I tumori ipofisari aggressivi

Minicorso 3

Venerdì 9 novembre 2018 h 8.00 – 10.00

(Replica Domenica 11 novembre 2018 h 10.30 – 12.30)

Obiettivi educazionali

- Sapere quando sospettare e come riconoscere un adenoma aggressivo
- Saper fare un bilancio ponderato fra inerzia e aggressività terapeutica
- Saper riconoscere il momento in cui chiedere aiuto

Le regole del “gioco”

Gli “attori”

Roma, 8-11 novembre 2018

ITALIAN CHAPTER

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Conflitti di interesse

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:

- **Maria Rosaria Ambrosio:** nessuno
- **Roberto Attanasio**: iscrizione a meeting scientifici da IBSA, Pfizer, Novartis
- **Andrea Lania**: Advisory board Novartis, finanziamenti per progetti di ricerca da Novartis, iscrizione a meeting scientifici da IBSA, Pfizer, Novartis, Shire
- **Marco Losa**: Advisory Board di HypoCCS (Eli-Lilly), fees per congressi da Eli-Lilly, Pfizer e Ipsen
- **Diego Mazzatenta**: nessuno
- **Giuseppe Minniti**: BrainLab honoraria fees
- **Maurizio Poggi**: iscrizione a meeting scientifici da Novartis, Eli Lilly e Ipsen

Clinical Practice Guideline | G Raverot and others | Aggressive pituitary tumour guidelines | 178:1 | G1–G24

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

Gerald Raverot[1,2,3], Pia Burman[4], Ann McCormack[5,6], Anthony Heaney[7], Stephan Petersenn[8], Vera Popovic[9], Jacqueline Trouillas[2,10] and Olaf M Dekkers[11,12] on behalf of The European Society of Endocrinology

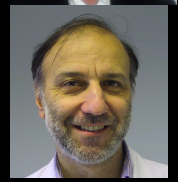
European Journal of Endocrinology (2018) **178**, G1–G24

Agenda

- Aggressività: definizione e diagnosi
- Terapia neurochirurgica
- Terapie radianti
- Terapie farmacologiche

~~Forme familiari~~
Metastasi ipofisarie




Caso clinico 1

Natascia, 58 anni, origine ucraina

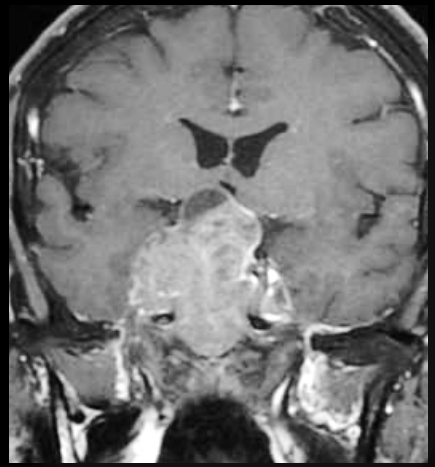
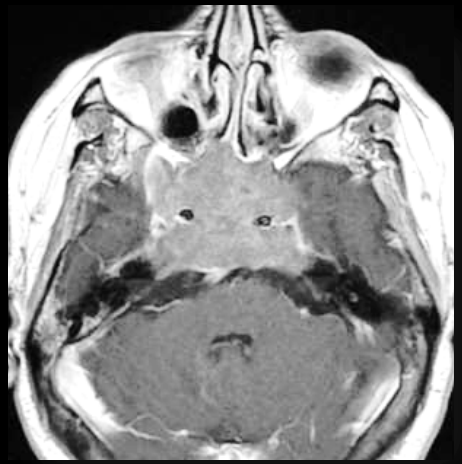
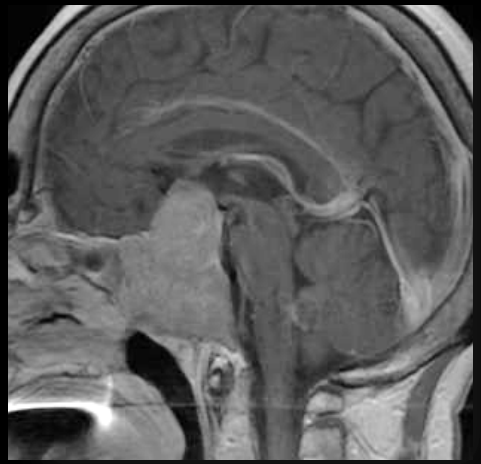
- Menopausa fisiologica a 51 anni
- A 30 anni asportazione nodulo mammario benigno
- Ipertensione arteriosa
- Cefalea cronica
- Nessuna terapia in corso

