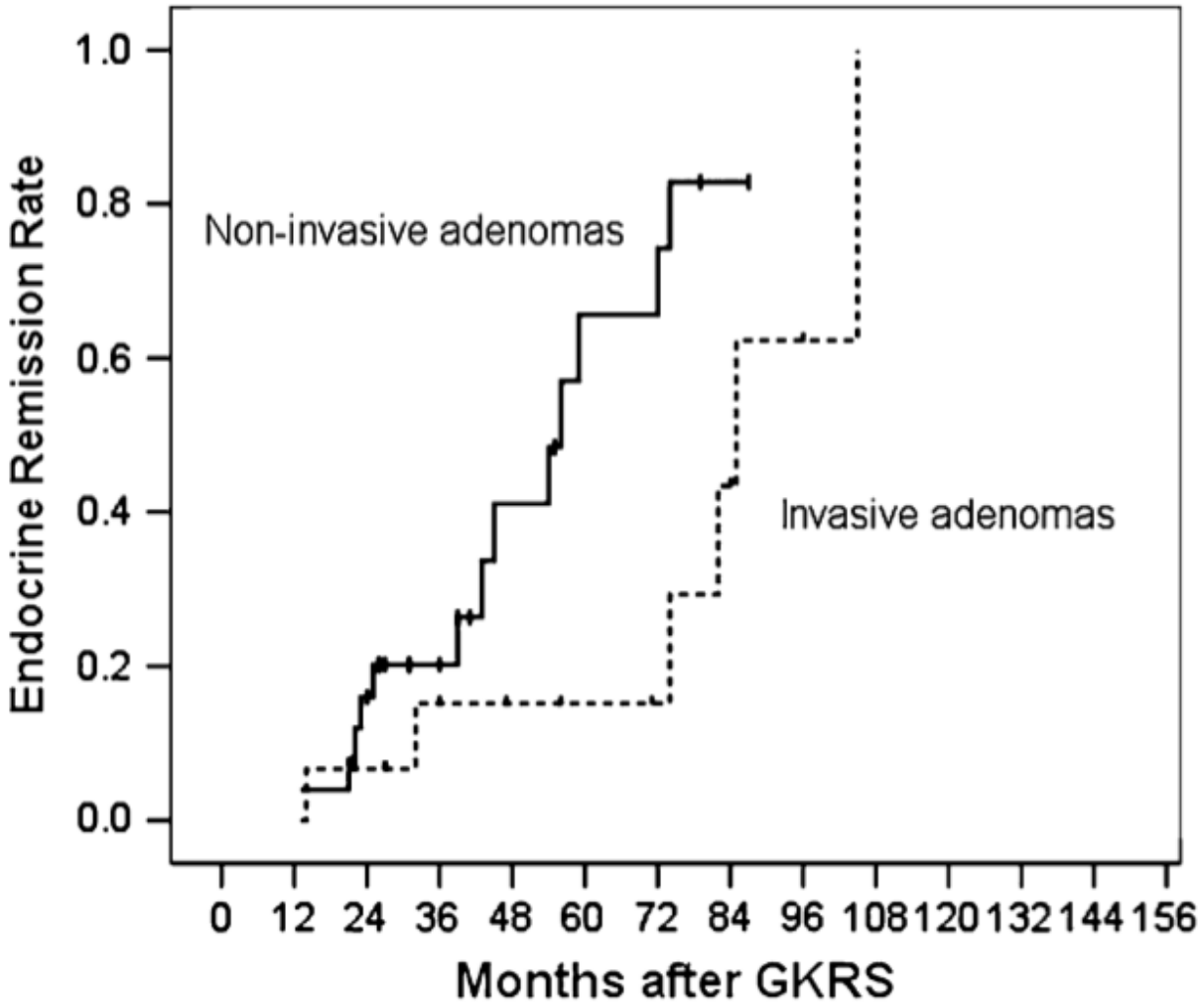
Radiosurgery for GH Tumors

Table 3 Factors associated with endocrine remission

Variables	*p* Value		Exp(B) (95 % CI)
	Univariate	Multivariate	
Age	0.722	NA	0.988 (0.962–1.015)
Gender (male)	0.388	NA	NA
Tumor volume	0.637	NA	1.027 (0.838–1.259)
Marginal dose	0.458	NA	1.143 (0.979–1.335)
IGF-1 index before GKRS[a]	0.003*	0.002*	0.103 (0.025–0.435)
Suppression medication at GKRS (yes)	0.797	NA	NA
Suppression medication after GKRS (yes)	0.043*	0.142	0.428 (0.138–1.328)
Tumor invasiveness (no)	0.035*	0.002*	8.981 (2.205–36.576)
Surgical resection pre-GKRS (yes)	0.292	NA	NA

19/40 patients (47%) had an endocrine remission

Endocrine Response for Radiosurgery



ACTH

TABLE 2. Radiation therapy for ACTH-secreting pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients	Hormone normalization
Mitsumori, 1998 (2)	1989–1995	SRT	45	30	54% CR, 62% PR
		SRS	15 (10–18)	18	33% CR, 50% PR
Höybye, 2001 (32)	1976–1985	GK	30–100/each, 1–4 tx	18	83% all, 44% 1 tx, 39% 2 t
Kobayashi, 2002 (11)	1991–1999	GK	28.7 (15–70)	20	85% CR/PR, 35% CR
				5	33% CR/PR
Devin, 2004 (33)	1991–2002	L-SRS	15	35	37% CR, 11% NL, 49% all
			14.7, mean (7–33)		
Voges, 2006 (22)	1990–2004	L-SRS	15.3, mean (8–20)	17	78.3% CR, 100% NL
Castinetti, 2007 (6)	1993–2003	GK	29.5 (15–40)	40	42.5% CR
Jagannathan, 2007 (34)	1990–2005	GK	25	90	54%
Petit, 2008 (35)	1992–2005	Protons	20 (15–20)	38	89% CR/PR
					58% CR
				33	52% CR
					36% NL
				5	100% CR
Castinetti, 2009 (36)	1993–2003	GK	28, mean (24–27)	18	50% CR
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	82	54% CR
