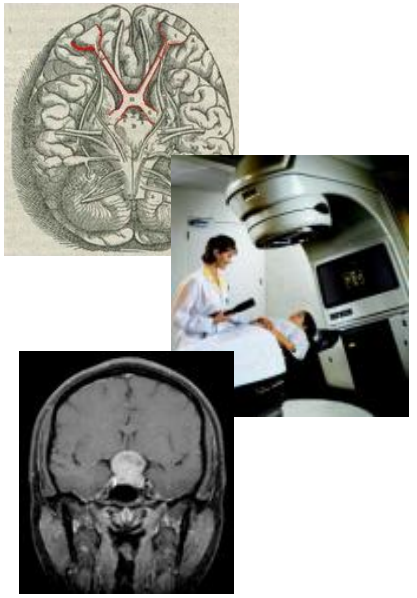
Approccio multidisciplinare dei tumori dell'area sellare: adenomi ipofisari La Radioterapia

G Minniti



Associazione Italiana Radioterapia Oncologica

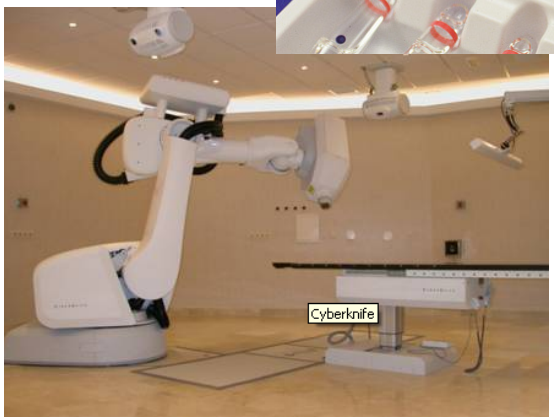
Radiation Oncology, Sant'Andrea Hospital,
University of Rome Sapienza

SAPIENZA UNIVERSITÀ DI ROMA

AZIENDA OSPEDALIERA SANT' ANDREA
FACOLTÀ DI MEDICINA E PSICOLOGIA

Treatment of pituitary tumours

- *Surgery*
- *Medical therapy*
- *Radiotherapy*



Radiation of pituitary adenomas: outline

- *Conventional RT*

- *New radiation techniques*
- *Fractionated RT*

  Conformal 3D RT

  Stereotactic RT

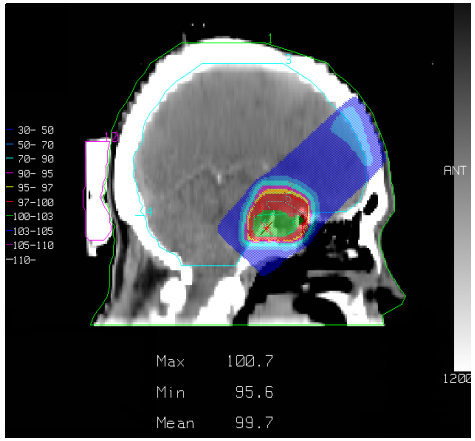
  IMRT/Tomotherapy

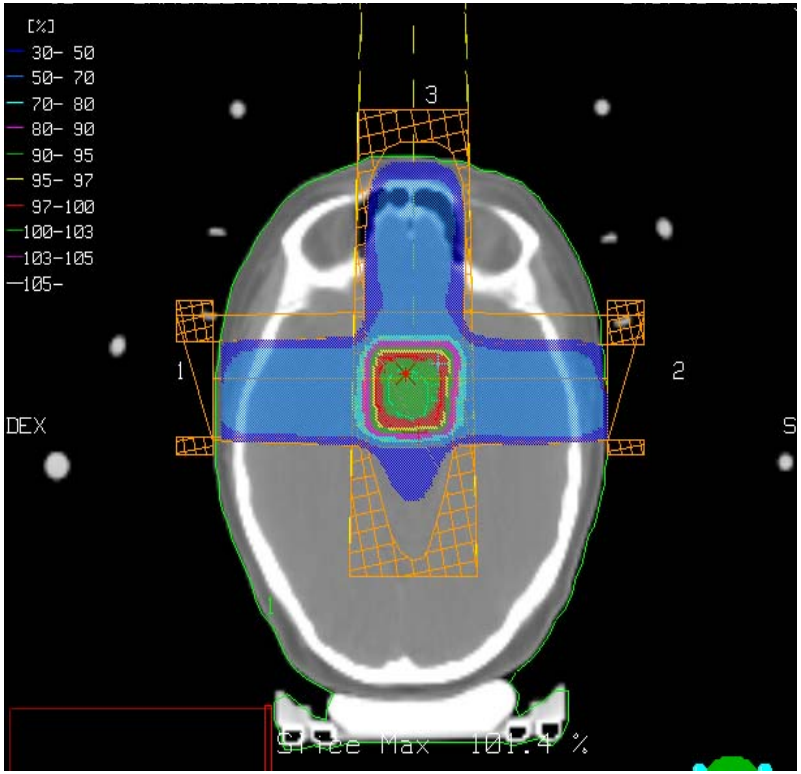
  Protons
- *Radiosurgery*

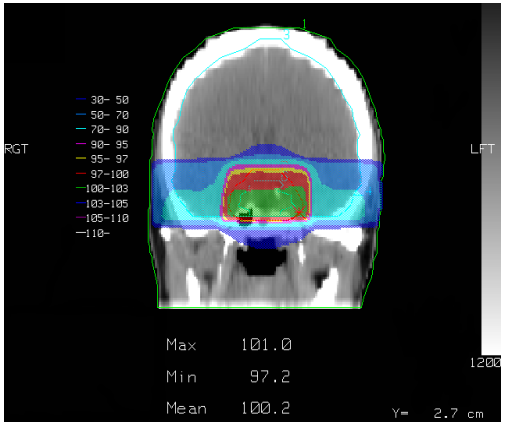
- *Nonfunctioning and secreting adenomas*

Radiotherapy for pituitary adenomas

conventional radiotherapy



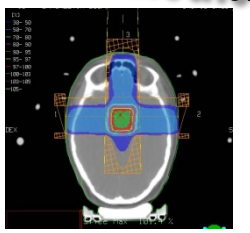




45 – 50 Gy in 25 - 30 fractions

Radiotherapy for pituitary adenomas

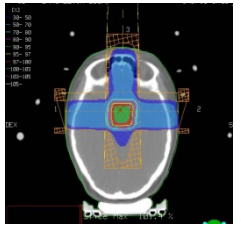
conventional radiotherapy



Authors	patients	follow-up	tumor control
Grigsby 1989	121*	11,7	89.9 at 10 years
McCollough 1991	105*	7,8	95 at 10 years
Brada 1993	411*	10,8	88 at 10 and 20 years
Tsang 1994	160		
Zierhut 1995	138*		
Rush 1997	70*		
Breen 1998	120	9	87.5 at 10 years
Gittoes 1998	126	7,5	93 at 10 and 15 years
Sasaki 2000	91*	8,2	93 at 10 years

10-year control > 85%

Recent published studies on the conventional radiotherapy of secreting pituitary adenomas



Authors	adenoma	patients	f-up	tumour control
Barrande 2000	GH	128	11	53 at 10 years
Biermasz 2000	GH	36	10	60 at 10 years
Epaminond				rs
Minniti 200				s
Estrada 19				ars
Minniti 2007	ACTH	40	9	79% at 5 years 84% at 10 years

10-year control 50- 60% (GH)

5-year control 80% (ACTH)

