



Simposio 12

Update sulla terapia farmacologica dell'acromegalia

venerdì 8 novembre h 17.15



Bari,
7-10 novembre 2013

Perché la terapia farmacologica

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Outline

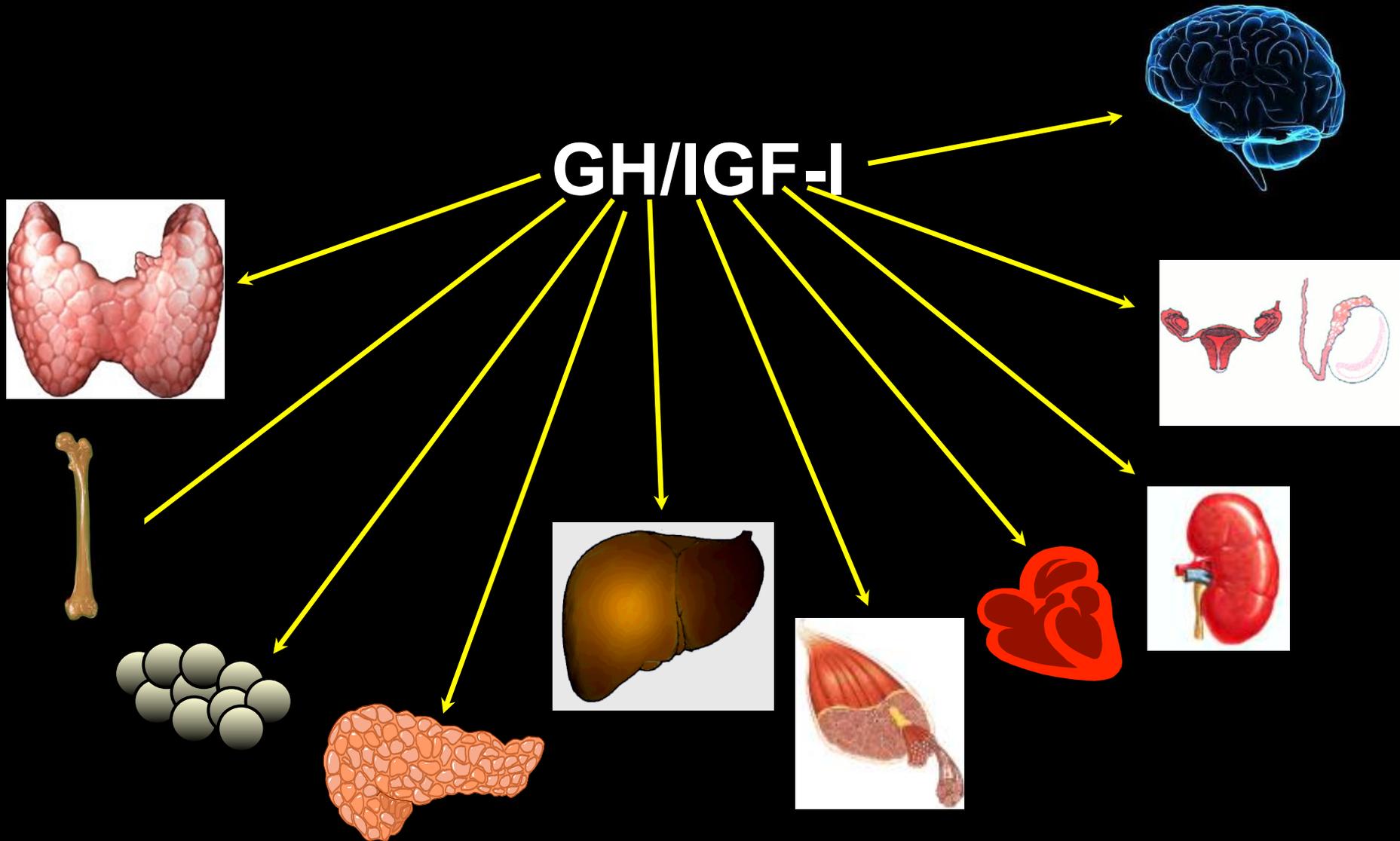


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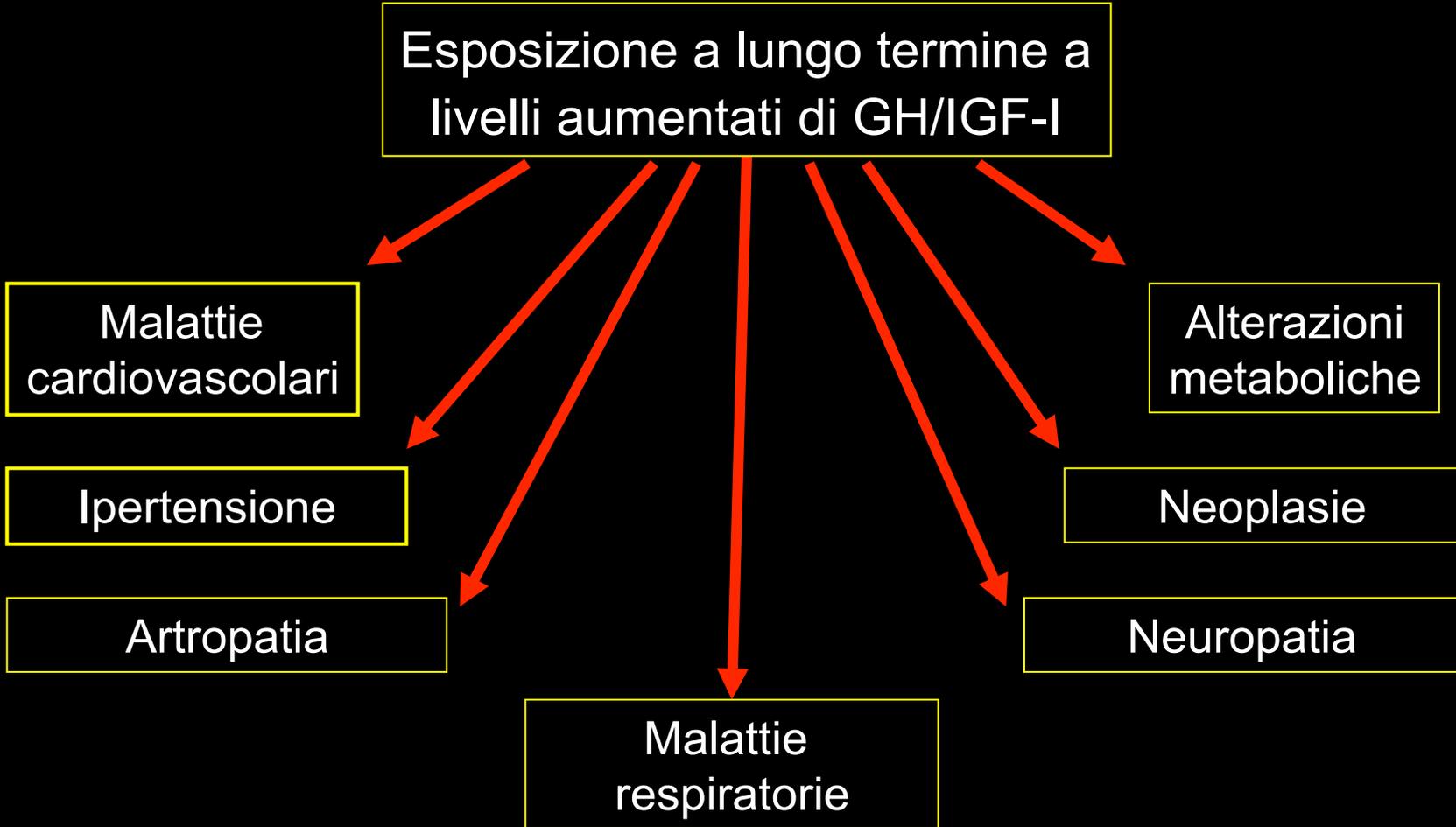
- Perché trattare
- Neurochirurgia
- Terapia radiante