- Lamenta: cefalea orbitaria ingravescente e riduzione visus OS
- EO: emianopsia omonima sin

Natascia: esami endocrini

- PRL (dopo diluizione e PEG): **55 ng/mL** (< 20)
- Cortisolo: 188 ng/mL (67-226)
- ACTH: 19 pg/mL (5-60)
- FT4: 9.3 pg/mL (5.5-12)
- TSH: 3.3 mU/L (0.25-4.5)
- GH: 1.6 ng/mL
- IGF-I: 85 ng/mL (54-204)
- FSH: 21 U/L (17-114)
- Na 138 mM/L, K 4.7 mM/L, osmolarità 286 mOsm/L (278-305)

Natascia: imaging

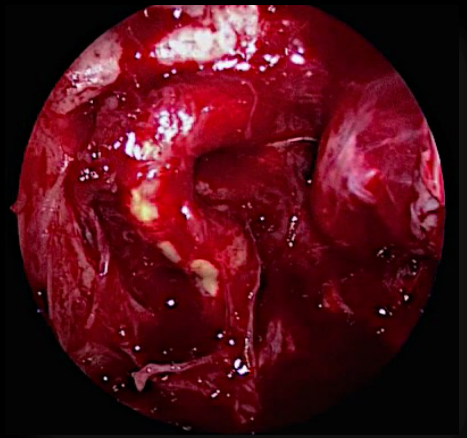




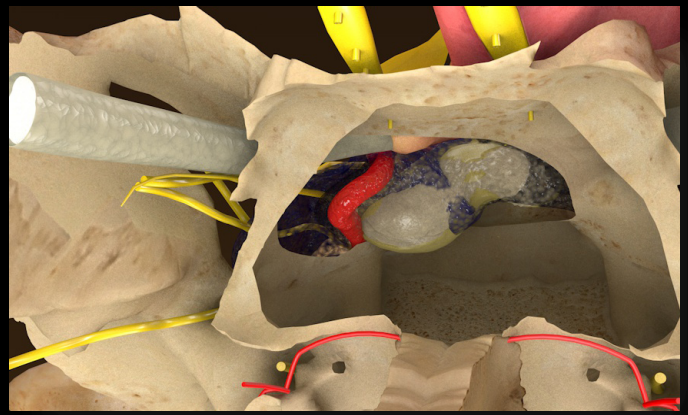
Diagnosi

- Macroadenoma ipofisario clinicamente non funzionante → modesta iperPRLemia da compressione/deviazione peduncolo (escluso macroprolattinoma)
- Funzionalità ipofisaria basale preservata

Natascia: terapia NCH

Intervento neurochirugico
trans-naso-sfenoidale con approccio esteso al
seno cavernoso bilateralmente