Late toxicity of radiotherapy

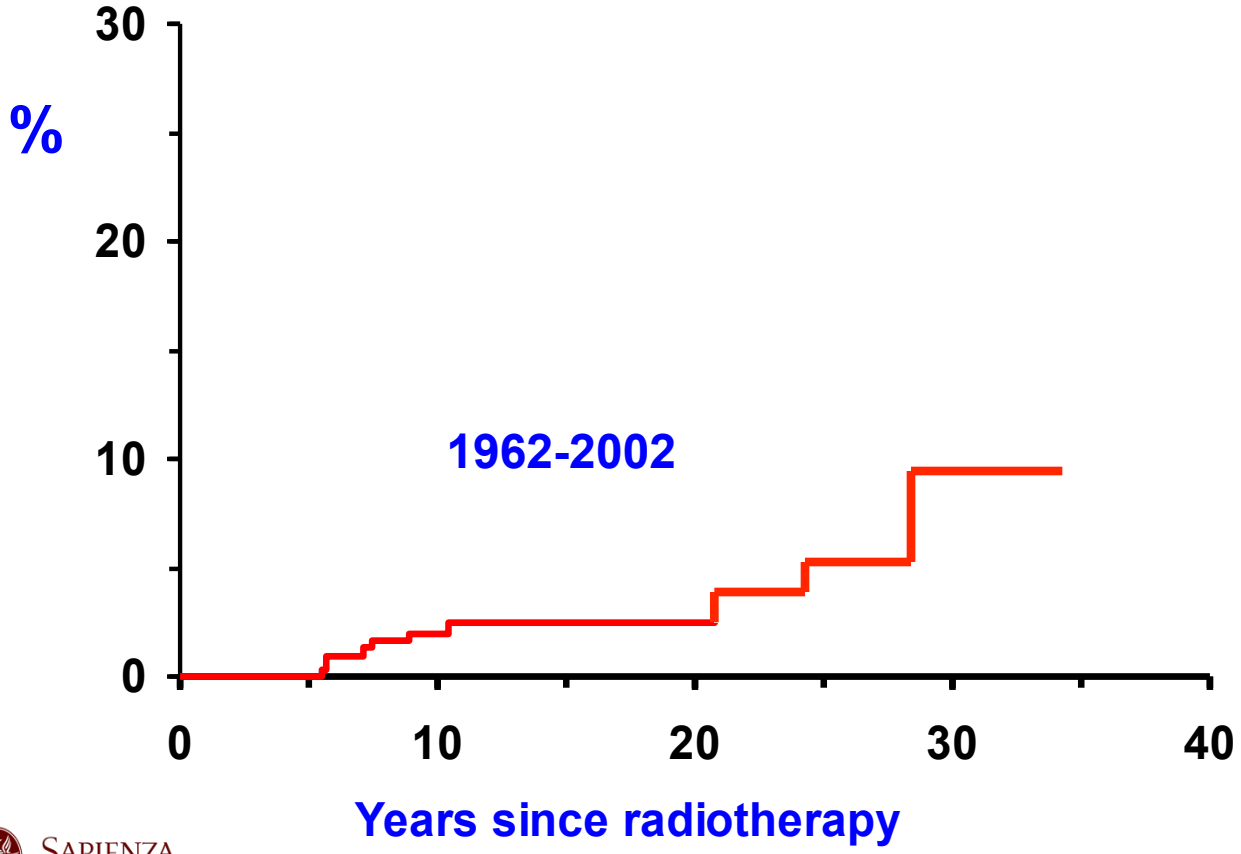
conventional radiotherapy

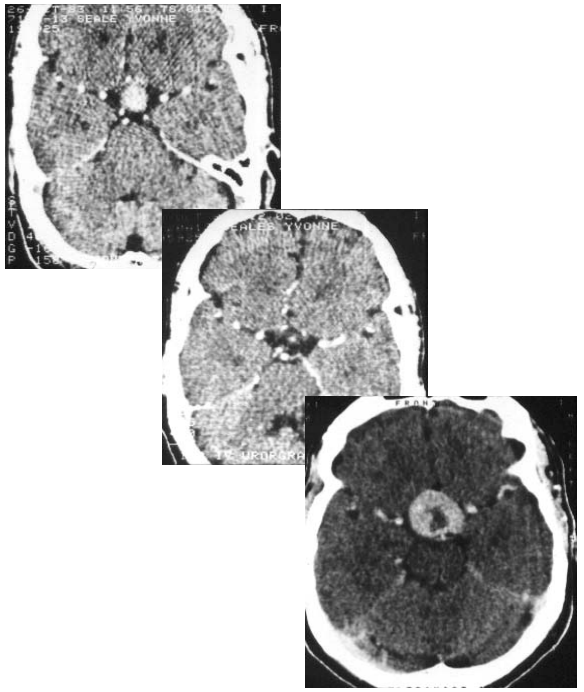
- *Hypopituitarism (30%-60% at 5 and 10 yrs)*
- *Radionecrosis (0%-3%)*
- *Optic neuropathy (0%-3%)*
- *Cranial nerves deficits (0-2%)*
- *Neurocognitive effects (0% - ?%)*
- *Radiation induced tumours (2% at 20-30 yrs)*
- *Increased CVA*

conventional radiotherapy

Second brain tumour in pituitary adenoma

Cumulative risk of second brain tumour

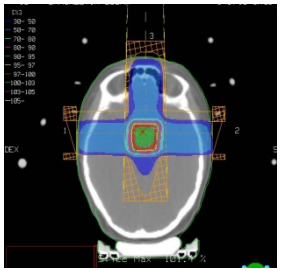




Minniti et al, JCEM 2005

conventional radiotherapy

Radiotherapy for pituitary adenoma



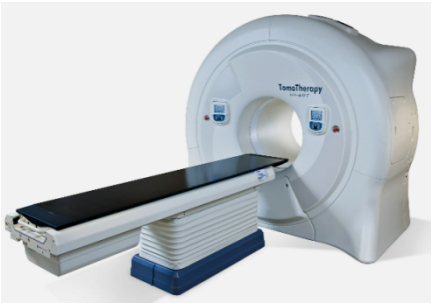
Survival - relative risk of death for CVA

observed	128
expected	81
relative risk	1.58
95%CI	1.32-1.90

Brada et al Clin Endocrinol 2002

New techniques of radiotherapy

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



Stereotactic techniques

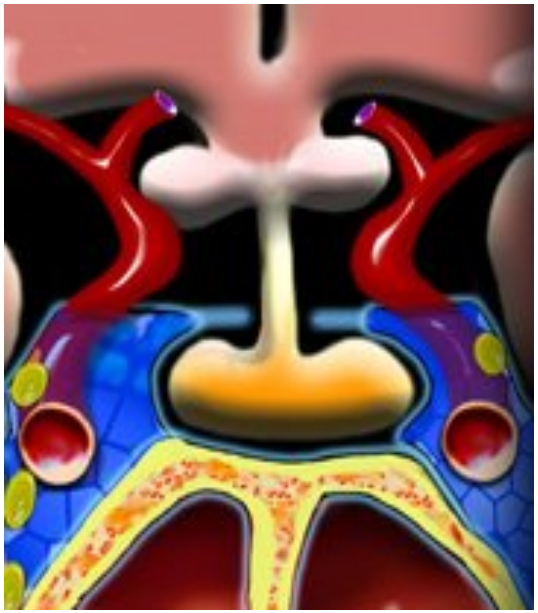
- *Radiosurgery (SRS) either Gamma Knife (GK), Cyberknife, or a linear accelerator (LINAC), delivered as a single treatment;*

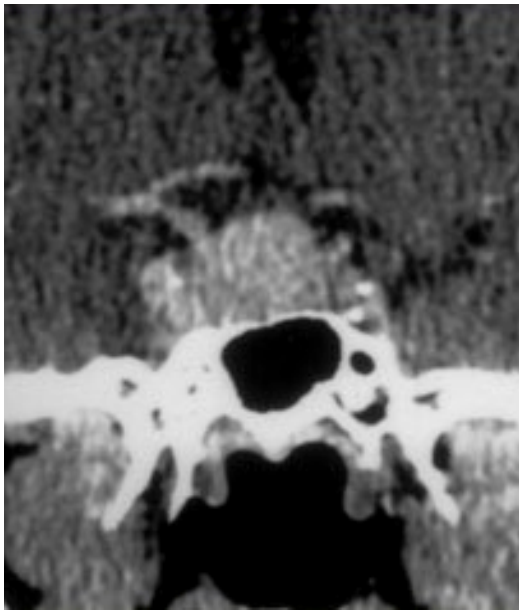
- *conformal stereotactic radiotherapy (FSRT) delivered as a fractionated treatment.*