Organi colpiti



Morbilità

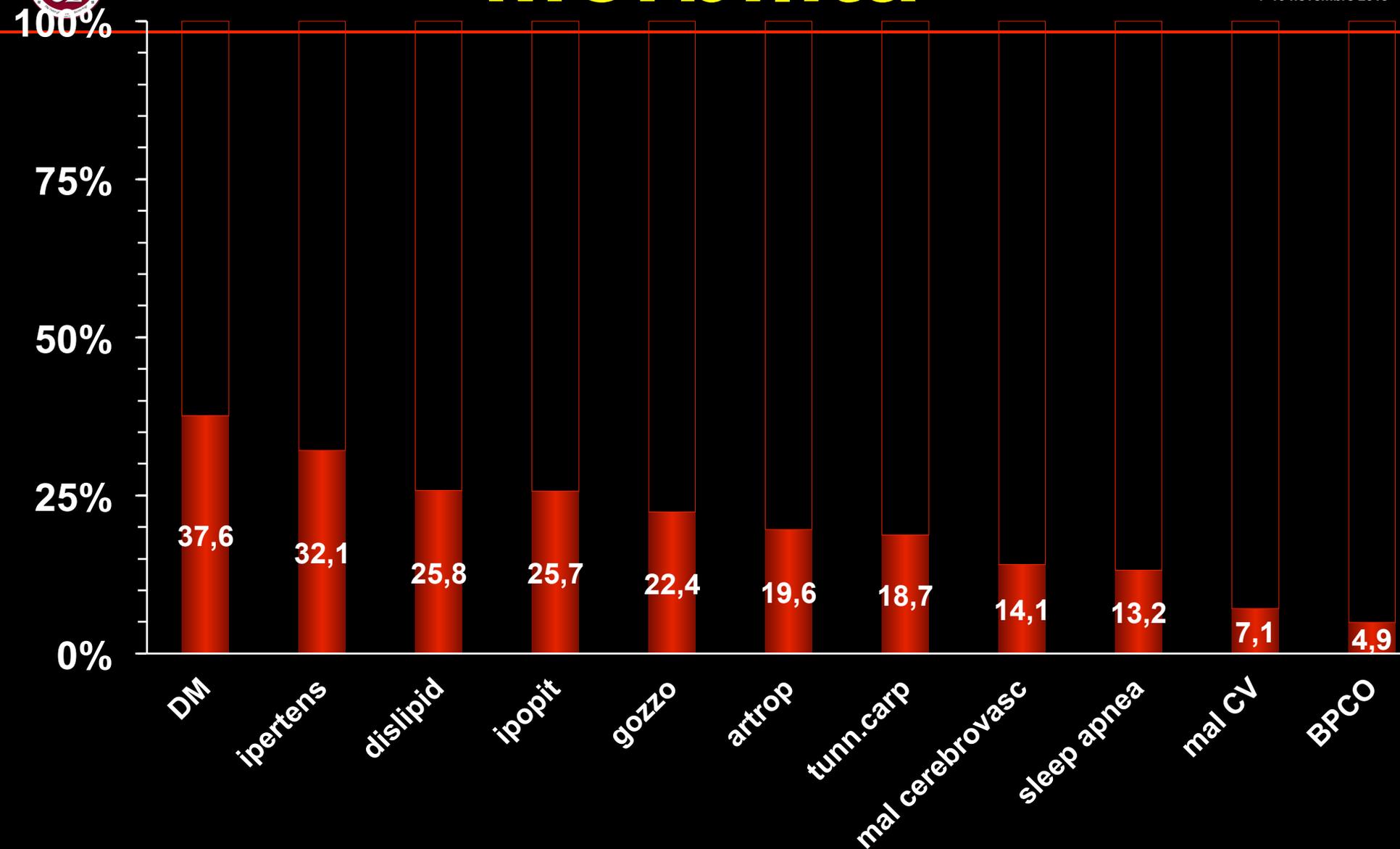




Morbilità



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7-10 novembre 2013





Mortalità



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7-10 novembre 2013

European Journal of Endocrinology (2012) 167 189–198

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CLINICAL STUDY

Predictors of morbidity and mortality in acromegaly: an Italian survey

M Arosio, G Reimondo¹, E Malchiodi², P Berchiolla³, A Borraccino³, L De Marinis⁴, R Pivonello⁵, S Grottoli⁶, M Losa⁷, S Cannavò⁸, F Minuto⁹, M Montini¹⁰, M Bondanelli¹¹, E De Menis¹², C Martini¹³, G Angeletti¹⁴, A Velardo¹⁵, A Peri¹⁶, M Faustini-Fustini¹⁷, P Tita¹⁸, F Pigliaru¹⁹, G Borretta²⁰, C Scaroni²¹, N Bazzoni²², A Bianchi⁴, M Appetecchia²³, F Cavagnini²⁴, G Lombardi⁵, E Ghigo⁶, P Beck-Peccoz², A Colao⁵ and M Terzolo¹ for the Italian Study Group of Acromegaly*

	Number of patients (M/F)	Age at diagnosis mean (M/F)	Macro-adenomas (%)	Diabetes mellitus (%)	Hypertension (%)	Disease control (%)	SMR (95% CI)
UK	419 (178/241)	47	–	–	–	46	1.26 (1.03–1.54)
E	1219 (478/741)	45	73	37.6	39.1	31	–
NZ	208 (125/83)	42	84	29.7	54.4	–	2.70 (2.10–3.50)
SF	334 (161/173)	47.5 (45/49)	67	–	–	55	1.16 (0.85–1.54)
B	418 (213/205)	44 (42/46)	79	25.3	39.4	49	1.39 (0.96–2.03)
D	1485 (677/808)	44 (41/47)	79	–	–	–	–
I	1512 (624/888)	45 (43/47)	70	16	33	65	1.13 (0.87–1.46)

Predittori di mortalità



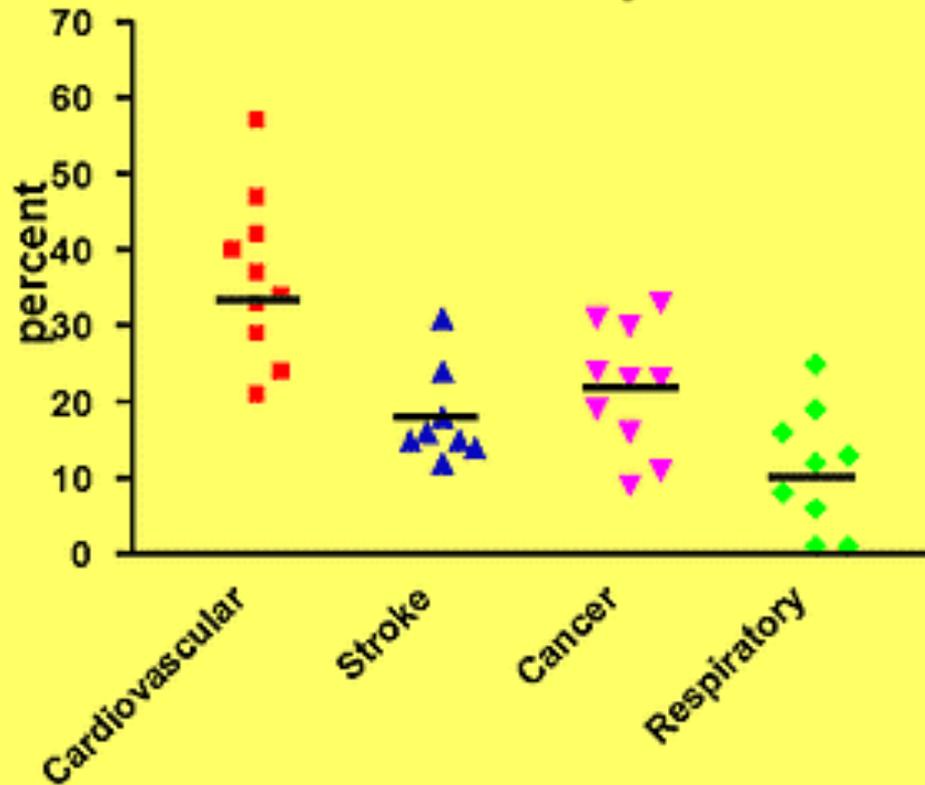
Table 3 Predictors of mortality.

