



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



Tumori ipofisari clinicamente non funzionanti

Radioterapia

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Conflitti di interesse



ITALIAN CHAPTER



Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Ipsen
- Novartis
- Pfizer



«guerra» all'adenoma con la radioterapia



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Razionale

Target

Armi

Quando sferrare l'attacco

Risultati

Conseguenze



RAZIONALE



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La resezione completa dell'adenoma si ottiene circa nel 50-80% dei casi

Assenza di residuo dopo la chirurgia

recidiva a 5-10 anni = 10-20%

Presenza di residuo dopo la chirurgia

recidiva a 5-10 anni = 40-50%
(importante anche se intra o extra sellare)



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TARGET



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Recidive

Residui extrasellari

Tumori aggressivi

**Table 1** Relevant features of the new 2017 WHO pituitary tumor classification Modified from Lopes MBS [8]

Adenoma type	Morphological variants	Hormones and immunomarkers	Transcription factors
Somatotroph	Densely granulated ^a	GH ± PRL ± alfa-subunit	PIT-1
	Sparsely granulated	GH ± PRL [CK]	PIT-1
	Mammosomatotroph	GH ± PRL (in same cells) ± alfa-subunit	PIT-1, ER-alfa
	Mixed somatotroph-lactotroph	GH ± PRL (in different cells) ± alfa-subunit	PIT-1, ER-alfa
Lactotroph	Sparsely granulated ^a	PRL	PIT-1, ER-alfa
	Densely granulated	PRL	PIT-1, ER-alfa
	Acidophilic stem cell	PRL, GH (focal and variable)	PIT-1, ER-alfa
Tyrotroph		Beta-TSH, alfa-subunit	PIT-1
Corticotroph	Densely granulated ^a	ACTH	T-PIT ^b
	Sparsely granulated	ACTH	T-PIT ^b
	Crooke's cell	ACTH	T-PIT ^b
Gonadotroph		Beta-FSH, beta-LH, alfa-subunit (combinations)	SF-1, GATA2, ER-alfa
Null cell		None	None
Plurihormonal and double adenomas	Plurihormonal PIT-1 positive (previously silent tpe 3)	GH, PRL, beta-TSH ± alfa-subunit	PIT-1
	Adenomas with unusual immunohistochemical combinations	Various combinations: ACTH/GH, ACTH/PRL	N/A



TARGET



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The 2017 World Health Organization classification of tumors of the pituitary gland: a summary

Acta Neuropathol

DOI 10.1007/s00401-017-1769-8

Low probability for recurrence	High probability for recurrence	Malignant (metastatic) tumor
Pituitary adenoma	Adenomas with elevated proliferative activity Special subtypes (variants) of adenomas: Sparsely granulated somatotroph adenoma Lactotroph adenoma in men Silent corticotroph adenoma Crooke cell adenoma Plurihormonal PIT-1 positive adenoma	Pituitary carcinoma



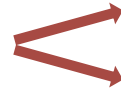
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ITALIAN CHAPTER

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Stereotactic radiosurgery (SRS)



Single-fraction (13-15 Gy)

Multi-fraction (2-5 fractions)

Fractionated stereotactic radiotherapy (FSRT)



40-50 Gy in 1.8-2.0 Gy per fraction

Goal: Concentrare le più alte dosi di radiazioni sul target, riducendo quelle sui tessuti normali circostanti

**Gamma Knife
Cyber Knife
LINAC**

Dose assorbita

1Gy = energia ceduta alla materia per unità di massa = 1 joule/Kg



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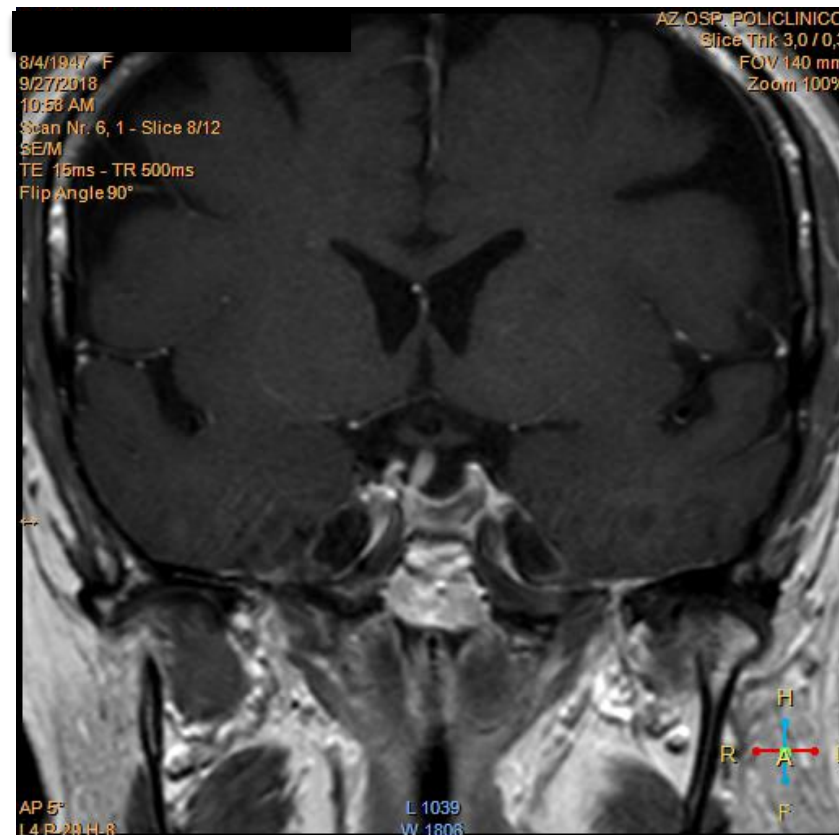
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ITALIAN CHAPTER