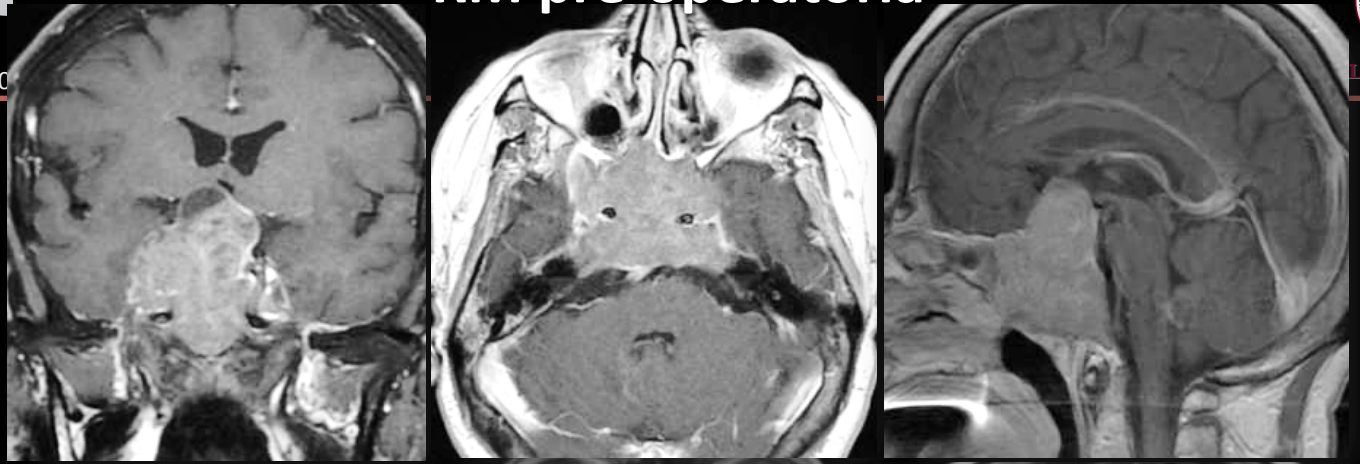


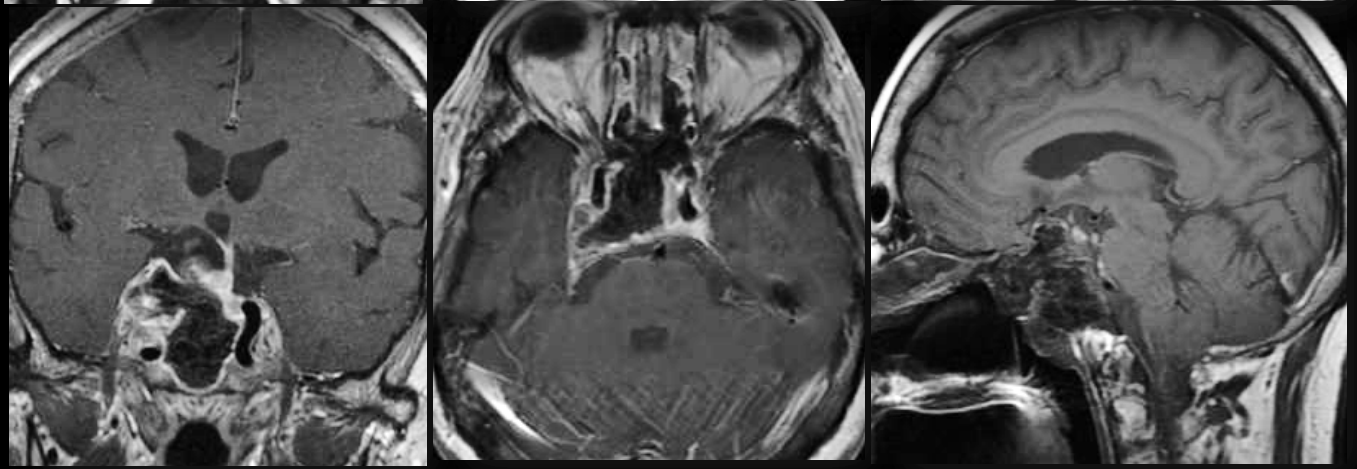
Natascia: esami post-op

- PRL: 12 ng/mL (< 20)
- Cortisolo: 200* ng/mL (67-226)
- FT4: 8.7 pg/mL (5.5-12)
- Na: 142 mEq/L (135-146)
- K: 4.2 mEq/L (3.5-5.3)
- Osmolarità: 296 mOsm/L (278-305)

Funzionalità ipofisaria basale anteriore preservata
Assenza di diabete insipido post-operatorio
Non altre complicanze chirurgiche

RM pre-operatoria





RM post-operatoria: minimo residuo cavernoso dx

Natascia: istologia

- Neoplasia composta da cellule arrangiate in nidi e formazioni papillari
- Immunoistochimica: debole positività per PRL (tutti gli altri ormoni ipofisari sono negativi)
- Ki-67: 2%