Variables	OR	95% CI	P value
Univariate model			
Age	3.55	2.42–5.21	<0.001
Male sex	1.06	0.63–1.78	NS
Macroadenoma	0.85	0.47–1.54	NS
Delay of diagnosis	1.29	0.98–1.69	NS
GH at diagnosis	1.02	1.00–1.04	NS
IGF1 at diagnosis (SDS)	1.12	1.00–1.25	0.05
GH at FU	1.03	1.00–1.06	0.05
IGF1 at FU (SDS)	0.99	0.82–1.21	NS
Malignancy	11.98	6.95–20.64	<0.001
Diabetes	1.09	1.02–3.51	0.04
Hypertension	2.29	1.37–3.83	0.002
Radiotherapy	2.35	1.36–4.09	0.002
Hypoadrenalism	0.51	0.07–3.79	NS
Hypogonadism	1.15	0.55–2.41	NS
No. of therapies	0.51	0.27–0.99	NS
Smoking	1.44	0.72–2.85	NS
Multivariate model			
Age	4.58	2.62–7.99	<0.001
IGF1 at diagnosis (SDS)	1.14	1.01–0.25	0.04
GH at FU	1.06	1.03–1.10	<0.001
Malignancy	7.26	3.54–14.86	<0.001
Diabetes	0.87	0.37–2.06	NS
Hypertension	0.81	0.40–1.65	NS
Radiotherapy	4.32	1.97–9.45	<0.001

Cause di morte



Causes of death in acromegaly
Data from major studies



Scopo della terapia



- Normalizzare i livelli di GH e IGF-I
- Controllare le dimensioni tumorali
- Eliminare sintomi e segni
- Controllare le patologie associate
- Normalizzare la mortalità
- Migliorare la qualità della vita



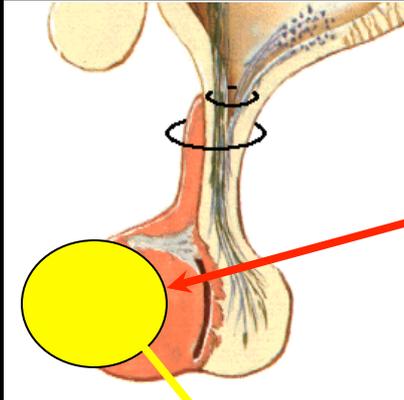
Criteri di guarigione/ controllo di malattia



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- Livelli medi di GH $< 2-2.5 \mu\text{g/L}$
- Livelli di GH $< 1 \mu\text{g/L}$ dopo OGTT
- IGF-I normale per età

Opzioni terapeutiche



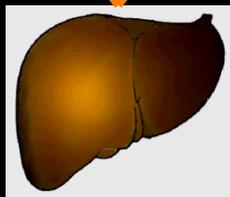
Terapie ablative:

- neurochirurgia
- radioterapia

Terapie farmacologiche:

- agonisti dopaminergici
- analoghi somatostatina
- antagonisti GHR

GH



IGF-I

Outline



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- Perché trattare
- Neurochirurgia
- Terapia radiante

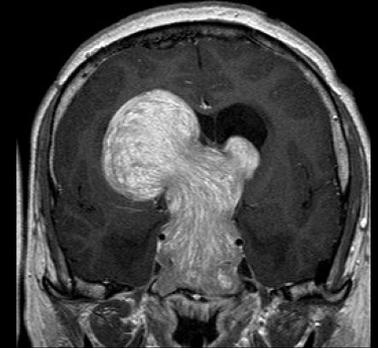


Neurochirurgia



Fattori predittivi del risultato:

- **invasività dell'adenoma**
- **livelli basali di GH alla diagnosi**
- **esperienza del neurochirurgo**



Invasività tumorale e guarigione chirurgica

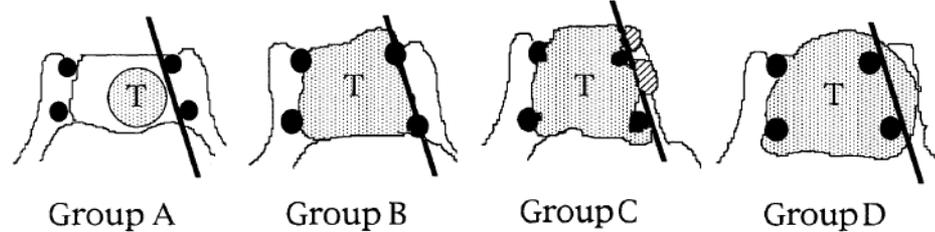


Table 4 Endocrinological remission rate in relation to tumour classification.

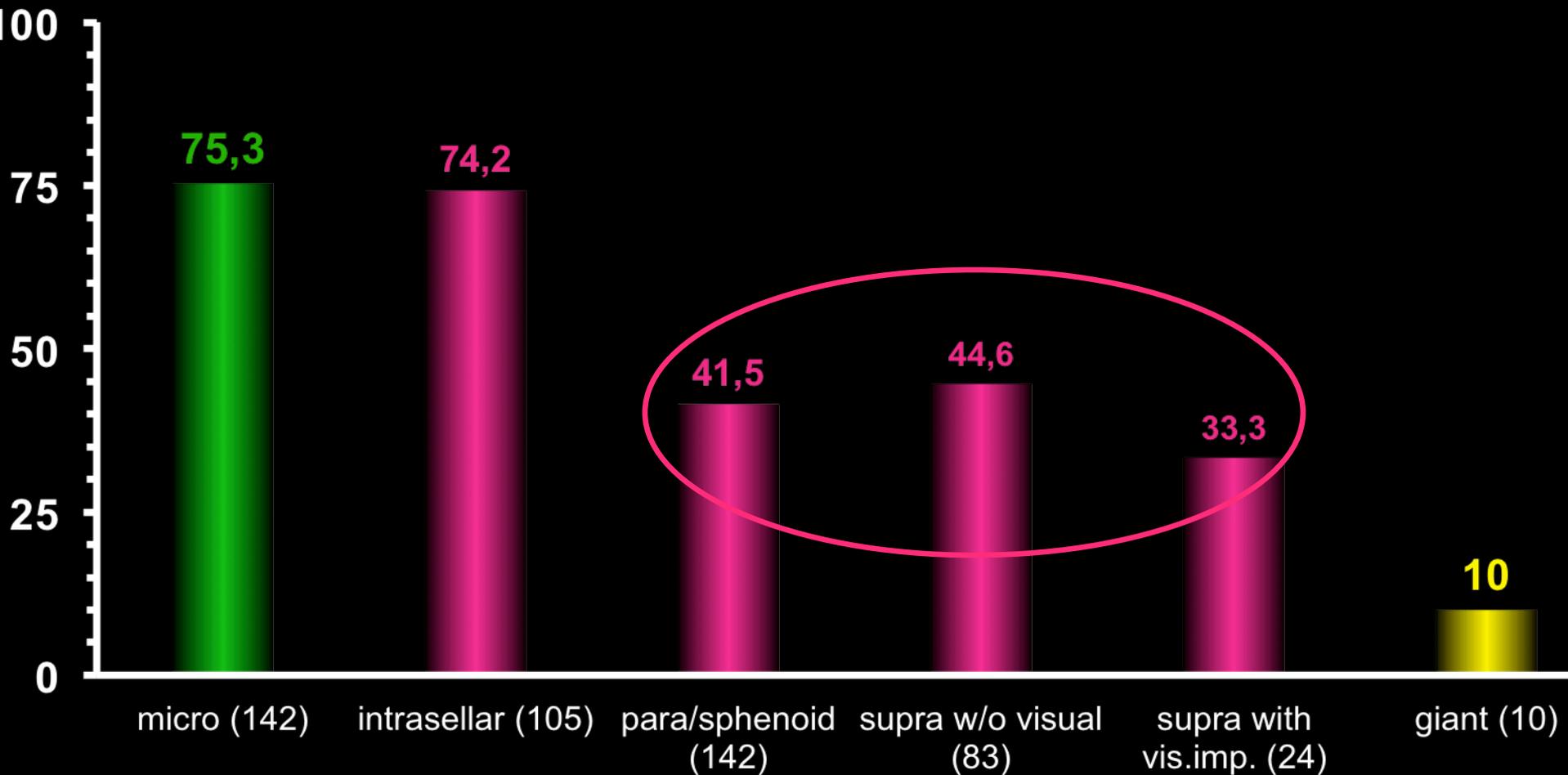
	Tumour classification			
	Group A	Group B	Group C	Group D
Octreotide pretreatment (<i>n</i> = 90)	100% (7/7)	95.20% (20/21)	81.40% (35/43)	0% (0/19)
Comparative series (<i>n</i> = 57)	92.90% (13/14)	87.50% (14/16)	73.90% (17/23)	0% (0/4)
<i>P</i> value†	>0.05	>0.05	>0.05	>0.05