Stereotactic radiosurgery (SRS)

**residui piccoli
distanti dal chiasma ottico
buona definizione del target**





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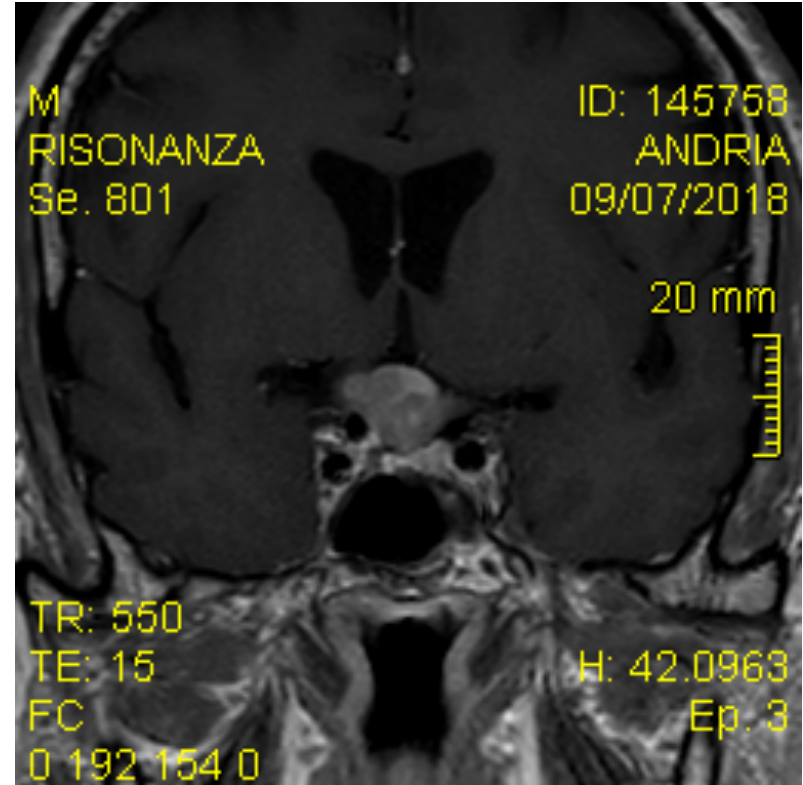
ITALIAN CHAPTER



Fractionated stereotactic radiotherapy (FSRT)

residui voluminosi
marginii tumorali poco definiti
interessamento parasellare
vicinanza al chiasma ottico

«Recovery and repair»