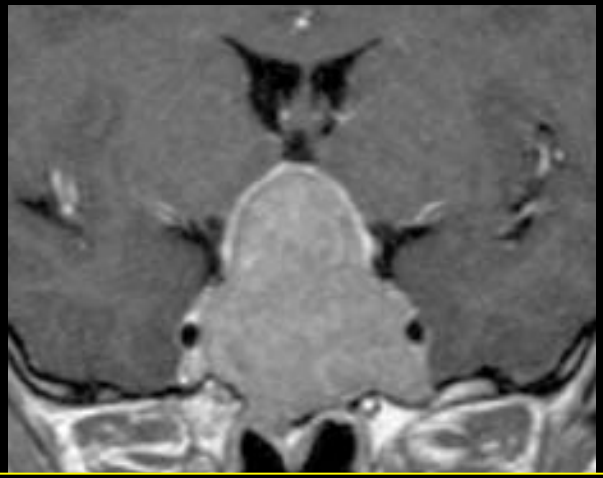
Null cell adenoma

Caso clinico 2

- Mario, 63 anni
- 1997: comparsa emianopsia e deficit acuità visiva
- PRL: **2300 ng/mL**
- Cortisolemia: 66 nM/L (165-607)
- FT4: 86 pM/L (90-230)
- Testosterone: 2.1 nM/L (9.7 − 38)
- IGF-1: 4 nM/L (4-32)

Mario: imaging

Tumore invasivo con estensione infra- e sovra-sellare (diametro max 25 mm)



Diagnosi: MacroPRL-oma con associato ipopituitarismo

Inizia cabergolina (2 mg/settimana)
e terapia sostitutiva (corticosteroidi, tiroxina e testosterone)

Mario: risposta alla terapia

Valori di PRL (ng/mL) in cabergolina

- Pre: 2300
- 1 mese : 618
- 3 mesi: 81
- 12 mesi: 34

- Shrinkage tumorale progressivo: regressione completa del disturbo visivo; completa scomparsa della porzione sovra-sellare, empty sella parziale

Nei successivi 3 anni

- Nessuna modifica della clinica
- PRL stabile ai controlli semestrali
- RM stabile

Natascia vs Mario

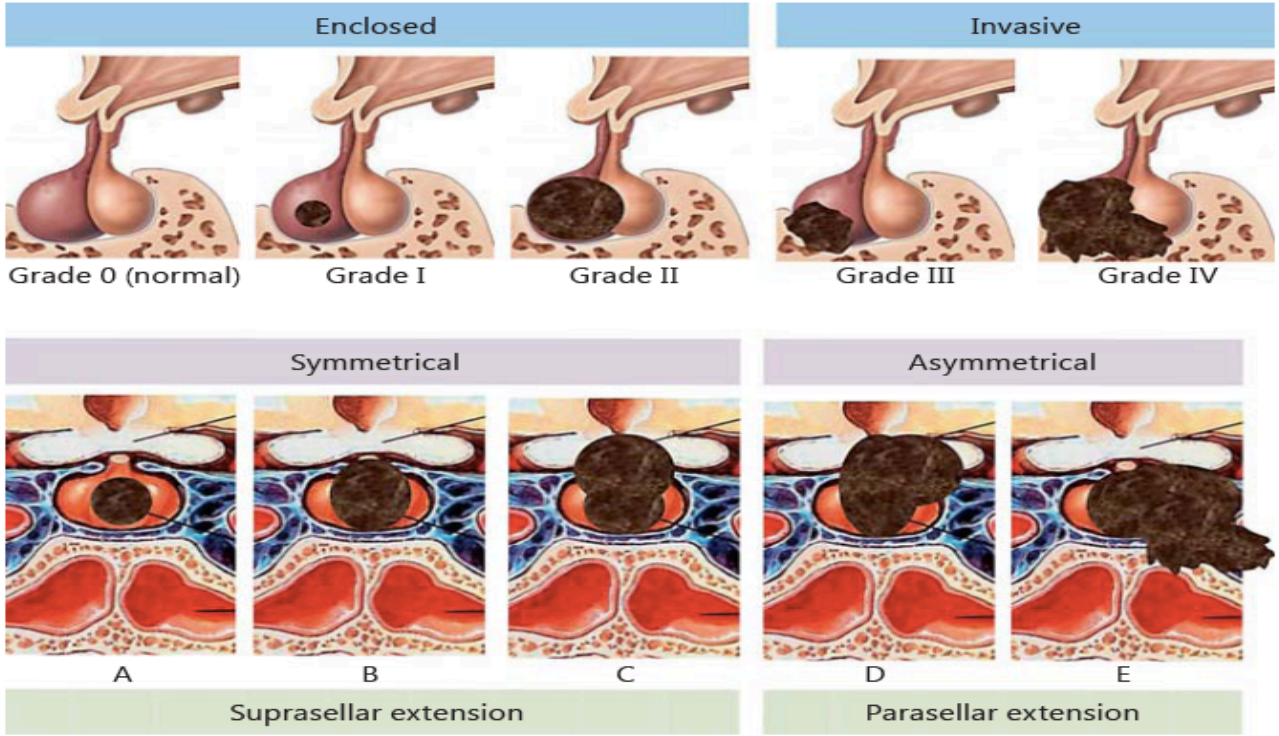
Chi dei 2 vi sembra più a rischio?