I “migliori” NCH



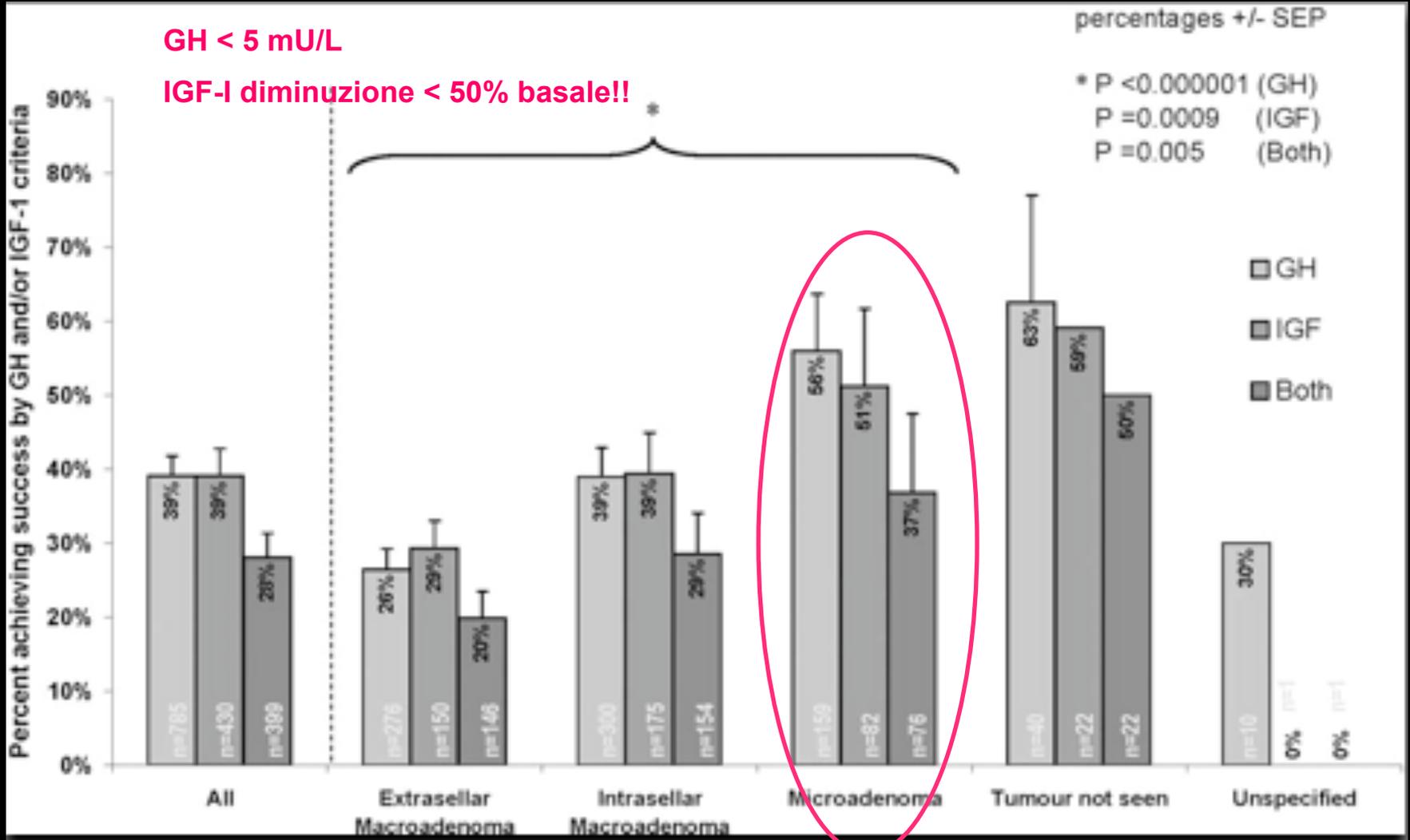
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macroadenoma

Nomikos et al, EJE 2005

I neurochirurghi “normali”



Razionale del trattamento medico pre-chirurgico



- i risultati chirurgici dovrebbero essere migliorati dall'impiego di qualunque trattamento che riduca le dimensioni dell'adenoma e i livelli di GH
- il trattamento prechirurgico *potrebbe* ottenere risultati su
 - secrezione ormonale
 - dimensioni ed estensione dell'adenoma
 - consistenza del tumore



Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates

J Neurosurg 104:899–906, 2006

NO

MARCO LOSA, M.D., PIETRO MORTINI, M.D., LAURA URBAZ, M.D., PAOLO RIBOTTO, M.D., TRISTANA CASTRIGNANÒ, M.D., AND MASSIMO GIOVANELLI, M.D.



ari,
mbre 2013

Preoperative Octreotide Treatment in Newly Diagnosed Acromegalic Patients with Macroadenomas Increases Cure Short-Term Postoperative Rates: A Prospective, Randomized Trial

NI

Sven M. Carlsen, Morten Lund-Johansen, Thomas Schreiner, Sylvi Aanderud, Øivind Johannesen, Johan Svartberg, John G. Cooper, John K. Hald, Stine L. Fougner, and Jens Bollerslev, on behalf of the Preoperative Octreotide Treatment of Acromegaly study group*

J Clin Endocrinol Metab. August 2008, 93(8):2984–2990

European Journal of Endocrinology (2010) 162 661–666

ISSN 0804-4643

CLINICAL STUDY

Sì

Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial

Zhi-gang Mao, Yong-hong Zhu¹, Hai-liang Tang², Dao-yuan Wang, Jing Zhou¹, Dong-sheng He, Hai Lan, Bai-ning Luo³ and Hai-jun Wang