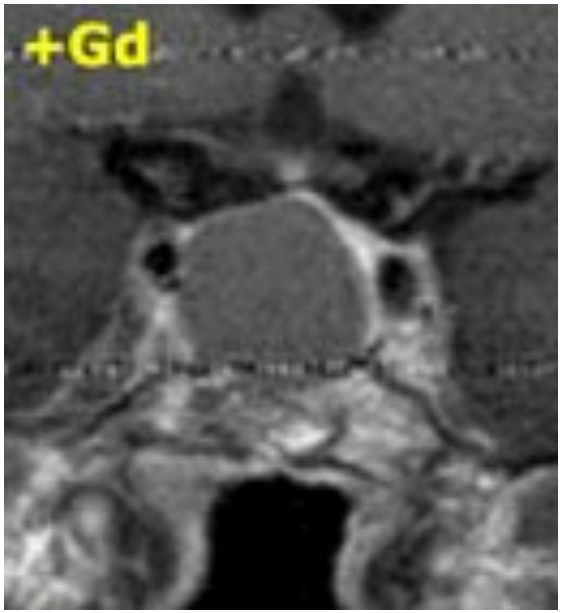
Imaging

CT

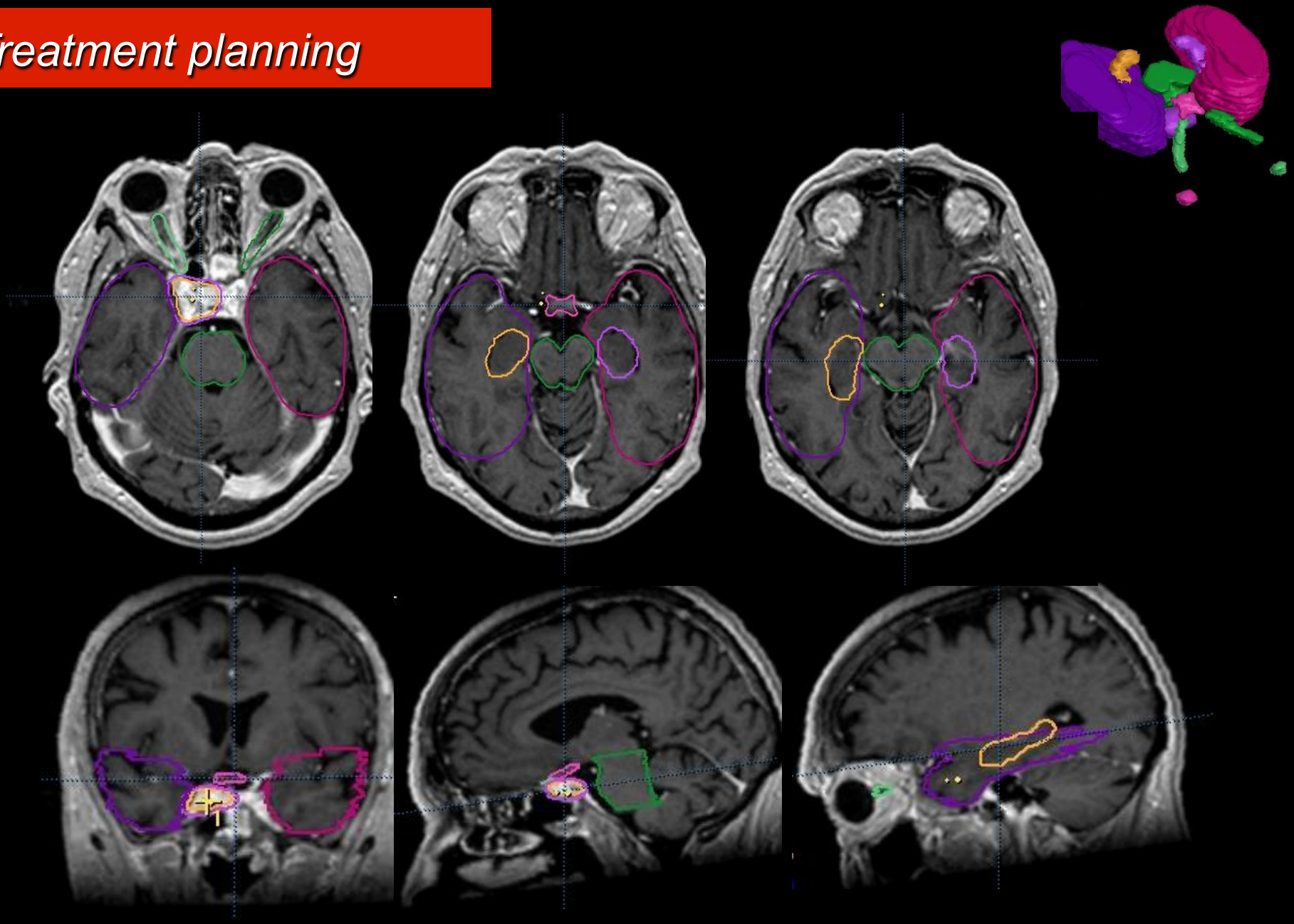
MRI



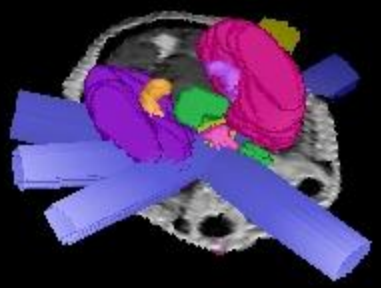


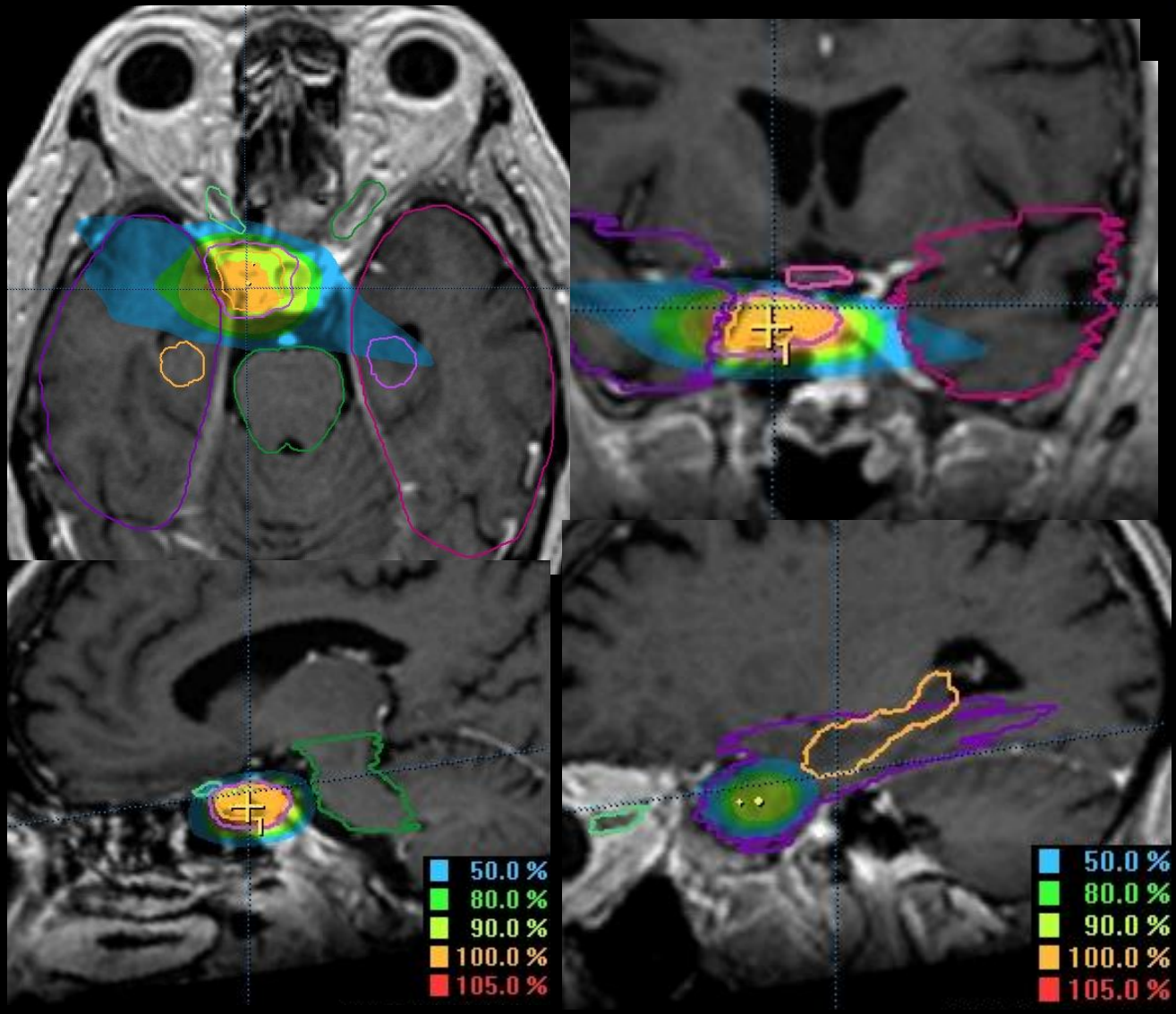


Treatment planning

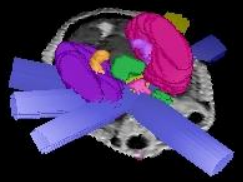


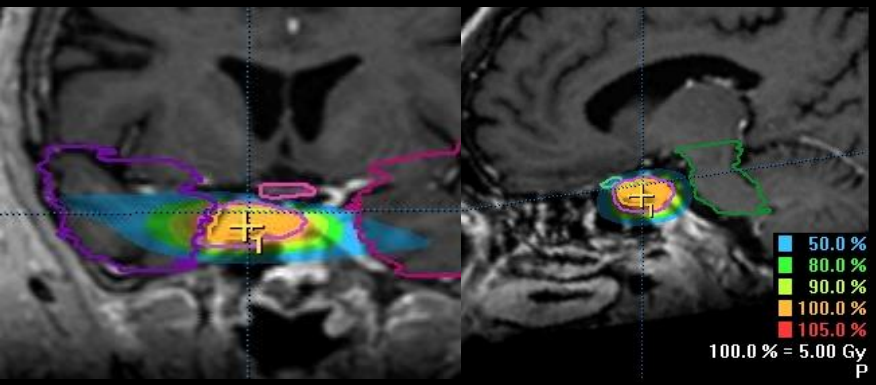
Treatment planning

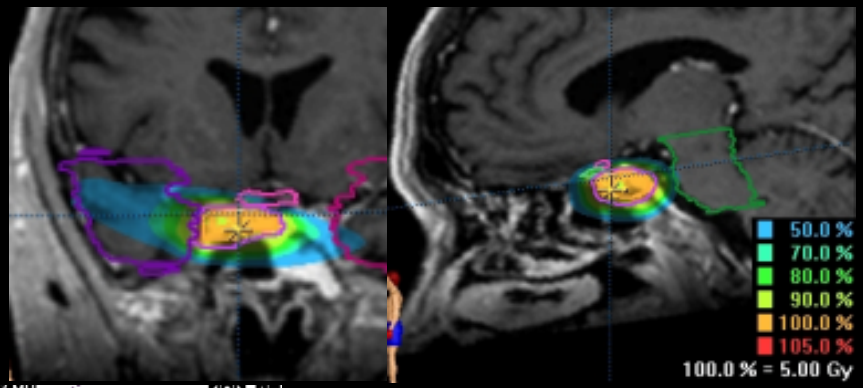


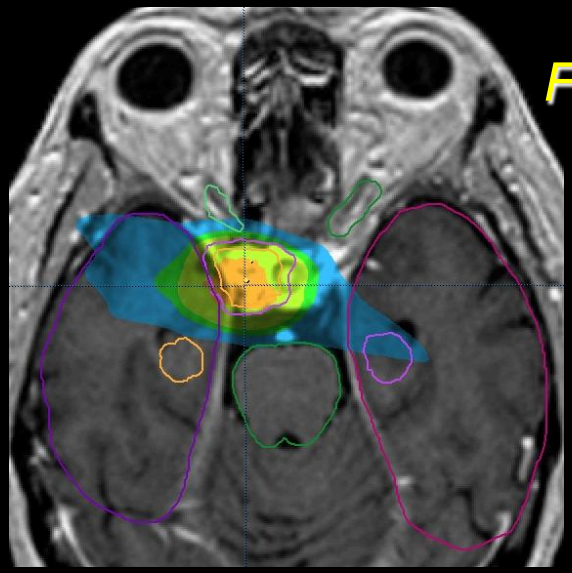


Treatment planning

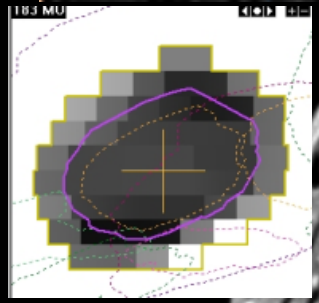




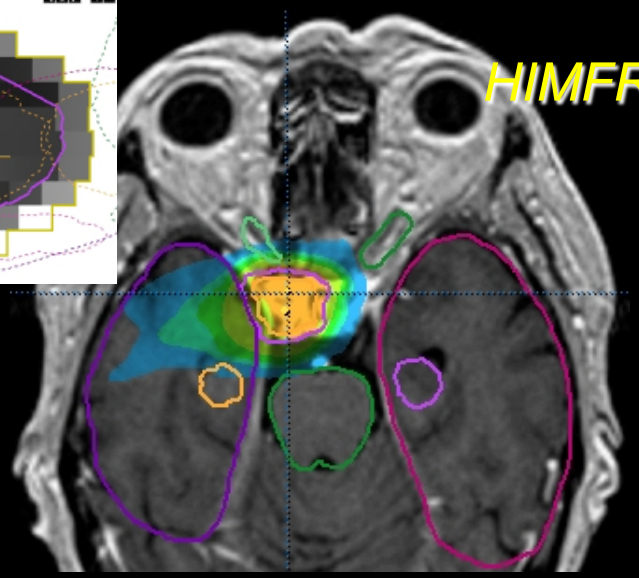




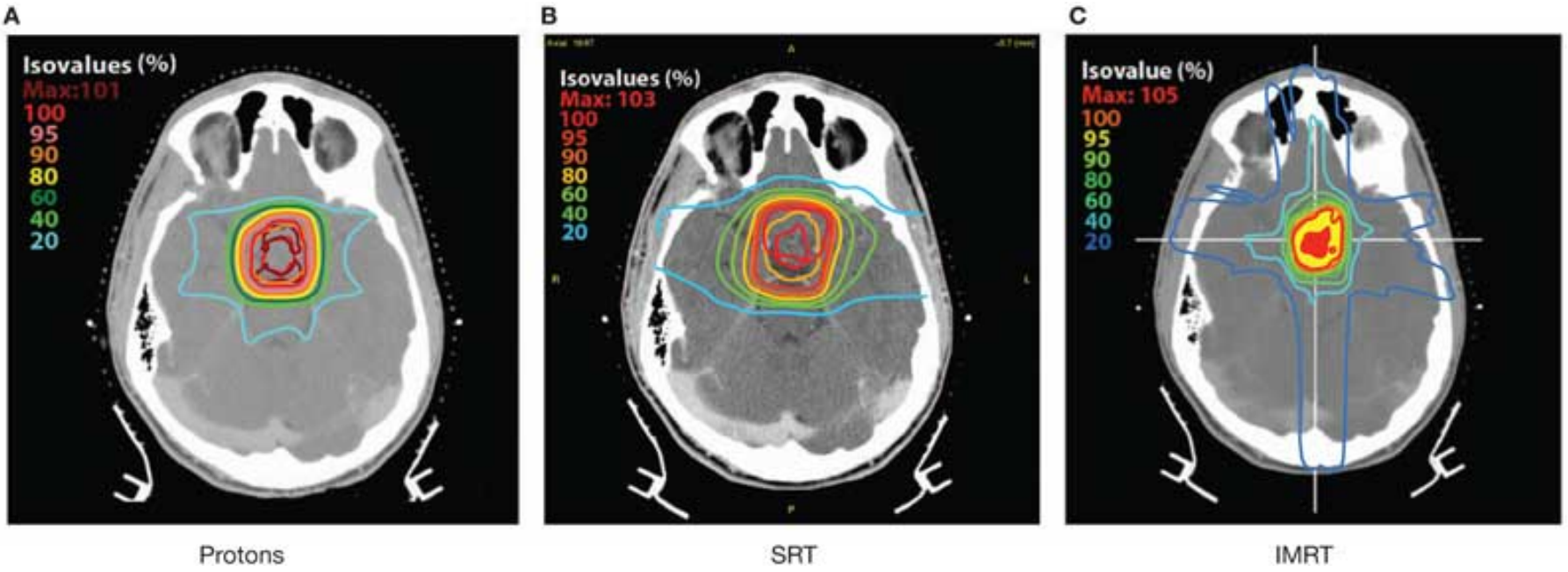
FSRT



HIMFRST

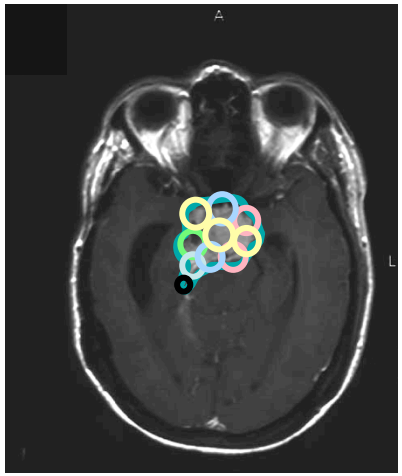


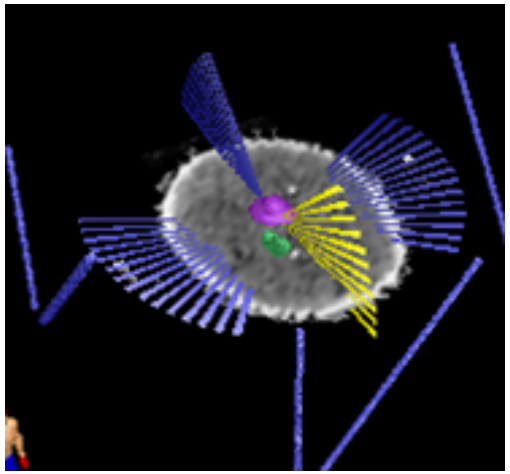
Comparison of radiation techniques