				22	20% CR
Estrada, 1997 (37)	1980–1993	Conv	50, mean (48–54)	30	83%
Colin, 2005 (26)	1990–1999	SRT	50.4	10	0% CR
Ronson, 2006 (27)	1991–2001	Protons	54, iso (50.4–55.94)	4	25% CR, 25% PR
Minniti, 2007 (38)	1988–2002	Conv	45 (45–50)	40	78%
					84%

RT, Radiation; LC, local control; L-SRS, linear accelerator-based stereotactic radiosurgery; Conv, conventional fractionated radiation; SRT, fractionated stereotactic radiotherapy; min, minimum; tx, treatment; CD, Cushing's disease; NS, Nelson's syndrome; CR, complete response; PR, partial response; NL, normalization with medication; H nl, hormonal normalization; iso, isocenter.

Prolactin

TABLE 4. Radiation therapy for prolactin-secreting pituitary adenomas

First author, year (Ref.)	Study years	RT type	RT dose (Gy), median (range)	No. of patients	Hormone normalization (%)
Pan, 2000 (52)	1993–1997	GK	Mean, 31.2 (9–35)	128	52.3% CR, most NL
Pouratian, 2006 (8)	1990–2003	GK	18.6 (0.3–25) 18.9 (0.3–25)	23 endo f/u 28 image f/u	26% CR
Voges, 2006 (22)	1990–2004	L-SRS	Mean, 15.3 (8–20)	13	16.7% CR 42.7% NL
Jezkova, 2009 (53)	1993–2005	GK	34 (20–49)	35	80% all, 37.1% CR, 42.9%
Castinetti, 2009 (36)	1993–2003	GK	Mean, 28 (24–27)	15	47% CR
Sheehan, 2011 (5)	1989–2006	GK	24 (9–30)	32	26% CR
Tsagarakis, 1991 (54)	1972–1981	Conv	45	36	50% CR, 28% PR
Tsang, 1996 (55)	1972–1986	Conv	50 (40–52)	64	25% CR
Sasaki, 2000 (56)	1969–1994	Conv	51 (44–70)	5	40% CR PRL 40% PR PRL
Colin, 2005 (26)	1990–1999	SRT	50.4	4	29% CR
Ronson, 2006 (27)	1991–2001	Protons	54 iso (50.4–55.94)	6	33% CR 66% PR
Erridge, 2009 (29)	1974–2003	Conv	45 (35–60)	58	