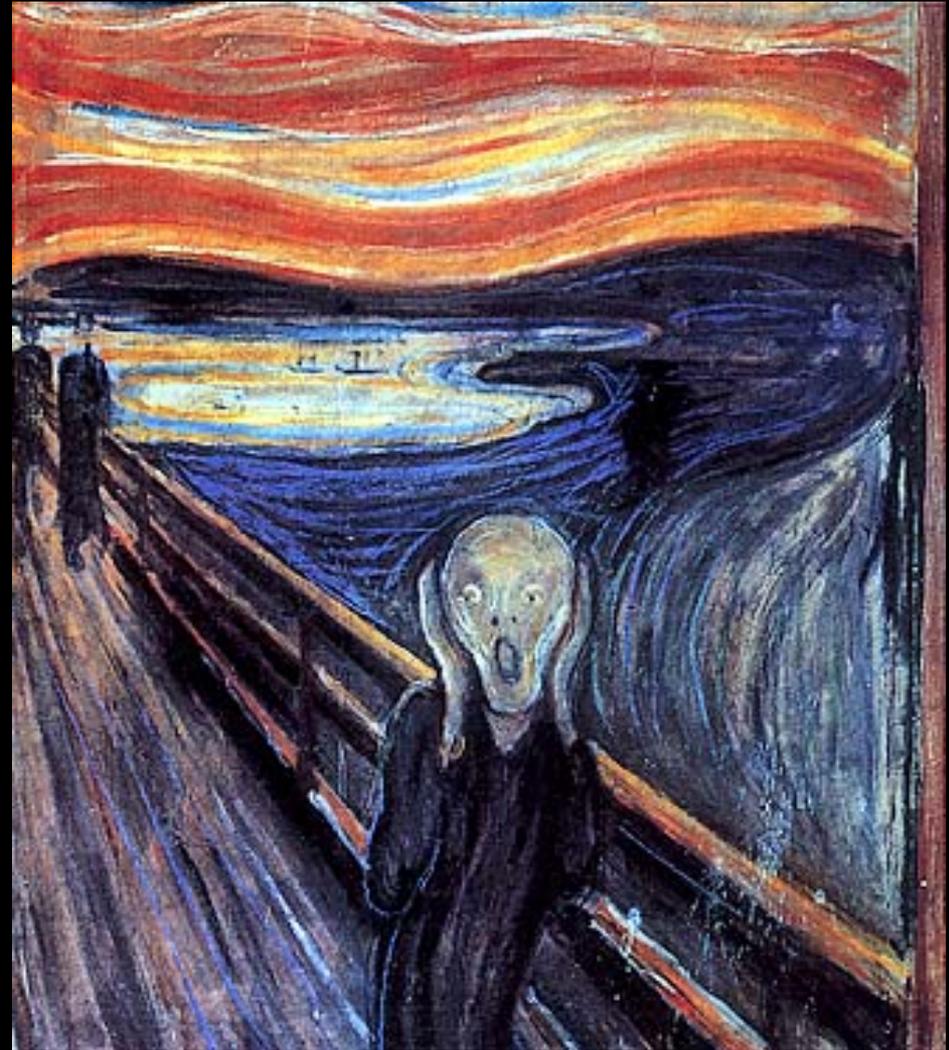
Department of Neurosurgery, The First Affiliated Hospital of Sun Yat-sen University, No. 58, Zhongshan Er Road, Guangzhou 510080, People's Republic of China, ¹Department of Histology and Embryology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou 510080, People's Republic of China, ²Department of Neurosurgery, Hua-shan Hospital affiliated to Fudan University, Shanghai 200040, People's Republic of China and ³Department of Radiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, People's Republic of China

Outline



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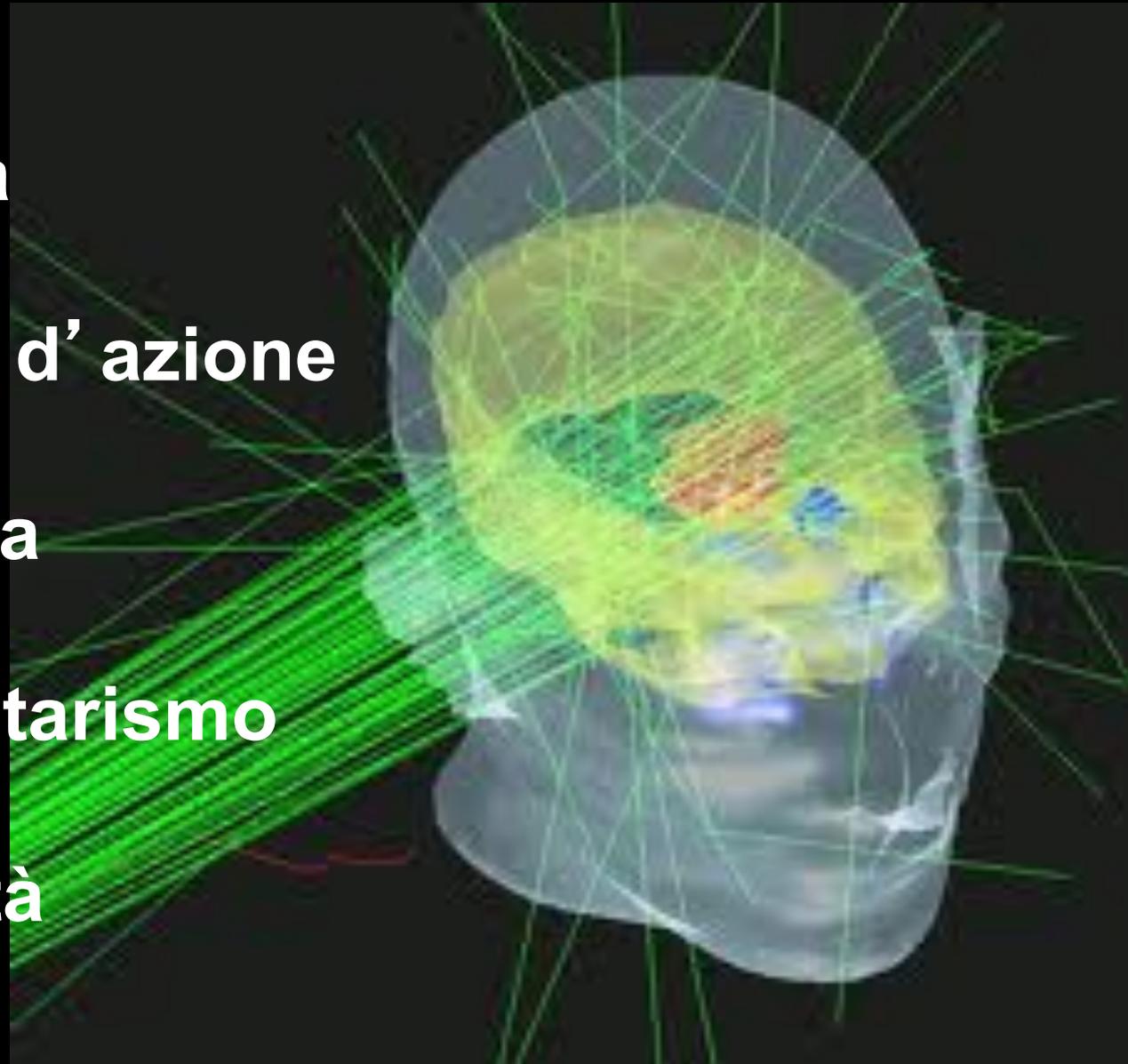
- Perché trattare
- Neurochirurgia
- Terapia radiante



Terapia radiante



- **Tecnica**
- **Ritardo d'azione**
- **Efficacia**
- **Ipopituitarismo**
- **Mortalità**





RT convenzionale frazionata



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Autore (anno)	N	Follow-up mediano(aa)	Normalizzazione IGF-I
Giannella-Neto (1988)	8	5	25%
Barkan (1997)	38	6.8	5%
Van der Lely (1997)	37	7	0
Thalassinos (1998)	14	> 10	28%
Swearingen (1998)	45	6.7	42%
Powell (2000)	31	5.2	45%
Barrande (2000)	47	15	79%
Bezerra (2000)	51	4	39%
Alfaro (2000)	91	10	42%
Gutt (2001)	41	12.8	34%
Cozzi (2001)	49	14	16%
Epaminonda (2001)	67	12	55%
Jaquet (2003)	40	7	10%
Jenkins (2006)	656	7	63%
Totale	1216		49%