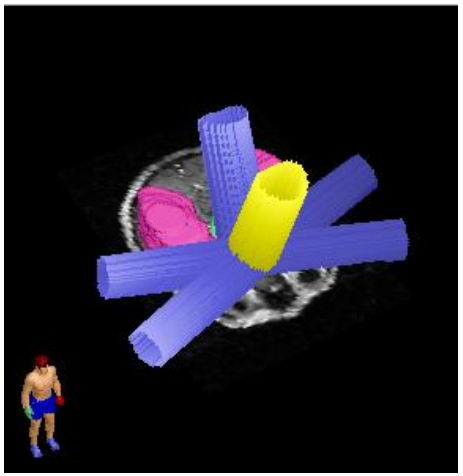


Reduced toxicity to be proved in long-term follow-ups

Treatment delivery







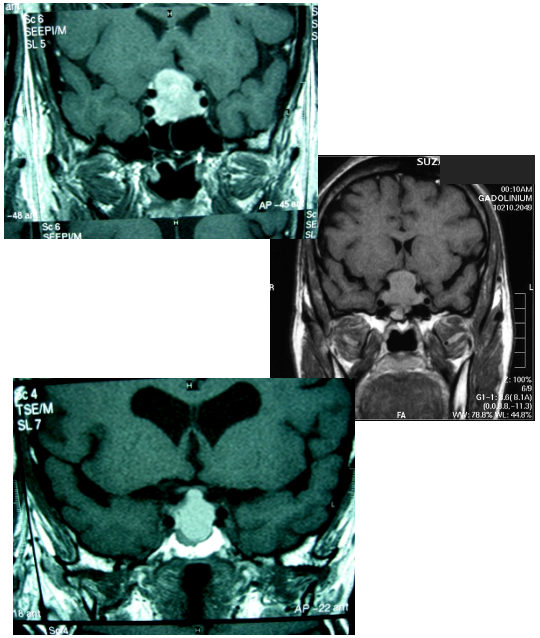
Immobilization

Technique	Immobilization system	Fractionation	Accuracy
Conventional RT	mask	conventional (25-30)	5-7 mm
IMRT	mask	conventional (25-30)	3-5 mm
Radiosurgery			
LINAC system	stereotactic fixed frame	single session	< 1mm
GammaKnife system	stereotactic fixed frame	single session	< 1mm
Proton RS	stereotactic fixed frame	single session	< 1mm
CyberKnife system	stereotactic mask	single session/ hypofractionation (3-5)	< 1mm
Proton therapy	stereotactic relocatable frame/mask	conventional (25-30)	1-2 mm