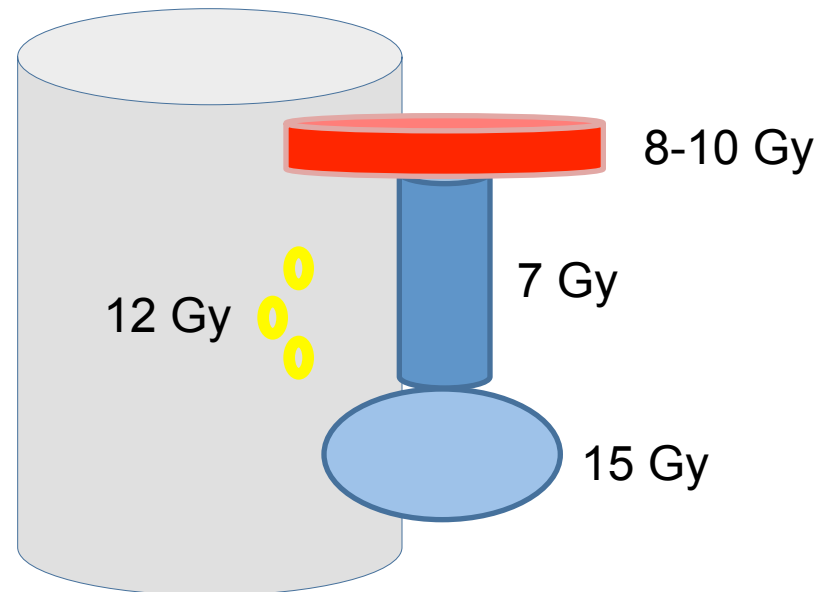
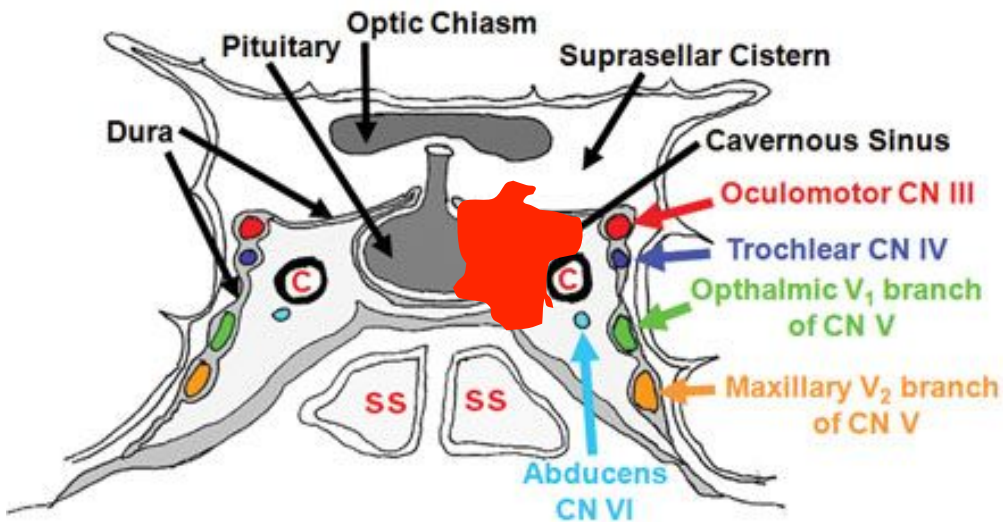


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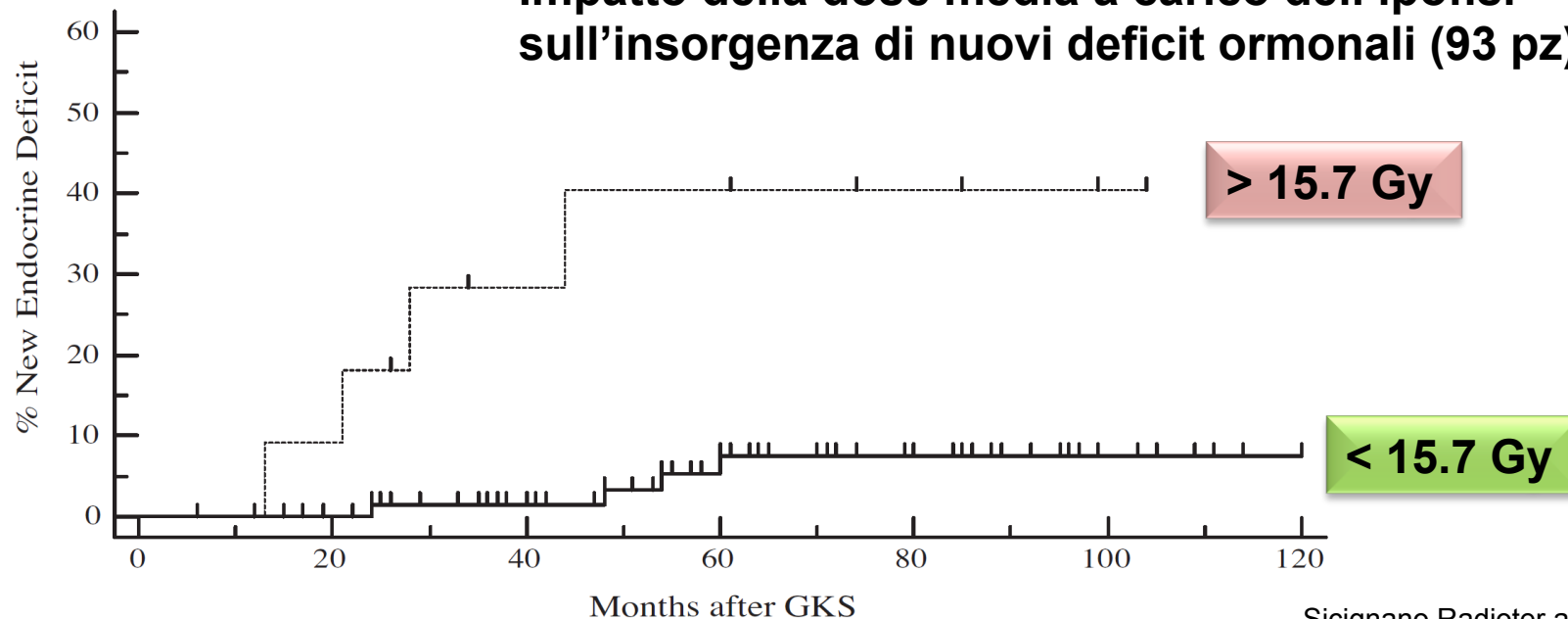
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Dosimetric factors associated with pituitary function after Gamma Knife Surgery (GKS) of pituitary adenomas