RT frazionata “moderna”

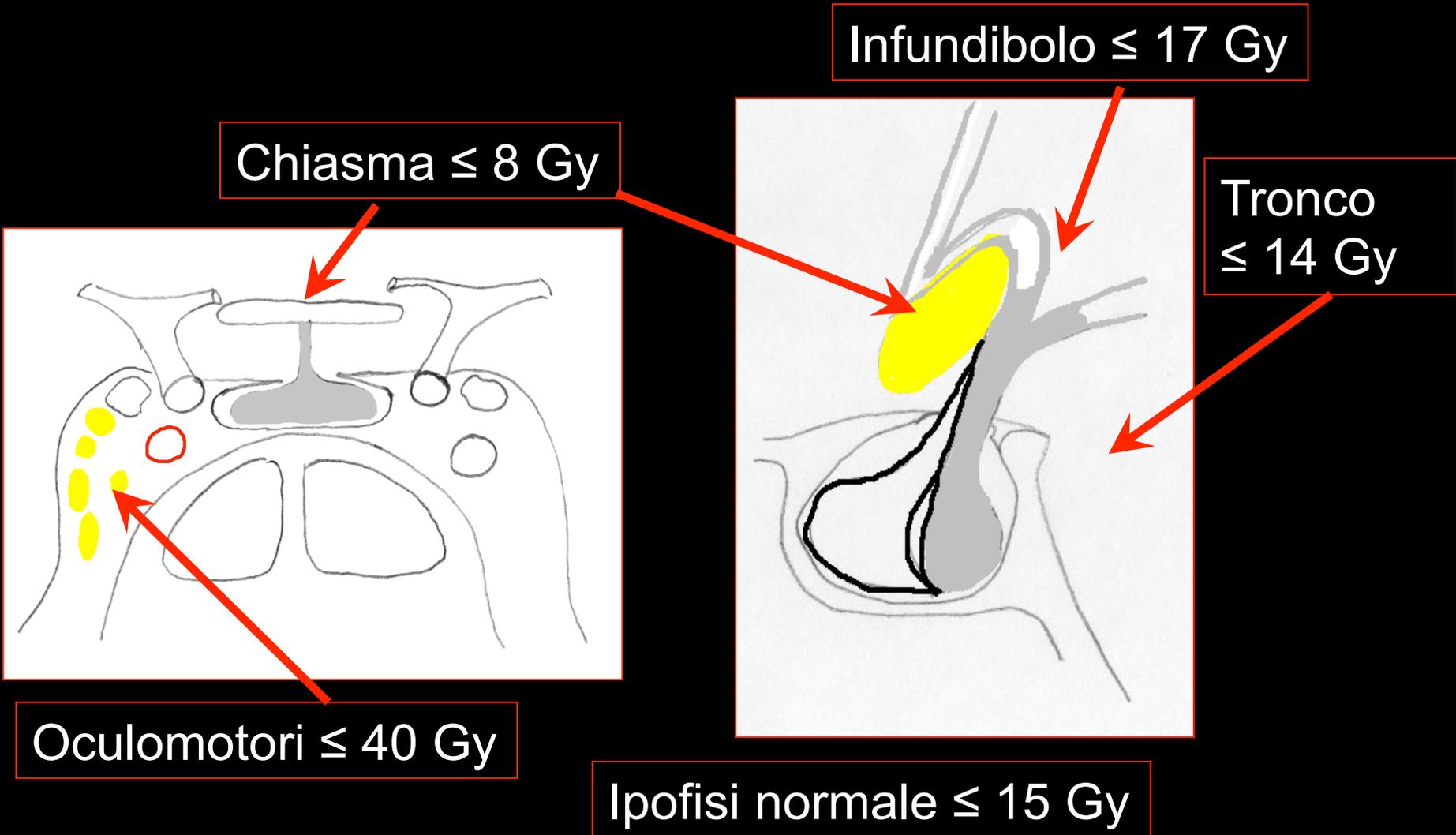


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Autore (anno)	N	Follow-up mediano (mesi)	Normalizzazione IGF-I
Roug (2009)	34	34	29%
Imran (2009)	12	28.5	8%
Selch (2006)	39	32	0
Minniti (2006)	92	32	35%
Colin (2004)	110	82	29%
Milker-Zabel (2003)	20	61.3	55%
Totale	307		12%

Roug et al, Eur J Endocrinol 2010

Tolleranza alle radiazioni



Risultati gammaknife



Autore (anno)	N	Follow-up (anni)	Normalizzazione IGF-I
Landolt (2000)	31	0.5-2.5	42%
Vladyka (2000)	91	2	43%
Attanasio (2003)*	30	4	23%
Castinetti (2005)	82	4	17%
Jezkova (2006)	96	4	60%
Vik-mo (2007)	61	5.5	38%
Losa (2008)	83	5.5	60%
Ronchi (2009)*	35	10	82%
Swords (2009)	10°	0.5-6.5	80%
Iwai (2010)	26	7	38%
Totale	515		47%