FSRT	stereotactic relocatable frame/mask	conventional (25-30)	1-2 mm

Minniti et al, Rad Oncol 2010

Stereotactic radiation for pituitary adenoma

- Efficacy
  - Tumour control
  - Endocrine control
- Toxicity



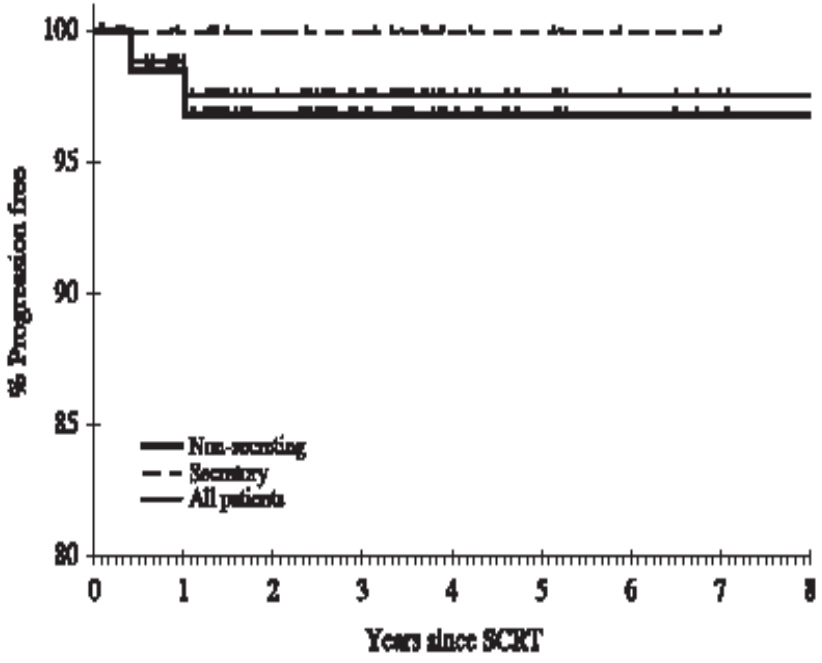
FSRT for NF pituitary adenoma

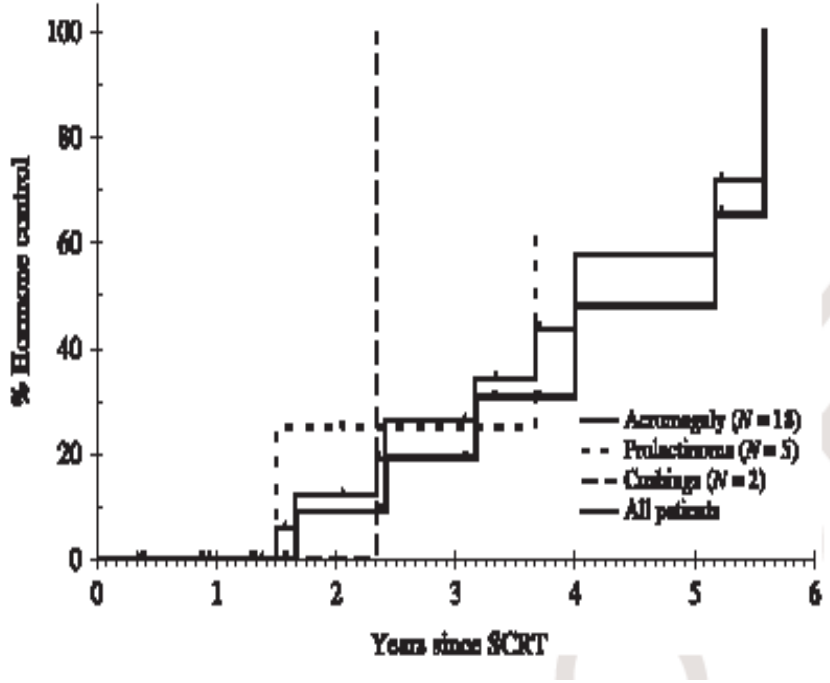
authors	patients	follow-up	control rate	late toxicity (%)	
		median (months)	%	visual	Hypopituitarism
Coke 1997	19*	9	100	0	0
Mitsumori 1998	30*	33	86 at 3 years	0	20
Milker-Zabel 2001	68*	38	93 at 5 years	4	5
Paek 2005	68	30	98 at 5 years	3	6
Colin 2005	110*	48	99 at 5 years	2	29 at 5 years
Minniti 2006	92*	32	98 at 5 years	1	22
Selch 2006	39*	60	100	0	15
Kong 2007	64*	37	97 at 4 years	0	11