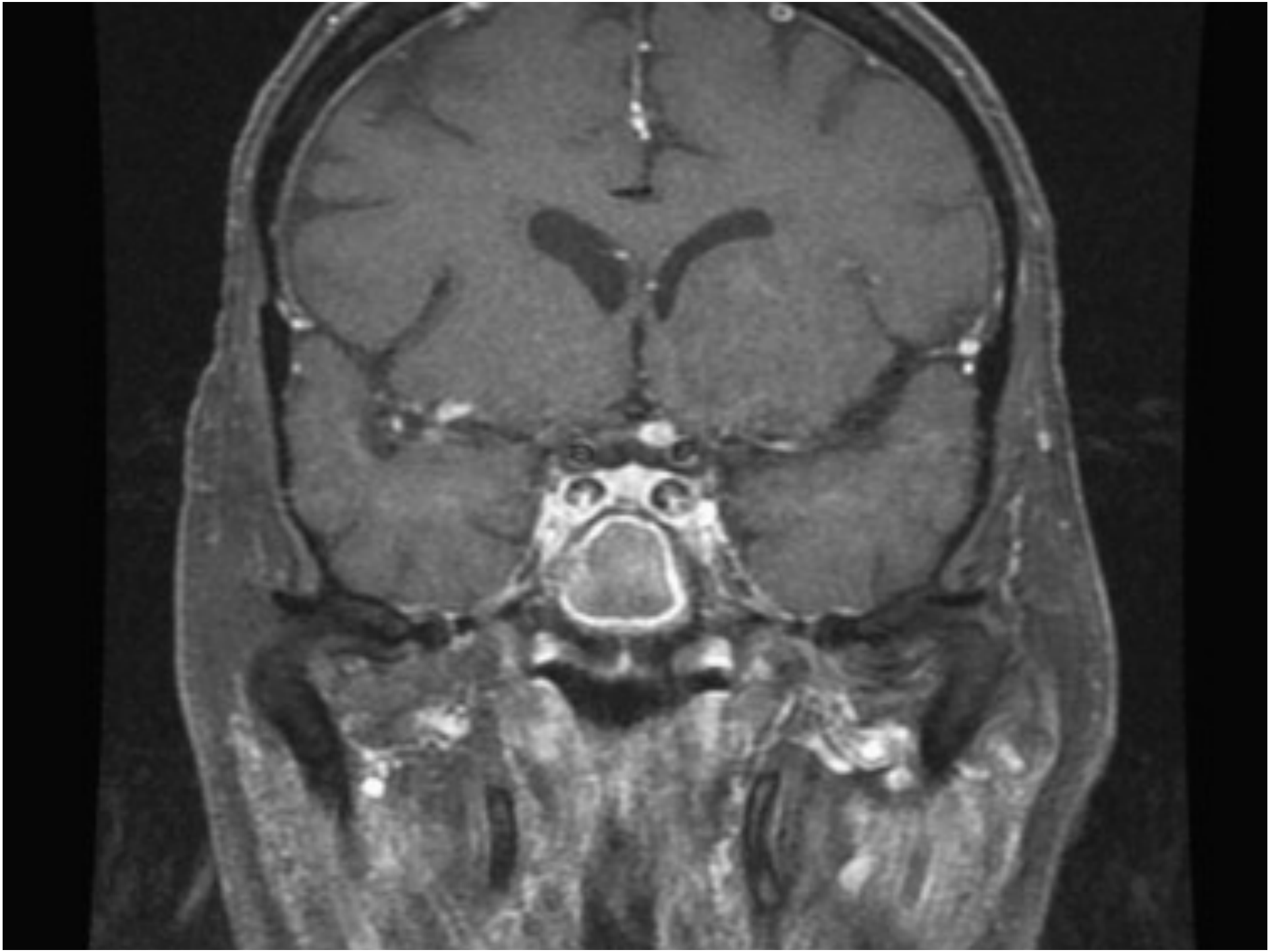
Optic Nerve Injury

Table 1. Characteristics of patients developing radiation optic neuropathy

Patient no.	Pathology	Prior treatment	ON* dose	Visual complication	Time to onset (months)
1	Meningioma	Surgery (3), EBRT (58.8 Gy)	7.0 Gy	Decrease visual acuity	93
2	Pituitary (ACTH)	Surgery; Pre-existing VF loss, dec. VA, and atrophy OD*	12.8 Gy	Complete OD visual loss	18
3	Pituitary (ACTH)	Surgery (2), EBRT (50.4 Gy)	9.0 Gy, 12.0 Gy	Complete OS visual loss‡	36, 61
4	Pituitary (ACTH)	Surgery, EBRT (45 Gy)	9.0 Gy	Bilateral decreased visual acuity†	24

Mayo Clinic, 4/218 patients treated to mean dose 10 Gy

Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 5, pp. 1177–1181, 2003



Oculomotor Injury

Injury to III, IV, VI reported but is more common with patients receiving retreatment

Optic nerve tolerance 8-10 Gy
Cavernous sinus ? (>40-60 Gy)