* sono gli stessi pazienti valutati a differenti intervalli di tempo

° tutti pregressa FRT

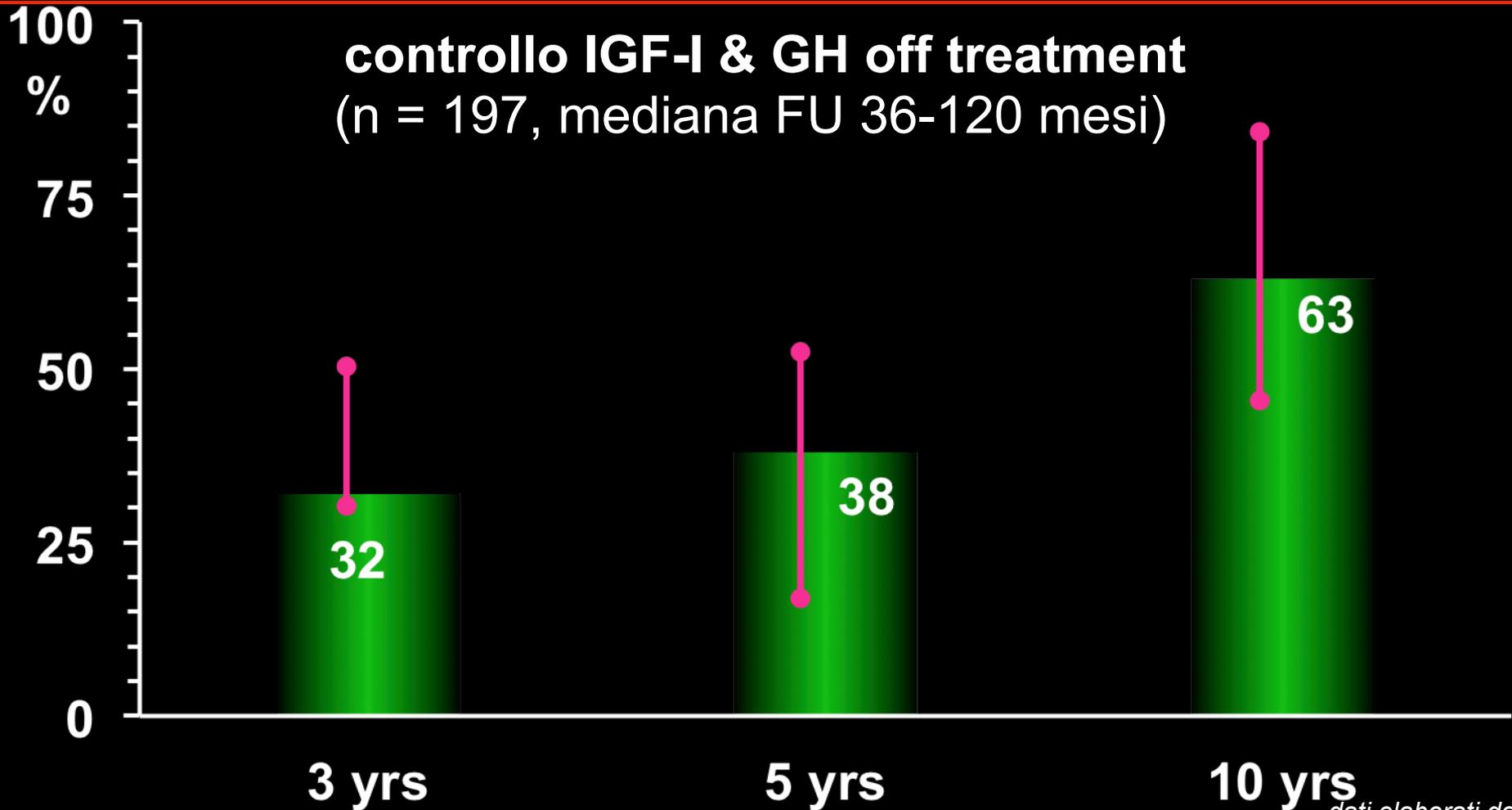


Radiochirurgia gamma-knife



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controllo IGF-I & GH off treatment
(n = 197, mediana FU 36-120 mesi)



dati elaborati da
Swords et al, *Eur J Endocrinol* 2009
Iway et al, *J Clin Neurosci* 2010
Losa et al, *J Clin Endocrinol Metab* 2008
Castinetti et al, *J Clin Endocrinol Metab* 2008
Ronchi et al, *Clin Endocrinol* 2009



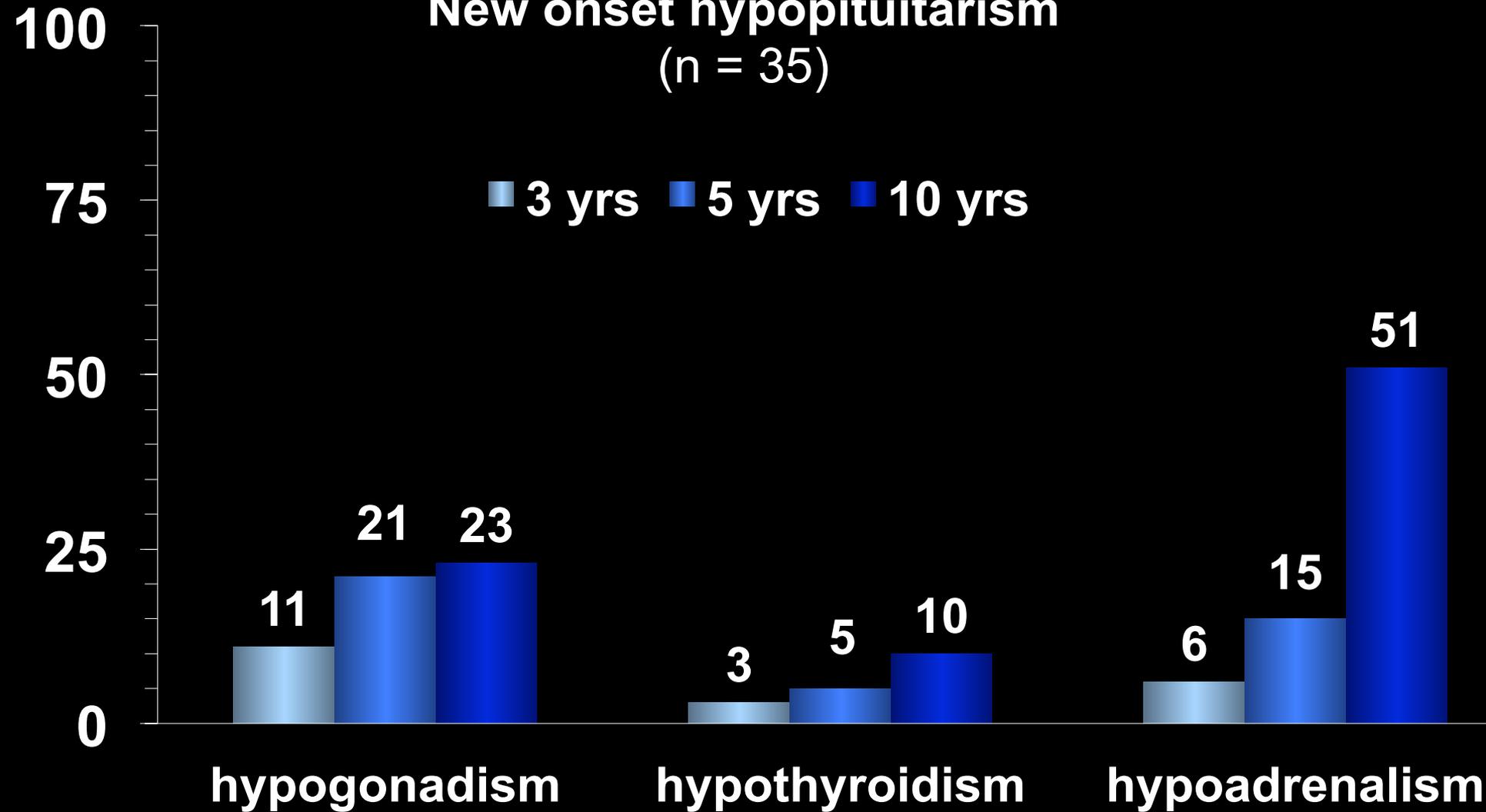
Radiochirurgia gamma-knife



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New onset hypopituitarism (n = 35)