*series include secreting pituitary adenomas

Minniti et al, Neurosurgical reviews 2008

FSRT for secreting pituitary adenomas



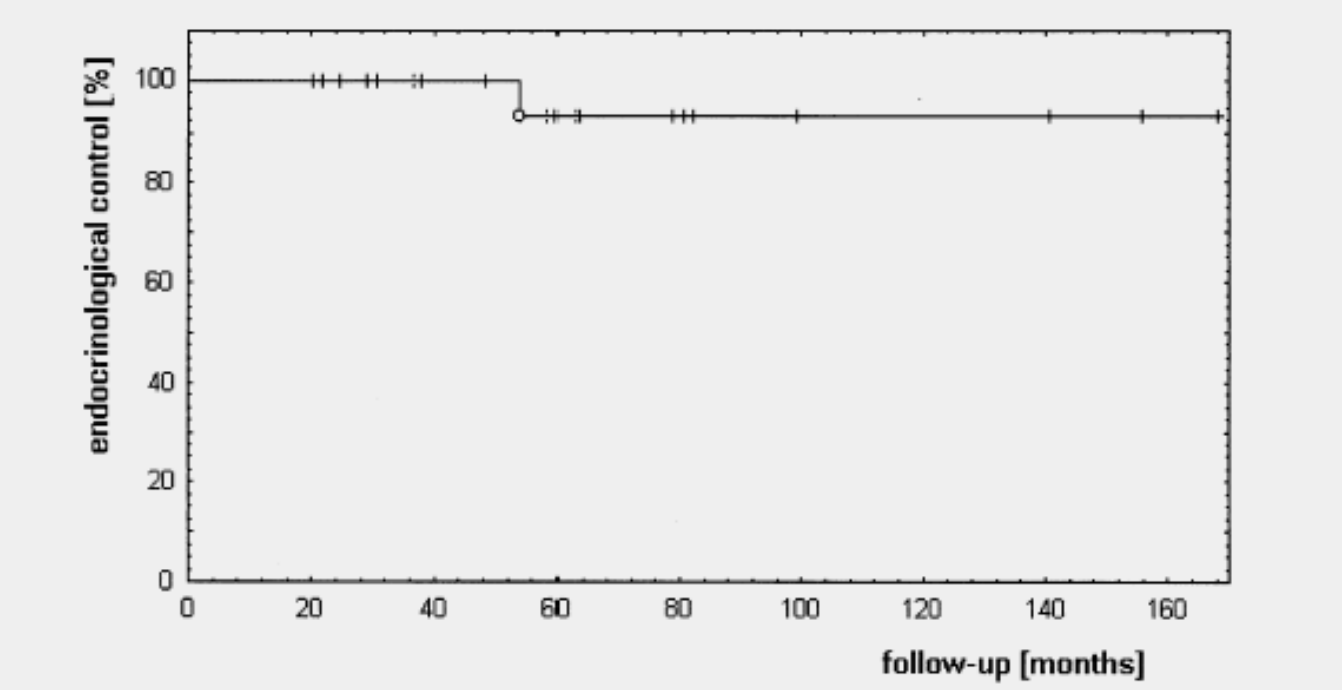


5-year control 97%

50% at 5 years

Minniti et al, Clin Endocrinol 2006

FSRT for secreting pituitary adenomas



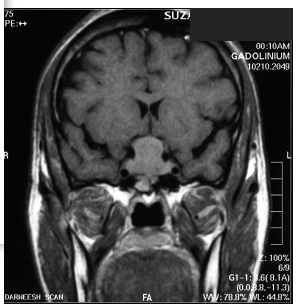
21/25 patients at 26 months follow-up

MILKER-ZABEL 2004, IJROBP

FSRT for pituitary adenoma

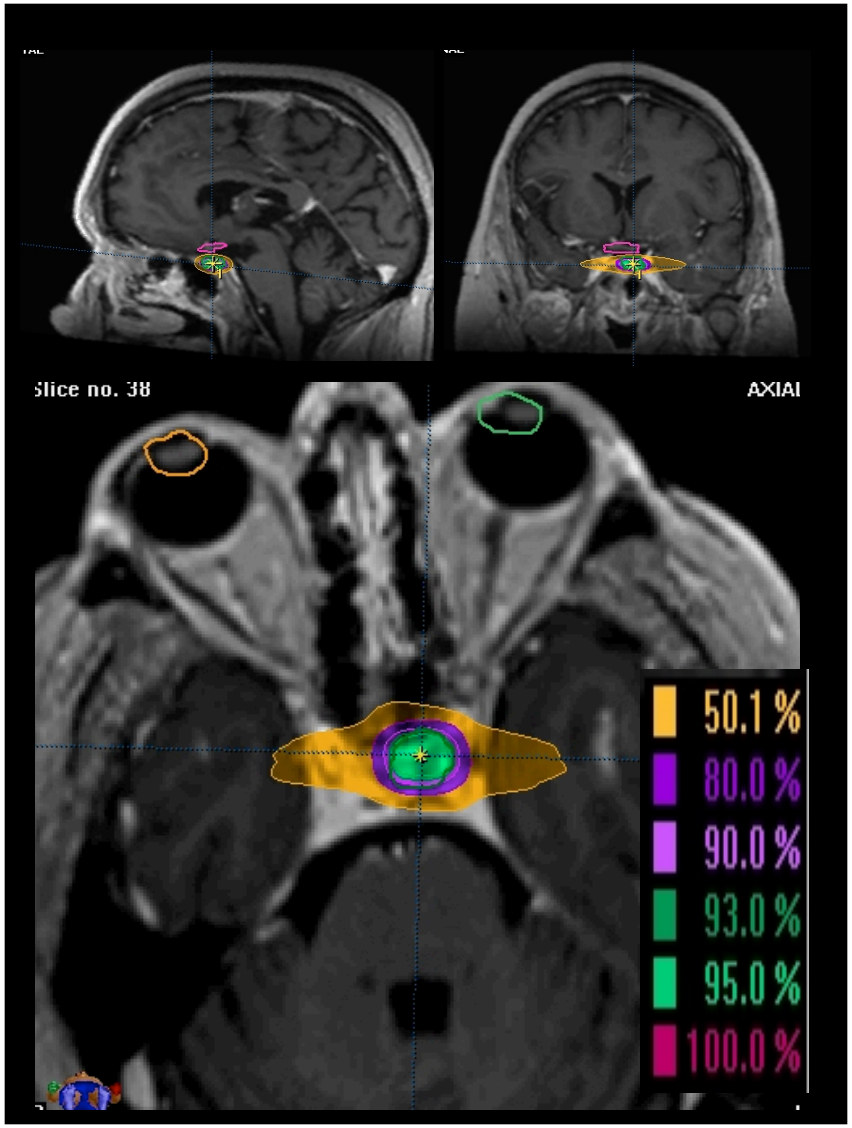
Long-term toxicity

- Endocrine failure (5-29%)
- Neurological damage (1-4%)
  - Vision
  - Cranial deficits
  - Cognitive function
- Second malignancy (0%)
- CVA (0%)



Radiosurgery for pituitary adenomas

- *NF adenomas*
- *Secreting adenomas*



Summary of results of published series on SRS for nonfuntioning pituitary adenomas

authors	patient	follow-up months	control rate %	late toxicity % visual	late toxicity % Hypopituitarism
Martinez 1998	14	26-45	100	0	0
Pan L 1998	17	29	95	0	0
Ikeda 1998	13	45	100	0	0
Mokry 1999	31	20	98	NA	NA
Hayashi 1999	18	>6	92	5	5
Izawa 2000	23	>6	91	4,3	NA
Sheean 2002	42	31*	97	2,3	0
Wowra 2002	45	55	93 at 3 yrs	0	14
Petrovich 2003	56	36	94 at 3 yrs	4	NA
Pollock 2003	33	43	97 at 5 yrs	0	41 at 5 yrs
Losa 2004	56	41*	88 at 5 yrs	0	24
Iwai 2005	34	60	93 at 5 yrs	0	6
Mingione 2006	100	45*	92	0	25
Liscack 2007	140	60	100	0	2
Pollock 2007	62	64	95 at 3 and 7 yrs	0	32 at 5 yrs

Minniti et al, Neurosurgical reviews 2008

Radiosurgery for acromegaly

SRS

Author	Number patients	follow-up (months)	normal GH %
Attanasio 03	30	46	30 at 5 yrs
Castinetti 05	82	50	17
Kobayashi 05	67	63	17
Jezkova 06	96	32	44 at 5 yrs
Voges 06	64	54	33 at 5 yrs
Total	***771***	***56***	***38% at 5 years***
Vik-mo	53	67	86 at 10 yrs
Losa 08	83	69	85 at 10 yrs
Jagannathan 08	95	57	53
Ronchi 09	35	114	46 at 10 yrs
Wan 10	103	67	37

Radiosurgery for acromegaly

SRS

retrospective comparison

SRS
25 Gy in one fraction
16 patients (1994-96)