Impatto della dose media a carico dell'ipofisi sull'insorgenza di nuovi deficit ormonali (93 pz)



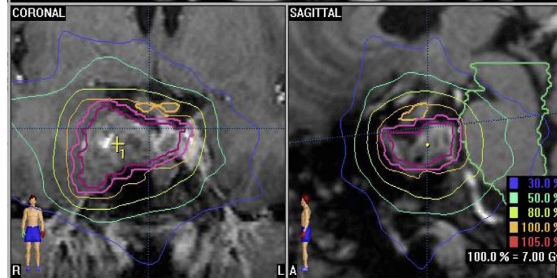
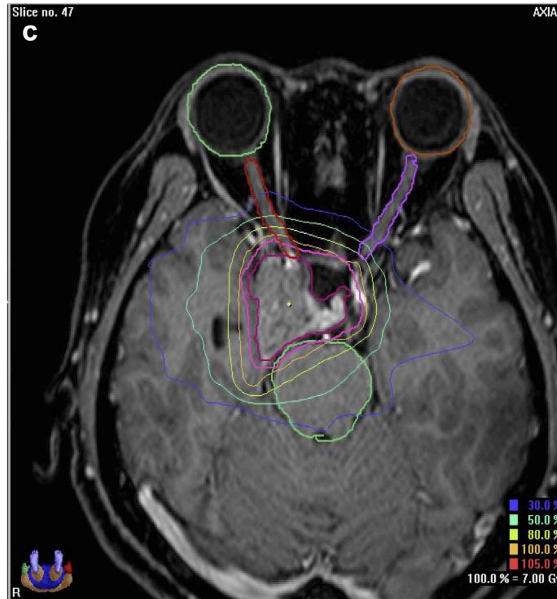
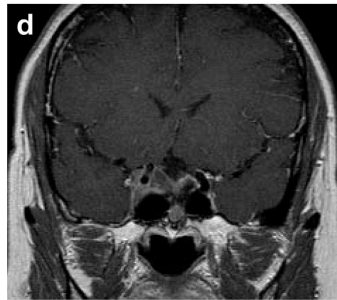
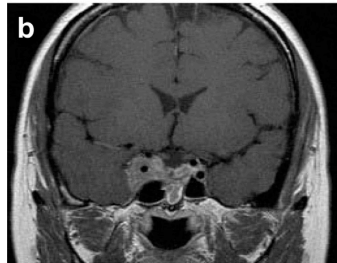
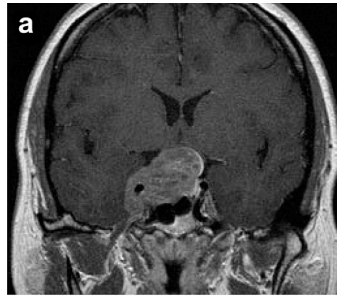


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Steep
gradient
index

Liao J Clin Neurosci 2014

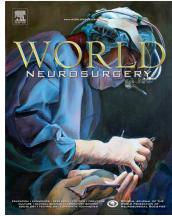


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QUANDO



ITALIAN CHAPTER



Treatment of Non-Functional Pituitary Adenoma Post-Operative Remnants: Adjuvant or Delayed Gamma Knife Radiosurgery?

Table 2. Imaging Outcomes of 50 Patients According to Treatment Group.

Treatment Group	Patients, n	Size Reduction, n	No Size Change, n	Tumor progression, n	Complications, n	Tumor Control Rate, % 10 years
Adjuvant	13	1	11	1	1*	92%
Delayed	37	11	25	1	2 [†]	97%
Total	50	12	36	2	3	96%

P=0.408

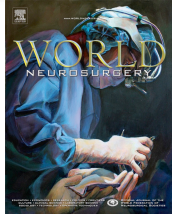


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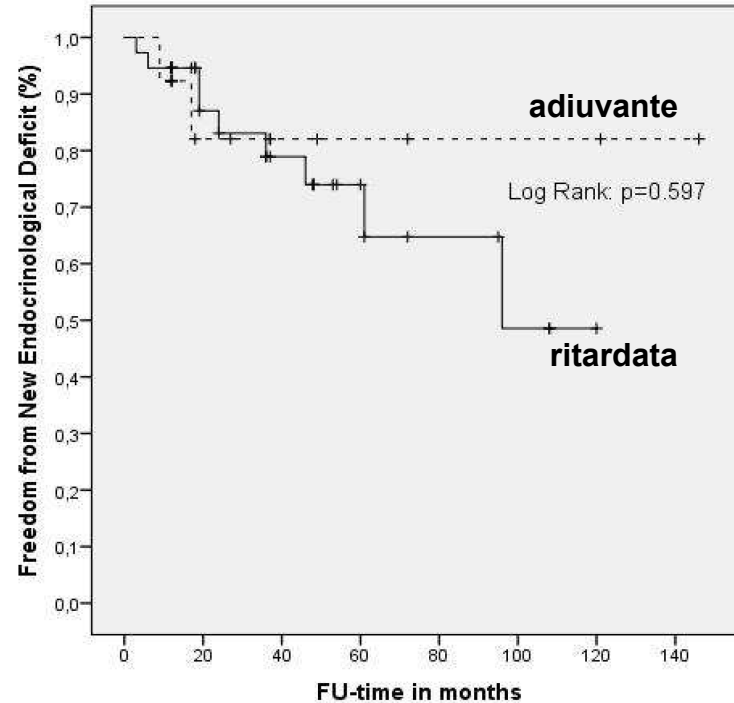
QUANDO