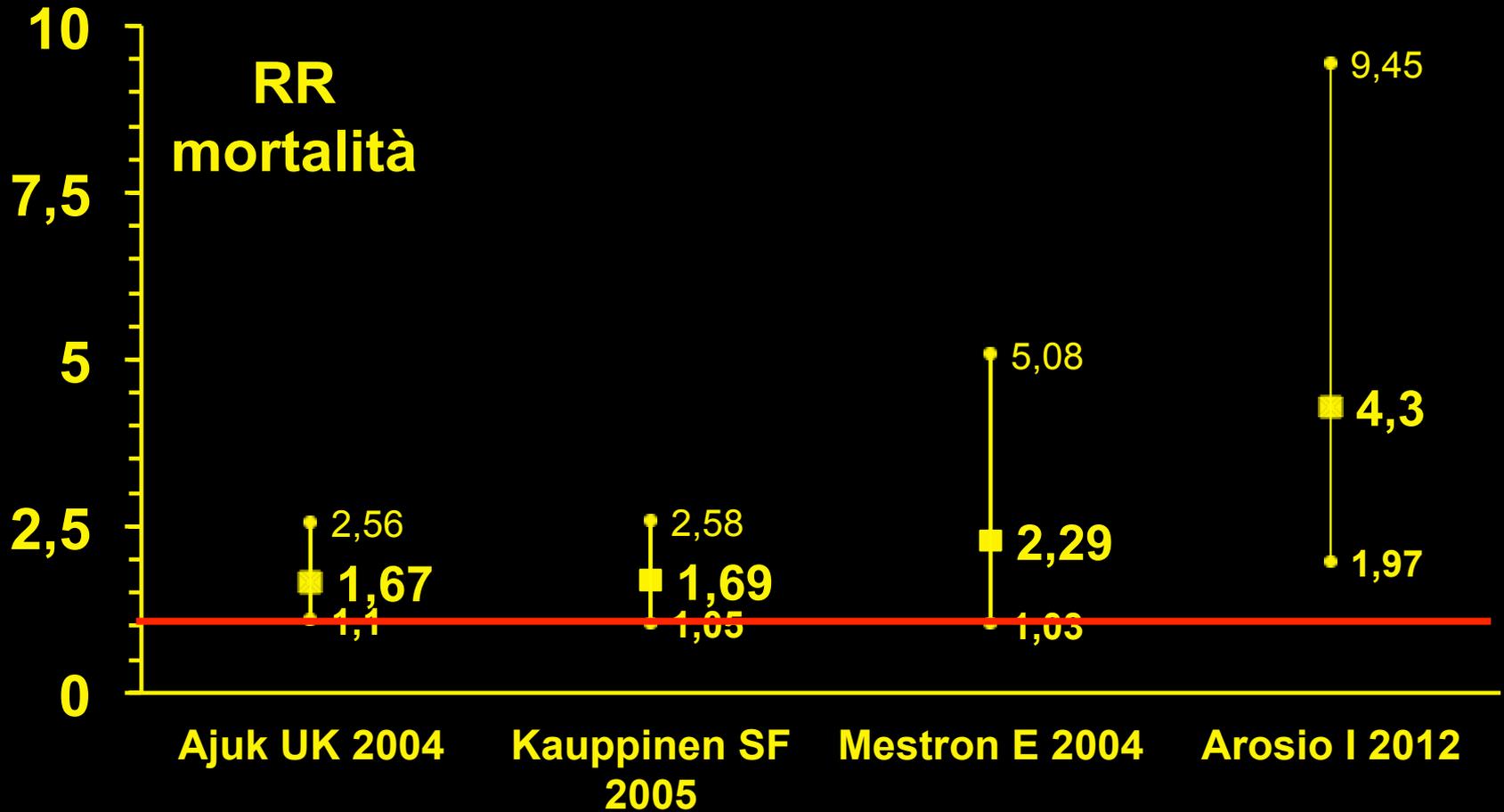
■ 3 yrs ■ 5 yrs ■ 10 yrs



dati elaborati da

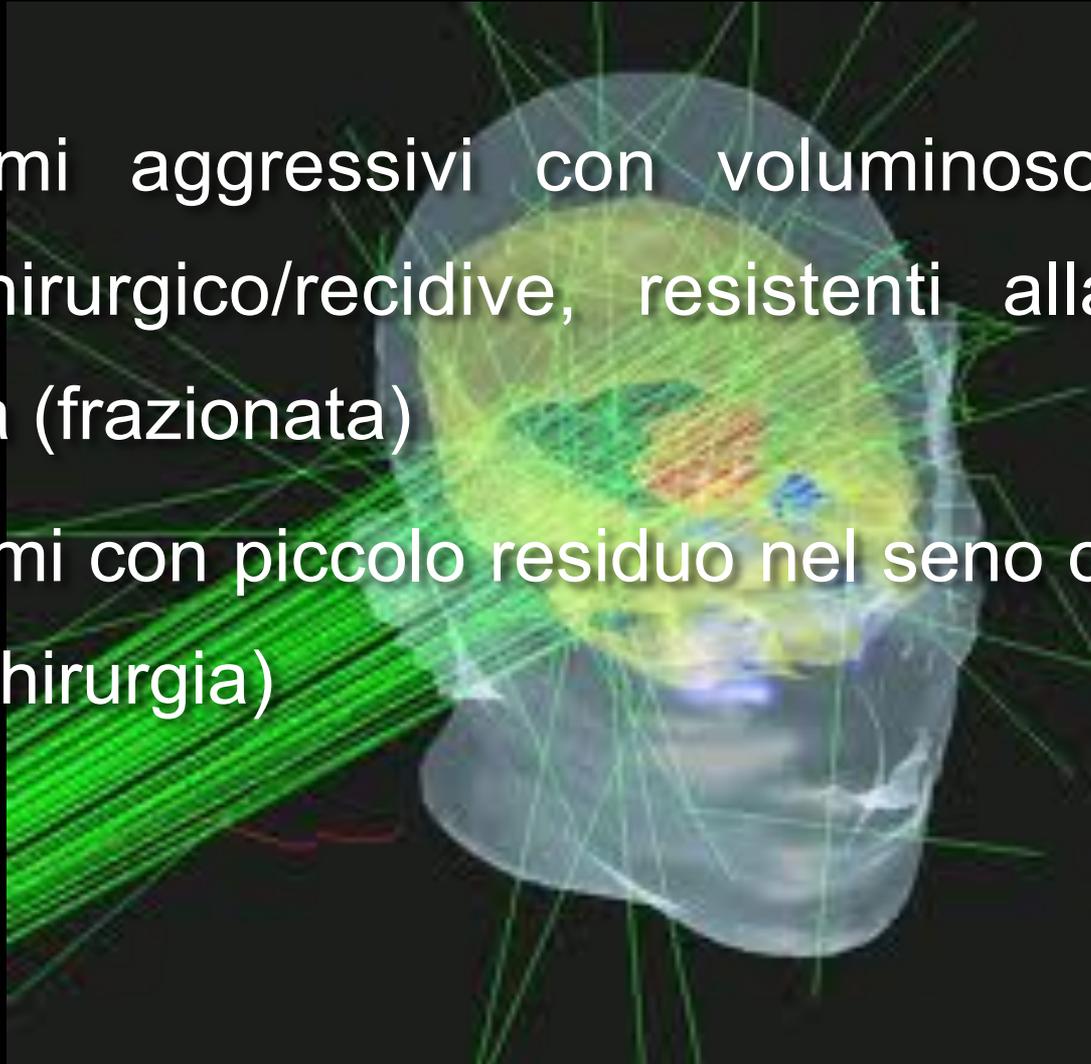
Ronchi et al, Clin Endocrinol 2009

Pregressa radioterapia e mortalità



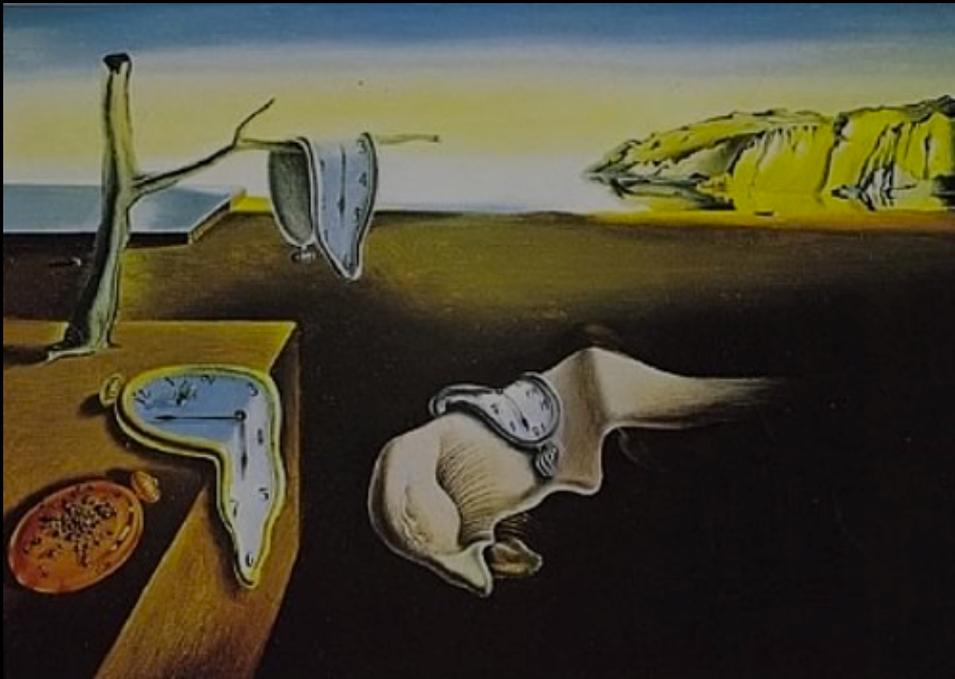
Indicazioni attuali alla terapia radiante

- Adenomi aggressivi con voluminoso residuo post-chirurgico/recidive, resistenti alla terapia medica (frazionata)
- Adenomi con piccolo residuo nel seno cavernoso (radiochirurgia)





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7-10 novembre 2013



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