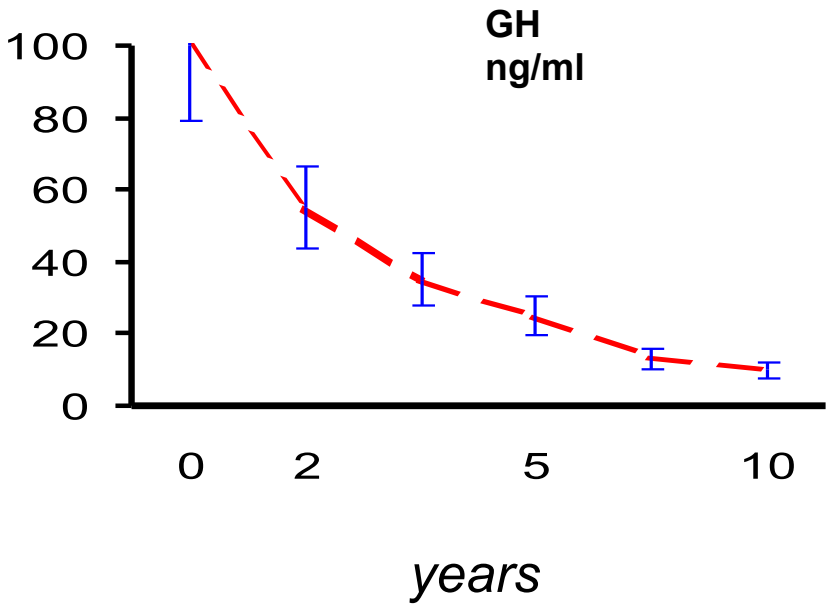
VS

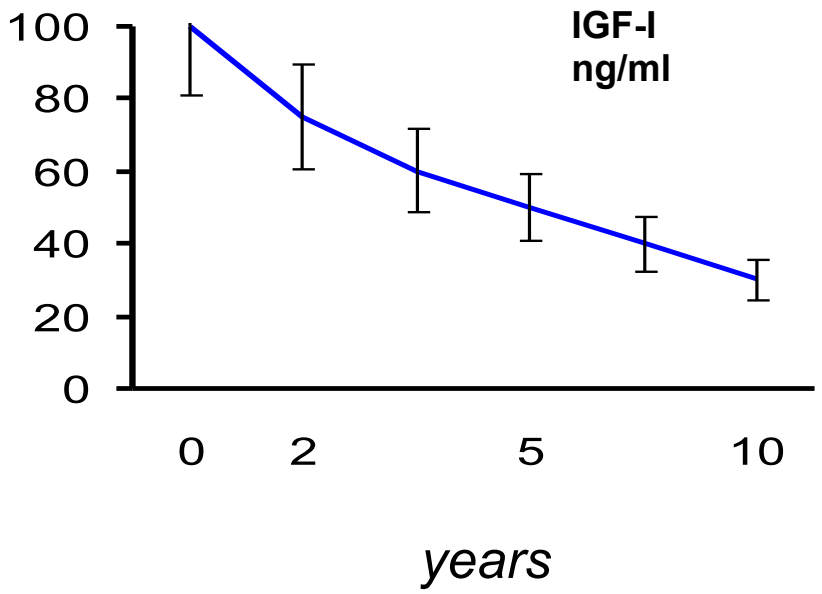
FSRT
40 Gy in 20 fractions
50 patients (1973-92)

	SRS	FSRT
mean time to normalization of GH & IGF-1 (years)	1.4	7.1
pretreatment GH (mIU/l)		
mean	18.0*	29.7
range	2.9-35	4-135

Landolt et al 1998

Hormone control in acromegaly after RT





Minniti et al, Clin Endocrinol 2005

Radiosurgery for Cushing SRS

Author	Number patients	follow-up months	normal ACTH %
Degerblad et al	29	72	48
Sheehan et al	43	44	63
Heybye et al	18	180	83
Total	**311**	**54**	**55**
Pollock et al	41	36	56
Jane et al	45	>18	63
Devin et al	35	35	49
Castinetti et al	40	54	42
Jagannathan et al	90	45	54

Radiosurgery for prolactinomas SRS

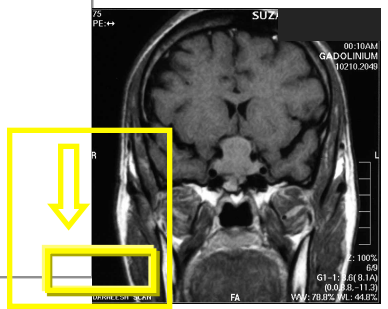
Author	Number patients	follow-up (months)	normal PRL %
Pan et al	27	29	30
Lim et a	19	26	50
Mokry et al	21	31	57
Total	***278***	***35***	***40***
Choi et al	21	43	23
Jane et al	19	>18	11
Pouratian et al	23	55	26

Radiotherapy for pituitary adenoma

SRS

Damaging effects of radiosurgery

- Endocrine failure (6-30%)
- Neurological damage (1-5%)
  - Vision
  - Temporal lobe damage
  - Cognitive function
- Second malignancy
- CVA



Radiation tolerance to radiosurgery SRS

Radiation induced optic neuropathy (RON)

dose to optic apparatus	incidence of RON
< 10 Gy	5%
10 - 15 Gy	27%
> 15 Gy	78%

Leber et al 1998

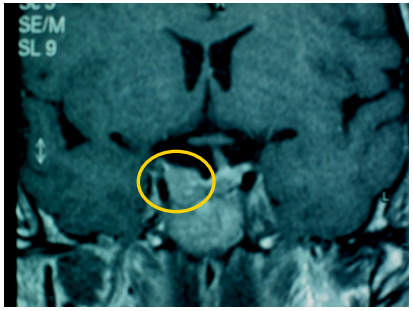
Results of SRS/FSRT in pituitary tumors

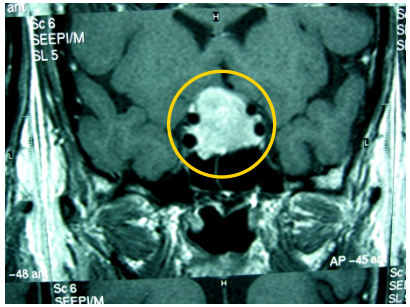
- *NF adenomas*
- *90-95% at 5 years / 90-100% at 5 years*
- GH-secreting adenomas
- *40-50% at 5 years / 30-55% at 5 years*
- ACTH-secreting adenomas
- *40-55% at 5 years / 70-80% at 5 years*
- *PRL-secreting adenomas*
- *30-40% at 5 years / 30-50% at 5 years*

Minniti et al, Rev Endocr Metab Disord. 2009

Limitation of radiosurgery

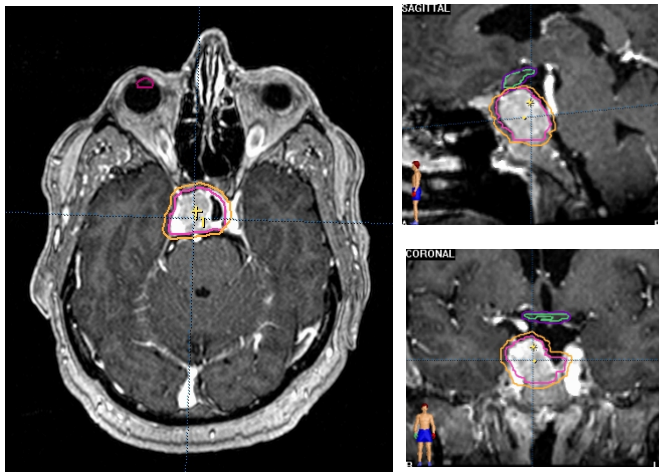
- Size of adenoma (more than 2.5-3.0 cm)
- Proximity to the optic chiasm (< 2-3 mm)





Hypofractionation for pituitary tumors

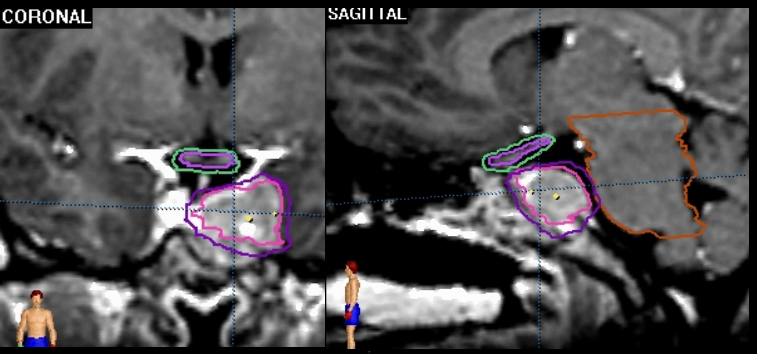
- 25 pts between 2006 and 2011
- Median age 50 years
- ***16 pituitary adenomas***
- 9 meningiomas
- median GTV 5.8 cc
- median PTV (GTV + 2/3mm) 10.3 cc
- 6-8 noncoplanar conformal fields

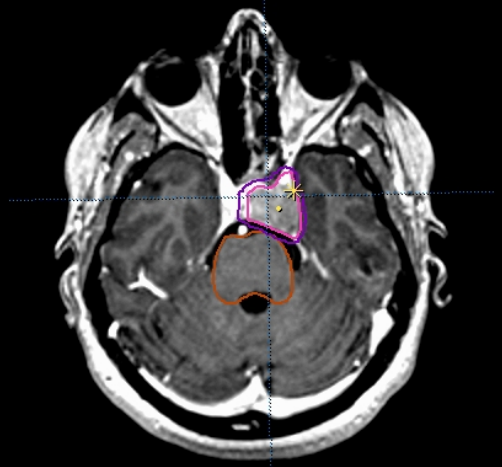


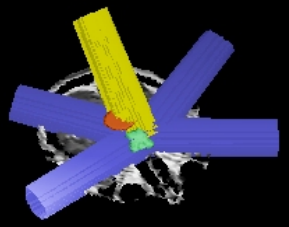
Dose:

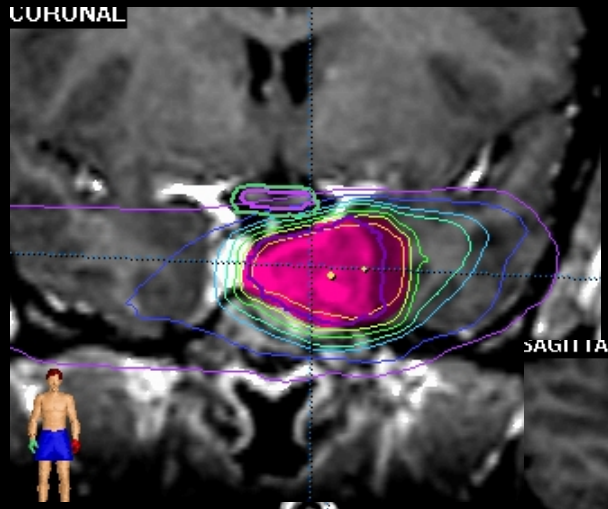
- meningiomas 5.5 Gy x 5
- adenomas 5 Gy x 5