ITALIAN CHAPTER



Treatment of Non-Functional Pituitary Adenoma Post-Operative Remnants: Adjuvant or Delayed Gamma Knife Radiosurgery?





QUANDO



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Early versus late Gamma Knife radiosurgery following transsphenoidal resection for nonfunctioning pituitary macroadenomas: a matched cohort study

Studio retrospettivo, 64 pz

TABLE 5. Outcomes

Variable	Early GKRS (≤ 6 mos)	Late GKRS (>6 mos)	p Value
Residual tumor at last FU, n (%)*	18 (56.3%)	27 (84.4%)	0.027
Tumor stable	17 (94.4%)	24 (88.9%)	
Tumor growth	1 (5.6%)	3 (11.1%)	
Growth or new residual	2 (6.3%)	9 (28.1%)	0.043
Pre-GKRS endocrinopathy, n (%)†	20 (62.5%)	21 (65.6%)	1.00
Fully resolved endocrinopathy	2	0	0.23
Pre-GKRS no endocrinopathy, n (%)	12 (37.5%)	11 (34.4%)	1.00
Completely new endocrinopathy	2	7	0.036
Post-GKRS endocrinopathy, n (%)‡	20 (62.5%)	28 (87.5%)	0.041
Secondary to tumor growth	0	8	0.014
Secondary to reoperation§	15	16	0.24
Secondary to radiosurgery	5	3	0.25
Unknown	0	1	1.00
Completely new endocrinopathy, n (%)¶	2 (16.7%)	7 (63.6%)	0.036
Secondary to tumor growth	0	1	1.00
Secondary to reoperation	1	3	1.00
Secondary to radiosurgery	1	3	1.00
New, n (%)§	4 (12.5%)	12 (37.5%)	
Hypogonadism, male	0	4	
Hypogonadism, female	1	0	
Hypocort	0	2	
Panhypopit	2	4	
Hypothyroid	0	2	
GH deficient	1	0	



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ITALIAN CHAPTER



Gamma knife surgery for patients with volumetric classification of nonfunctioning pituitary adenomas: a systematic review and meta-analysis

17 studi, 925 pz	Gruppo 1 (< 2 ml)	Gruppo 2 (2-4 ml)	Gruppo 3 (> 4 ml)
Tumor control rate	99%	96%	91%
Neuropatia ottica	1%	1%	2%
Deficit ormonale	1%	7%	22%



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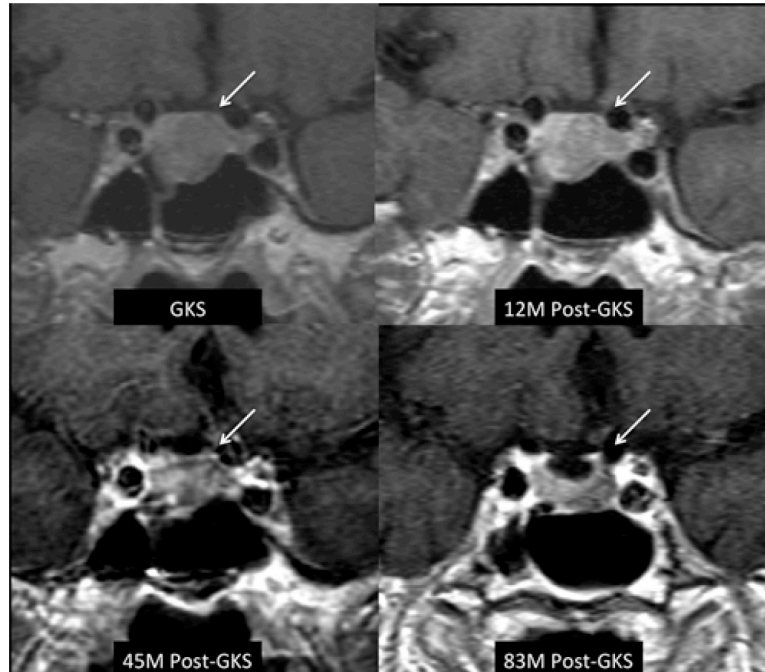
QUANDO



ITALIAN CHAPTER

Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas

Lee CC *J Neurosurg* 120:647–654, 2014



Anziani
Comorbidità
Rifiuto chirurgia
Localizzazione intracavernosa
Non compressione chiasma