E sulla base di quale criterio?

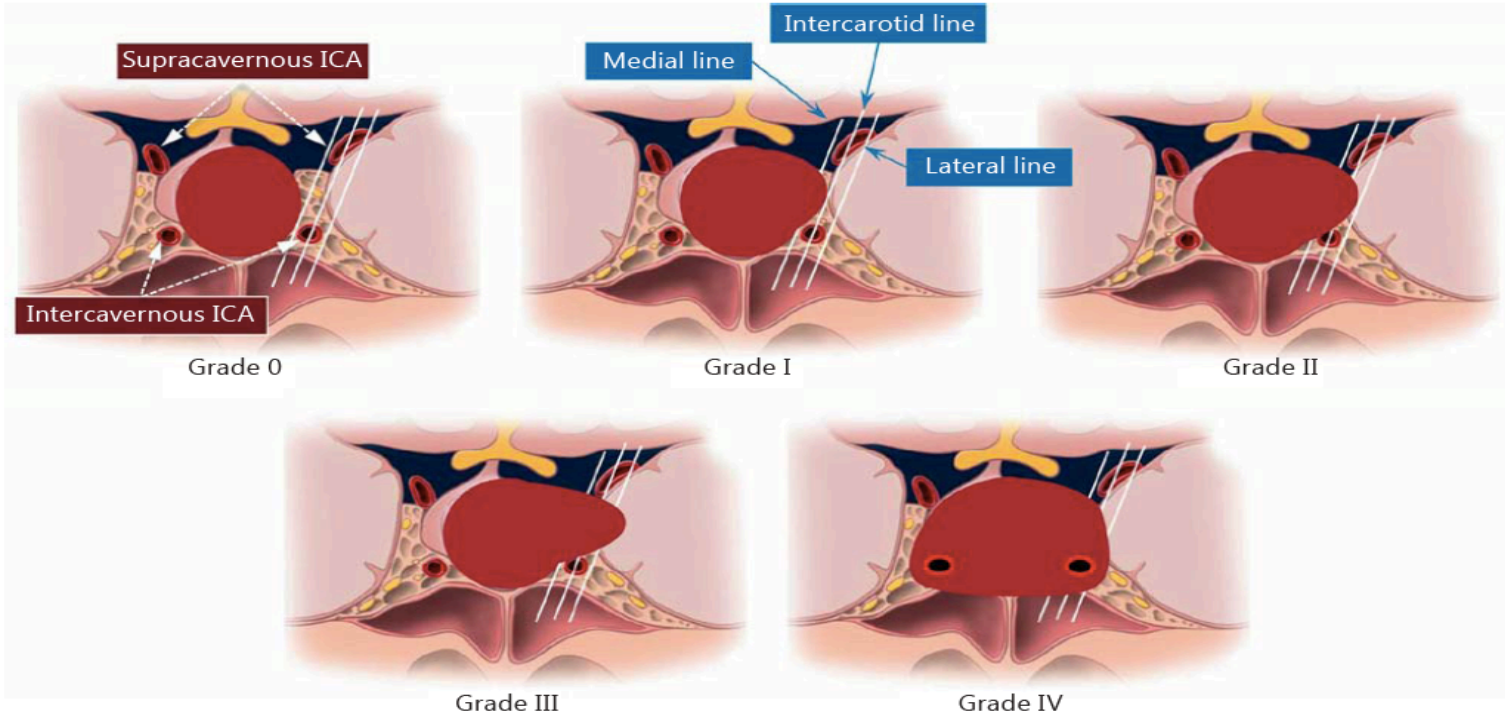
Definizioni e criteri diagnostici

- Atipico, aggressivo, invasivo, maligno, resistente: sinonimi?
- È tutto chiaro dal punto di vista classificativo?
- Il “cattivo” lo è fin dall’inizio? O diventa tale perché lo trattiamo “male”?
- Esistono criteri (clinici, radiologici, …) per riconoscere il “cattivo”dall’inizio?
- O dobbiamo aspettare il pezzo operatorio? E lì è tutto chiaro?