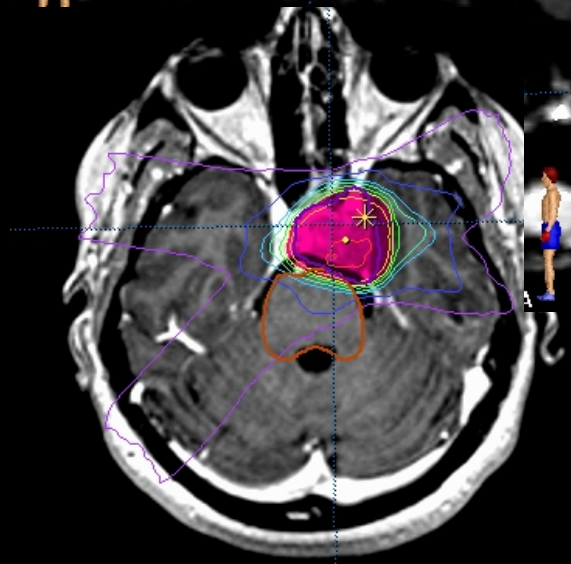
Hypofractionated SRT

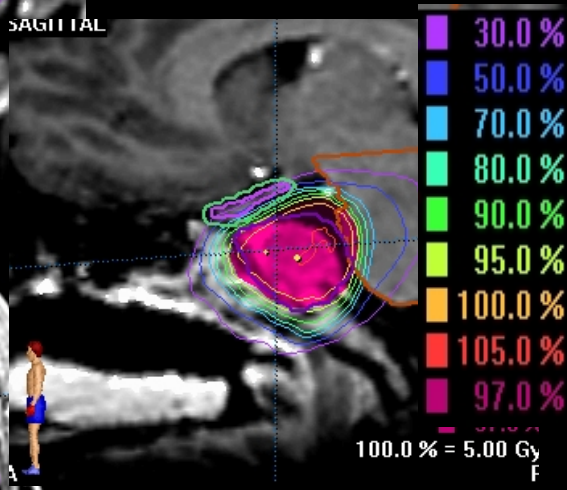




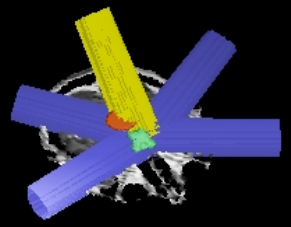


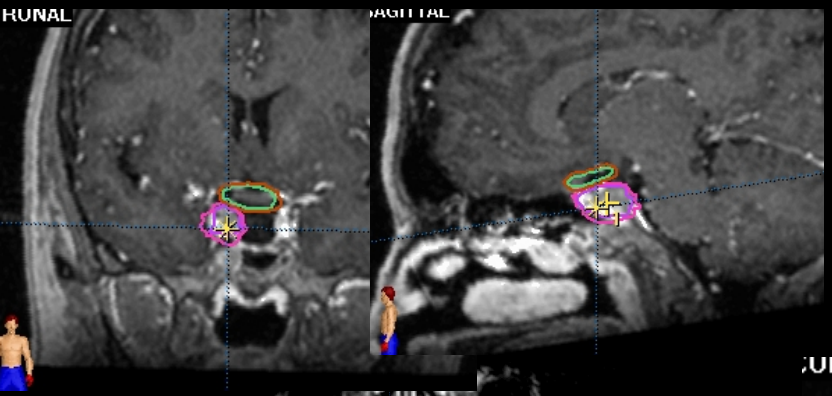


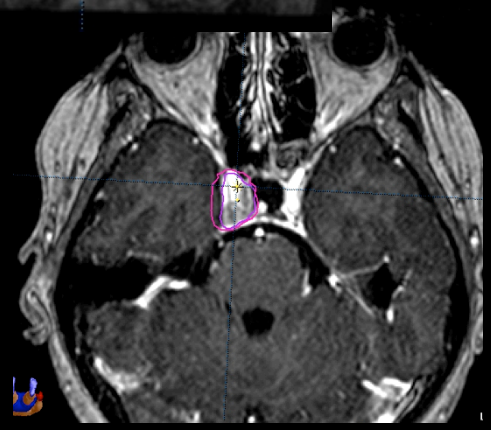


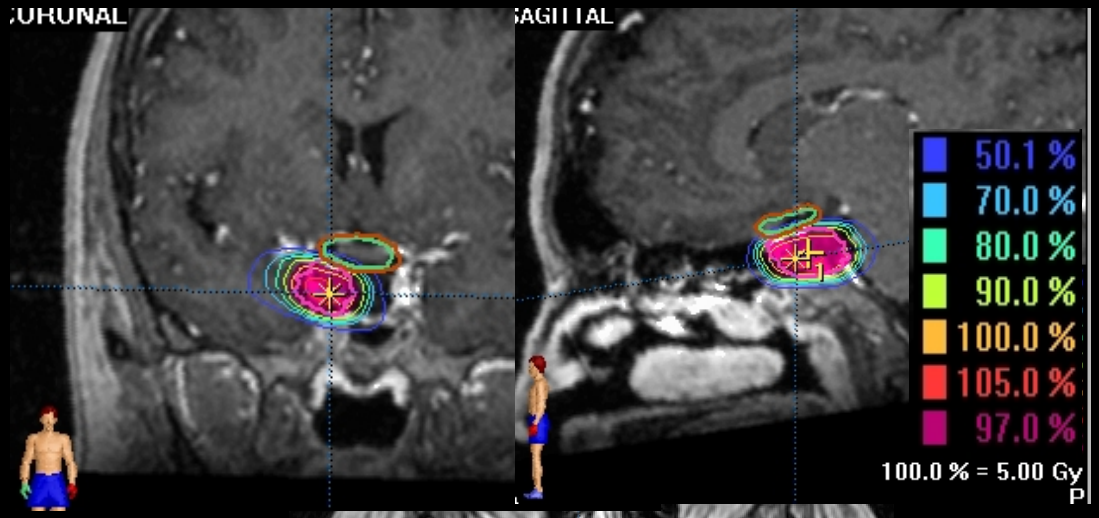


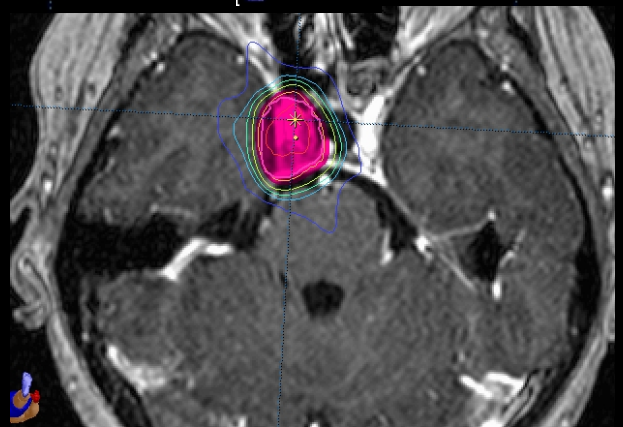
Hypofractionated SRT





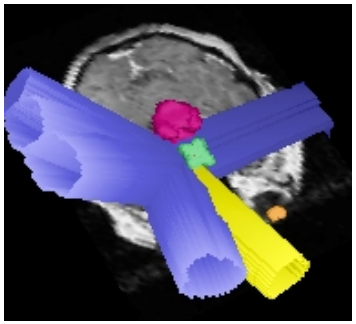


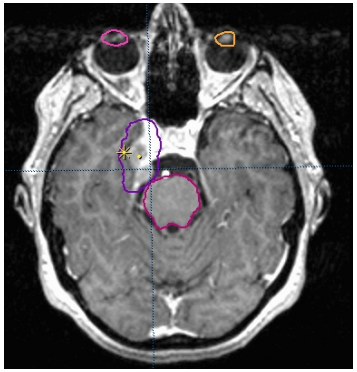




Outcome

- *Median follow-up: 21 months*
- *3-year control 100%*
- *3-year survival 100%*
- *Neurological improvement in 15% of patients*
- *No toxicity*





Conclusions

- *New techniques are apparently effective and may reduce the potential long-term toxicity of radiation, but longer follow-ups need to confirm the promising reported results*

- *Both FSRT and SRS are feasible options for patients with otherwise uncontrolled pituitary adenomas*

- *Radiosurgery should be employed only for small (< 2.5-3 cm) adenomas 3-5 mm away from the optic chiasm.*

….Grazie per l'attenzione...