RISULTATI



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Table 2 Selected series on SRS for nonfunctioning pituitary adenomas (NFAs)

Authors	Patients	Type of SRS	Dose (Gy)	Follow-up	Tumor control (%)	Late toxicity (%)	Hypopituitarism
Stereotactic radiosurgery (SRS)							
Feigl et al. [52]							40
Sheehan et al. [53]	42	GK	16 ^a	31.2	97.6	2.4	0
Wowra and Stummer [54]	30	GK	16 ^a	55	93.3 (93 at 5 years)	0	10
Petrovich et al. [55]	56	GK	15 ^a	36	100	3	4
Controllo del tumore nel 90-95% dei casi (5 anni)							
Iwai et al. [58]	54	GK	12.5	39.6	87.1 (95 at 5 years)	0	0.5
Picozzi et al. [59]	51					0	18
Mingione et al. [60]	100					0	19.7
Voges et al. [61]	37					1.4	12.3
Shrinkage nel 20-60%							
Miglioramento delle funzioni visive fino al 25%							
Hayashi et al. [65]	43	GK	18.2 ^a	36	100	0	0
Gopalan et al. [66]	48	GK	18.4 ^a	95	83.3	0	39
Iwata et al. [67]	100	CK	3×7/5×5	33	98	1	3
Park et al. [68]	125	GK	13 ^a	62	90 (94 at 5 years)	0,8	24
Starke et al. [69]	140	GK	18 ^a	50	89.6 (97 at 5 years)	0	30.3
Runge et al. [70]	61	LINAC	13	83	98	0	9.8
Wilson et al. [71]	51	LINAC	14	50	100	0	0
Sheehan et al. [72]	512	GK	16 ^a	36	93.4 (95 at 5 years)	7.9	21
Lee et al. [73]	41	GK	12 ^a	48	92.7 (85 at 10 years)	2.4	24.4
Bir [74]	57	GK	15 ^a	45.5	93 (90% at 10 years)	0	8.8

SRS stereotactic radiosurgery, GK gamma knife, LINAC linear accelerator, CK cyberknife

^aMarginal dose

Minniti Pituitary 2013



RISULTATI



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Roma, 8-11 novembre 2018

Table 3 Selected studies on fractionated stereotactic radiotherapy (FSRT) for nonfunctioning pituitary adenomas (NFAs)

Authors	Fractionated stereotactic radiotherapy (FSRT)						Late toxicity (%)	
	(Gy)				(months)		Visual	Hypopituitarism
Milker-Zabel et al. [78]	68	NFA, SA	50.4	1.8	38	93 at 5 years	7,5	5
Paek et al. [79]	68	NFA, SA	50	1.8-2.0	30	98 at 5 years	3	6
Colin et al. [80]	110	NFA, SA				99 at 5 years	1,8	29 at 4 years
Minniti et al. [81]	92	NFA, SA				98 at 5 years	1	22
Kong et al. [82]							0	27.3 at 5 years
Schalin-Jantti et al. [83]							0	40
Wilson et al. 2012 [84]	67	NFA	50	1.8	60.1	93 at 5 years	1,5	7
Kopp et al. [85]	37	NFA, SA	49.4	1,8	57	91,9	5	5
Kim et al. [86]	76	NFA, SA	50.4	1.8	80	97,1 at 7 years	0	48
Barber et al. [87]	75	NFA, SA	54	1.8-2.2	72	97.9 at 6 years	5.3	6.4
Minniti et al. [88]	68	NFA	45	1.8	75	97 and 91 at 5 and 10 years	3	40 at 5 years

Fractionated stereotactic radiotherapy (FSRT)

Controllo del tumore nel 95% dei casi (5 anni)

Shrinkage nel 20-50%

Miglioramento delle funzioni visive fino al 30%



CONSEGUENZE



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Table 1 Selected published results of SRS (2000–2015) for the treatment of nonfunctioning pituitary adenomas

Authors	Patients	Type of SRS	dose (Gy)	Follow-up (months)	Tumor control (%)	Late toxicity (%)	
						visual	hypopituitarism
Feigl et al., 2002 [33]	61	GK	15 ^a	55.2	94	NA	40
Sheehan et al., 2002 [58]	42	GK	16 ^a	31.2	97.6	2.4	0
Wowra & Stummer, 2002 [59]	30	GK	16 ^a	55	93.3 (93 at 5 years)	0	10
Petrovich et al., 2003 [60]	56	GK	15 ^a	36	100	3	4
Losa et al., 2004 [61]	52	GK	16.6 ^a	41	96.3 (88.2 at 5 years)	0	9.3
Muacevic et al., 2004 [62]	51	GK	16.5 ^a	21.7	95	0	3.9
Picozzi et al., 2005 [63]	51	GK	16.5 ^a	40.6	96.1	NA	NA
Iwai et al., 2005 [64]	34	GK	12.3 ^a	59.8	87.1 (93 at 5 years)	0	6.5
Mingione et al., 2006 [65]							19.7
Voges et al., 2006 [66]							12.3
Liscak et al., 2007 [67]							2
Pollock et al., 2008 [68]							27
Kobayashi et al., 2009 [69]	71	GK	14.1 ^a	50.2	96.7	2.8	8.2
Hayashi et al., 2010 [70]	43	GK	18.2 ^a	36	100	0	0
Gopalan et al., 2011 [71]	48	GK	18.4 ^a	95	83.3	0	39
Iwata et al., 2011 [44]	100	CK	3x7/5x5	33	98	1	3
Park et al., 2011 [72]	125	GK	13 ^a	62	90 (94 at 5 years)	0.8	24
Starke et al., 2012 [73]	140	GK	18 ^a	50	89.6 (97 at 5 years)	0	30.3
Runge et al., 2012 [74]	61	LINAC	13	83	98	0	9.8
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Ipopituitarismo