Vaphiades et al: J Neuro-Ophthalmol 2011; 31: 210-213

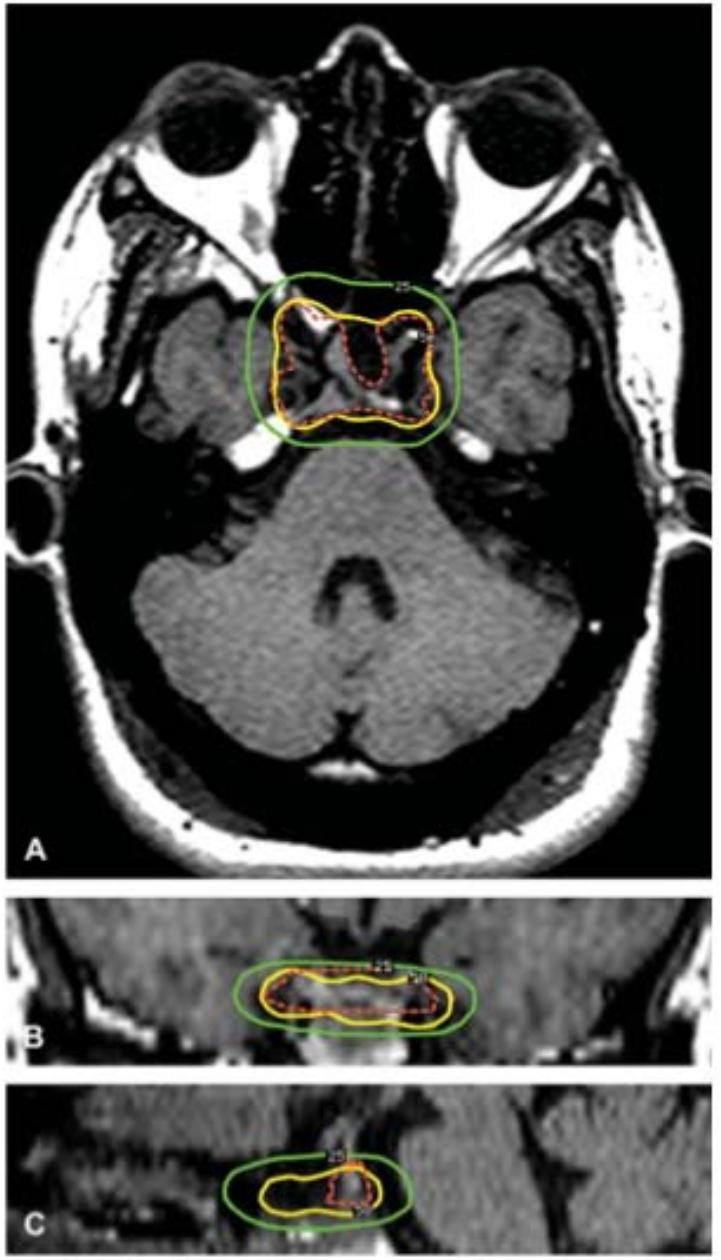


FIG. 1. *Case 1.* T1 axial (**A**), coronal (**B**), and sagittal (**C**) MRI used for radiosurgery. The radiosurgery dose was 20 Gy prescribed to the 50% isodose line. Hatched lines denote primary target (orange) and the 50% (yellow) and 25% (green) isodose curves.