Invasività


Enclosed
Invasive
Grade 0 (normal)
Grade I
Grade II
Grade III
Grade IV
Symmetrical
Asymmetrical
A
B
C
D
E
Suprasellar extension
Parasellar extension

Invasività


Supracavernous ICA
Intercavernous ICA
Grade 0
Intercarotid line
Medial line
Lateral line
Grade I
Grade II
Grade III
Grade IV

Definizione di aggressività

1. Espansione tumorale invasiva delle strutture anatomiche circostanti
2. Rapida recidiva (6–12 mesi post-op)
3. Resistenza alle terapie convenzionali

Study	Total adenomas	Atypical adenomas (prevalence)	NFPA	PRL	GH	ACTH	Recurrence
Scheithauer et al. [129]	78	6 (14.7%)	n.a.	n.a.	n.a.	n.a.	5/6
Saeger et al. [19]	451	12 (2.7%)	5	1	3	3	n.a.
Zada et al. [20]	121	18 (14.8%)	9	2	5	2	4/18
Yildirim et al. [21]	146	13 (8.9%)	9	3	1	1	5/13
Total	796	49 (6.2%)	23	6	9	6	14/37

n.a. = Not available.

Imaging

Case study

Predictors of aggressive clinical phenotype among immunohistochemically confirmed atypical adenomas

Hasan A. Zaidi, David J. Cote, Ian F. Dunn, Edward R. Laws Jr. *

Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, 15 Francis Street, Boston, MA, United States

Lesioni clinicamente aggressive hanno con maggiore probabilità:

- dimensioni RM maggiori (2.9 ± 1.9 cm vs. 1.9 ± 0.7 cm, p = 0.02)
- maggiore incidenza di invasione cavernosa (65.2% vs. 20.8%, p < 0.01)
- maggiore incidenza di estensione clivale (60.9% vs. 0%, p < 0.01)

all'imaging pre-op

Adenomi aggressivi

Adenomi ipofisari “atipici”

- Indice di proliferazione (MIB-1 = Ki-67) ≥ 3%
- Estesa immunoreattività nucleare p53
- Aumentata attività mitotica

Classificazione WHO 2004

Adenomi ipofisari "atipici"

- Indice di proliferazione (MIB-1 = Ki-67) ≥ 3%
- Estesa immunoreattività nucleare p53
- Aumentata attività mitotica

Cosa aggiungere:

- conta mitotica e indice Ki-67
- parametri morfologici come invasione tumorale (RM e/o giudizio intra-operatorio)

Classificazione WHO 2017

Classificazione WHO 2017

Prolattinomi nel maschio

Adenoma a cellule di Crooke

Adenomi ipofisari ad alto rischio

Adenomi corticotropi silenti

GHomi sparsamente granulati

Adenomi pluri-ormonali Pit-1-positivi

Carcinomi ipofisari

Definiti solo dalla presenza di metastasi

Rari: circa 0.2% dei tumori ipofisari (solo 132 casi riportati dal 1961 al 2009)

No single morphological feature is able to predict pituitary carcinomas [18, 34]. Likewise, there are no morphologic criteria to distinguish locally aggressive or even markedly atypical adenomas from pituitary carcinomas when the tumor is still confined to the sella [18, 34]. Morphologic features associated with malignancy including hypercellularity, nuclear and cellular pleomorphism, increased mitotic activity, necrosis, and dural and/or bony invasion are commonly present but are not necessarily diagnostic of carcinoma.