**TSH
FSH LH
ACTH
GH**

**Nuovo deficit o peggioramento
nel 10-40% dei casi a 5 anni**



CONSEQUENZE



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ITALIAN CHAPTER

Factors Associated With Endocrine Deficits After Stereotactic Radiosurgery of Pituitary Adenomas

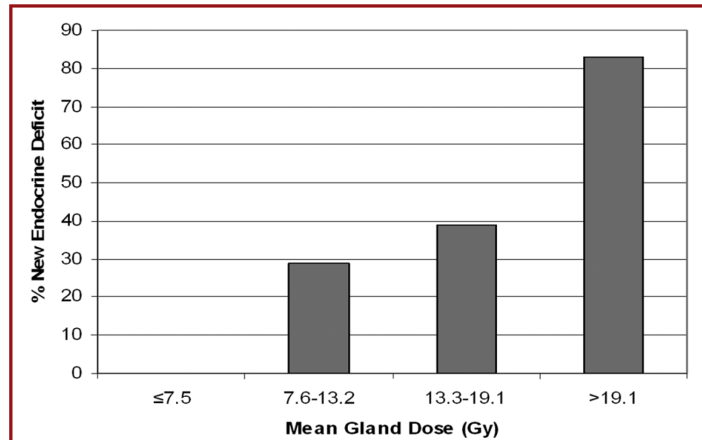


FIGURE 4. Effect of increasing mean radiation dose to the pituitary gland on the incidence of new anterior pituitary deficits after pituitary adenoma SRS.



CONSEQUENZE



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Leenstra Neurosurgery 2010

Factors Associated With Endocrine Deficits After Stereotactic Radiosurgery of Pituitary Adenomas

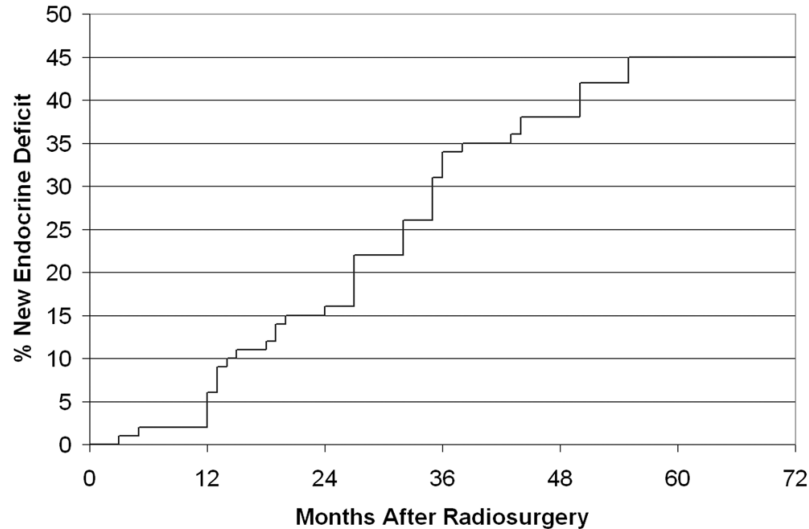


FIGURE 2. Risk of new anterior pituitary deficits after pituitary adenoma SRS. Seventy-seven patients were being monitored beyond 1-year, 44 patients beyond 3 years, and 20 patients beyond 5 years.

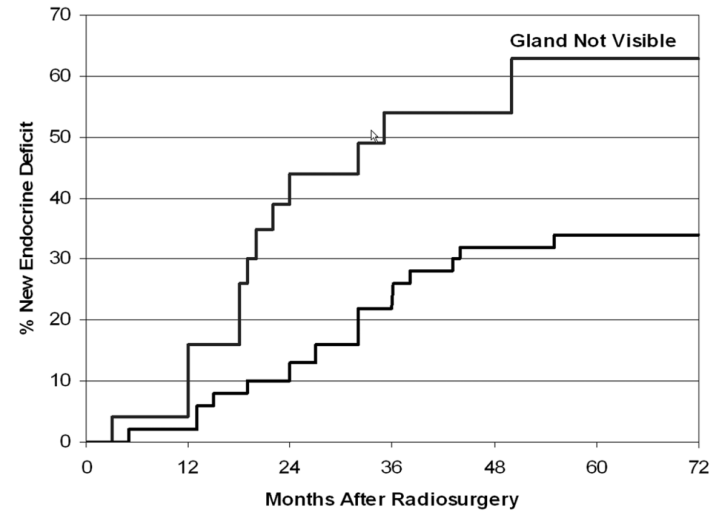


FIGURE 3. Effect of pituitary gland visualization on new anterior pituitary deficits after pituitary adenoma SRS. Patients whose pituitary gland was poorly visualized had an increased risk of new anterior pituitary deficits compared with patients whose pituitary gland was well visualized (HR = 2.63, 95% CI = 1.10-6.25, P = .03).