Marginal Dose Predicts Hypopituitarism

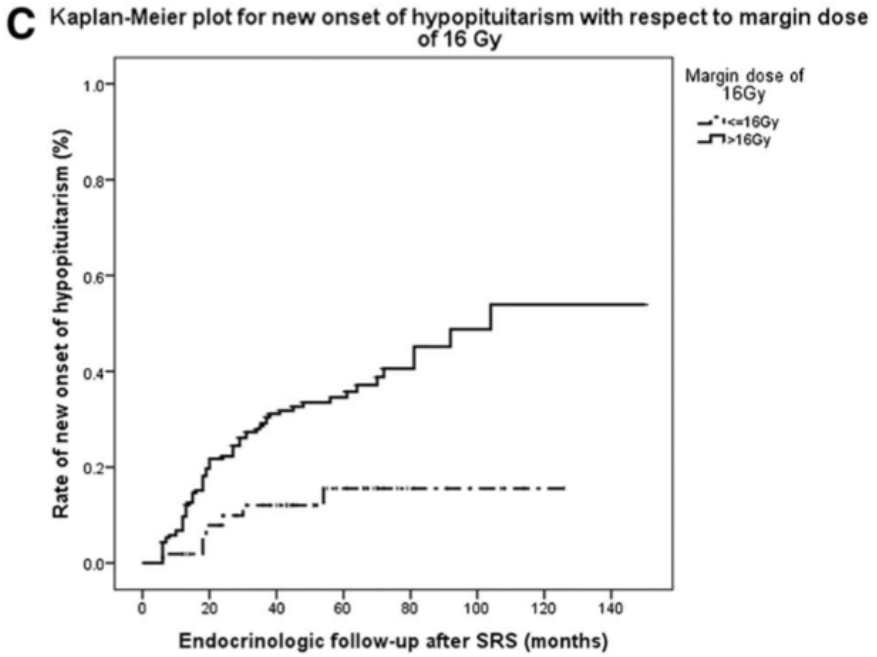


TABLE 4. Univariate and Multivariate Analyses of Potential Prognostic Factors Contributing to the New Onset of Hypopituitarism After Stereotactic Radiosurgery (Logistic Regression Model)[a]