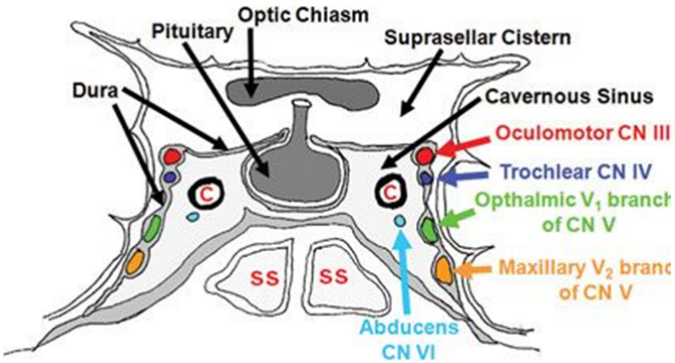
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ITALIAN CHAPTER

Roma, 8-11 novembre 2018

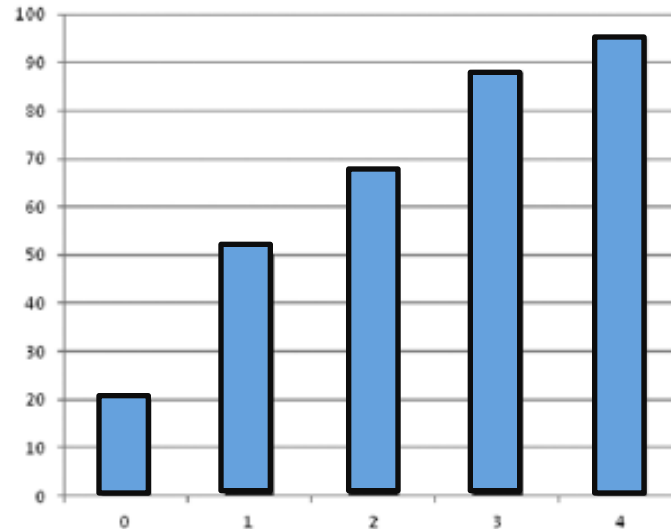
danno neurologico



1-4% dei casi (se dosi < 10Gy)

Radiosurgical pituitary score

Età > 50	Punti
No precedente radioterapia	1
Volume < 5 cm ³	2
	1





Roma, 8-11 novembre 2018

CONSEGUENZE



ITALIAN CHAPTER



Neoplasie
Stroke
Stenosi carotidea
Diplopia
Necrosi del lobo temporale
Deficit cognitivo (ippocampo)

Rare, assenti o transitorie



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CONCLUSIONI



ITALIAN CHAPTER



European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas

European Journal of Endocrinology
(2018) 178, G1-G24

3.2 Role of radiotherapy

R 3.2.1 We recommend radiotherapy in patients with clinically relevant tumour growth despite surgery in non-functioning tumours or surgery and standard medical treatment in functioning tumours (++00).

R 3.2.2 We suggest that adjuvant radiotherapy should be considered in the setting of a clinically relevant invasive tumour remnant with pathological markers (Ki-67 index, mitotic count, p53 immunodetection) strongly indicating aggressive behaviour (+000).

R 3.2.3 We suggest discussion with an expert radiation oncologist regarding the different radiotherapeutic options taking into consideration tumour size and location, as well as pathology, prior RT and dose.



CONCLUSIONI



ITALIAN CHAPTER

Roma, 8-11 novembre 2018

Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline for the Management of Patients With Residual or Recurrent Nonfunctioning Pituitary Adenomas

NEUROSURGERY

VOLUME 79 | NUMBER 4 | OCTOBER 2016

Conventional radiotherapy and radiosurgery are both recommended (level II) in residual or recurrent NFPA. If minimal or no residual tumor, observation is feasible (level II). Single session radiosurgery (> 12 Gy) or fractionated radiotherapy (45–54 Gy) is recommended for local control over 90% at 5 years (level II). Assessment of proliferative index and ACTH staining to identify silent corticotroph adenomas recommended to advice earlier adjuvant radiation (level III). Repeat operation recommended in symptomatic residual or recurrent tumors (level III). Radiation for residual or recurrent inoperable tumors (level III). Delayed hypopituitarism is the most common complication of radiation. All retreated patients need long-term or indefinite follow-up