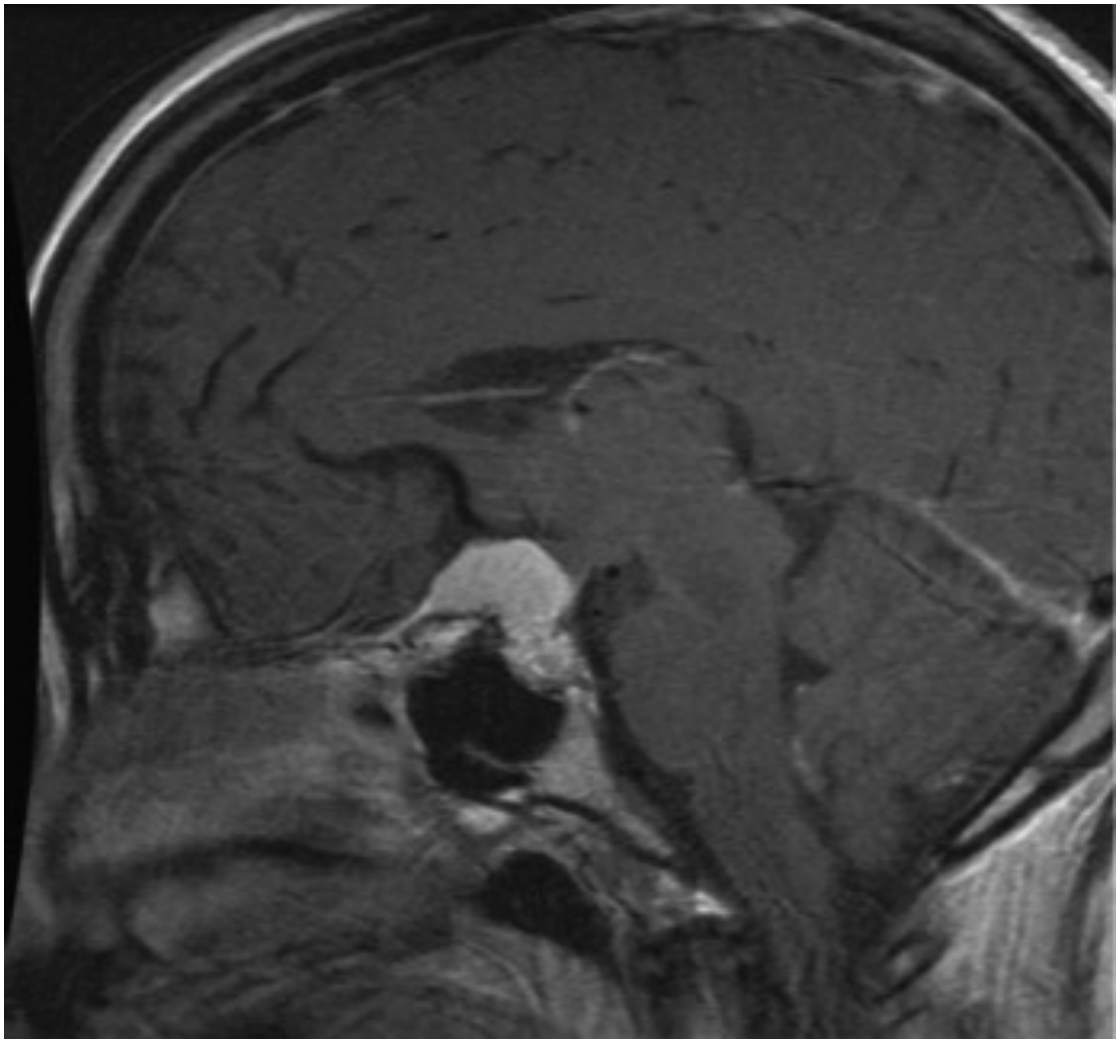
	Univariate Analysis				Multivariate Analysis			
			95% CI				95% CI	
Variables	*P*	OR	Lower	Upper	*P*	OR	Lower	Upper
Age at SRS	.45	0.993	0.975	1.011	...	...	...	...
Volume	.80	0.989	0.910	1.075	...	...	...	...
Suprasellar extension	.10	1.582	0.910	2.749	.03	1.895	1.064	3.376
CS invasion	.87	0.957	0.562	1.632	...	...	...	...
Whole sella turcica treatment	.61	1.220	0.574	2.592	...	...	...	...
Margin dose	.01	1.075	1.018	1.135	.004	1.086	1.027	1.149
Maximum dose	1.0	1.000	0.972	1.029	...	...	...	...
Hypopituitarism at the time of SRS	.74	0.894	0.459	1.741	...	...	...	...

[a]CI, confidence interval; CS, cavernous sinus; OR, odds ratio; SRS, stereotactic radiosurgery.

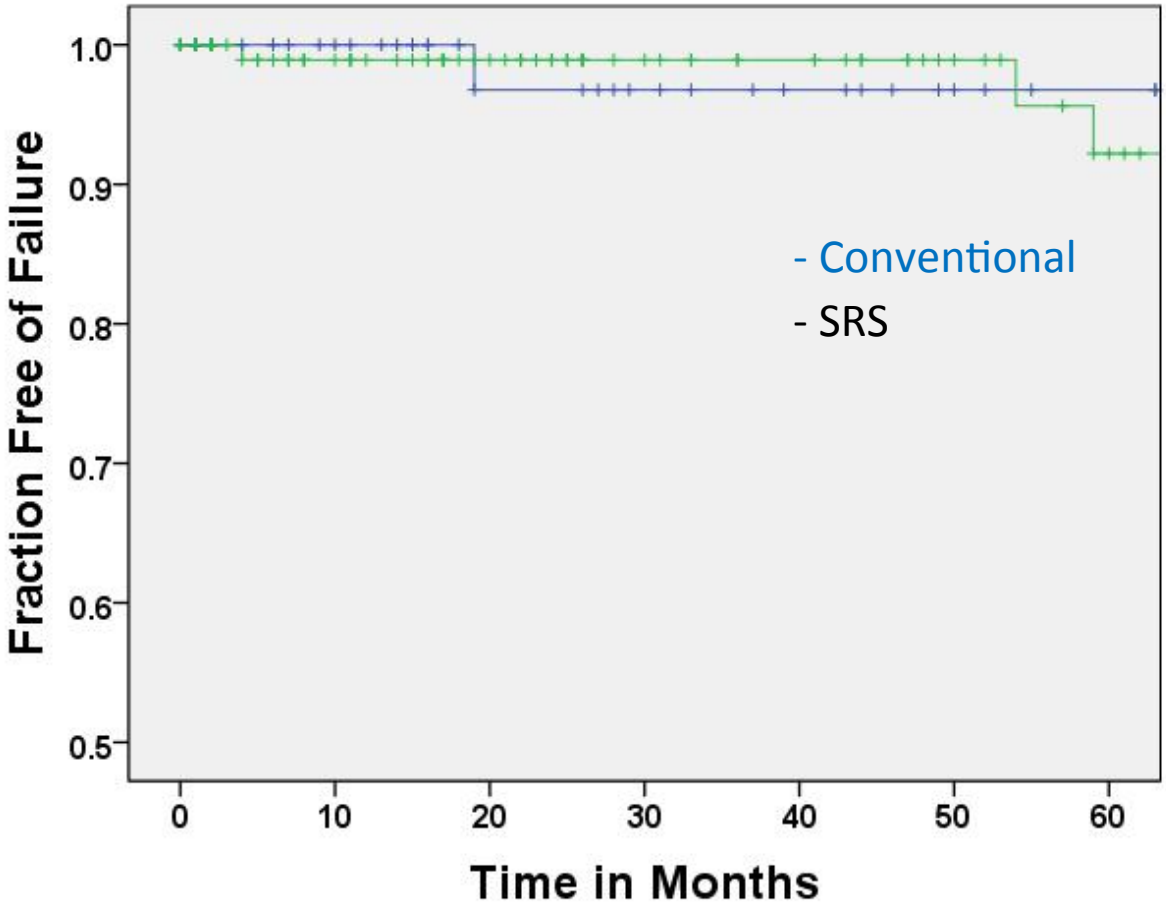
UVA 262 patients

Neurosurgery 72:630–637, 2013

Meningioma vs Pituitary Adenoma



Local Control of Unbiopsied Presumed Meningioma



p=0.684

Conventional 5 yr LC
96.7%

SRS 5 yr LC
95.5%

Conclusion

- Fractionated RT and radiosurgery are effective for tumor growth control control as a second line therapy
- Decline in hormone secretion occurs more rapidly with radiosurgery than fractionated RT
  - About half respond
- Dose schedule is dependent upon tumor volume and proximity of optic apparatus
- Optimal timing must be considered carefully due to potential for injury

Questions?

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