	AIRTUM POOL (period of diagnosis 2000-2010)								ITALY
							65+ yrs		
					CI	RATE	95% CI		ESTIMATED NEW CASES 2015
TUMOURS OF THE ENDOCRINE ORGA					.60	0.88	0.80-0.97		244
CARCINOMAS OF PITUITARY GLAND					.07	0.08	0.05-0.11		22
CARCINOMAS OF PARATHYROID GLAND					.13	0.12	0.09-0.16		33
CARCINOMAS OF ADRENAL CORTEX					.46	0.68	0.61-0.77		189

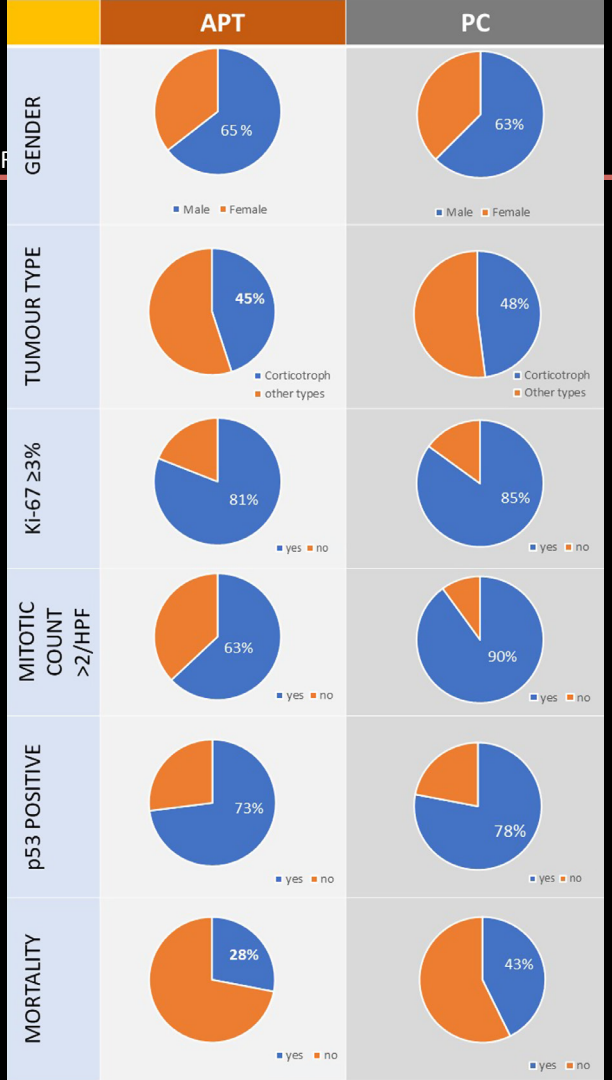
							E PREVALENCE		ITALY
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	ESTIMATED PREVALENT CASES 2010
TUMOURS OF THE ENDOCRINE ORGANS	0.46	0.33-0.63	0.56	0.42-0.74	2.33	2.02-2.67	3.74	3.21-4.27	2 222
CARCINOMAS OF PITUITARY GLAND	0.05	0.01-0.12	0.21	0.12-0.33	0.62	0.47-0.81	1.07	0.77-1.36	627
CARCINOMAS OF PARATHYROID GLAND	0.08	0.03-0.17	0.11	0.06-0.21	0.47	0.34-0.64	0.77	0.53-1.01	448
CARCINOMAS OF ADRENAL CORTEX	0.33	0.22-0.48	0.24	0.15-0.37	1.24	1.02-1.50	1.91	1.54-2.27	1 147

Non sempre è facile distinguere l'adenoma aggressivo dal carcinoma dal punto di vista clinico e patologico

Treatment of aggressive pituitary tumours and carcinomas: Results of a European Society of Endocrinology (ESE) survey 2016

Ann McCormack[1], Olaf M Dekkers[2], Stephan Petersenn[3], Vera Popovic[4], Jacqueline Trouillas[5], Gerald Raverot[6], Pia Burman[7]

	Aggressive pituitary tumour	Pituitary carcinoma	p-value
Total (n)	125	40	
Age at diagnosis, mean (SD)	42.7 (16.2)	44.7 (15.1)	0.51
Gender (n=164)			0.82
Female (n=59)	44 (35.5%)	15 (37.5%)	
Male (n=105)	80 (64.5%)	25 (62.5%)	
Clinical subtype (n=165)			0.018
Clinically functioning (n=97)	72 (57.6%)	25 (62.5%)	
Initially silent becoming functional (n=17)	9 (7.2%)	8 (20.0%)	
Clinically non-functioning (n=51)	44 (35.2%)	7 (17.5%)	
Pathological subtype(s) at last surgery (n=165)			0.14
Corticotroph (n=75)	56 (44.8%)	19 (47.5%)	
Gonadotroph (n=6)	5 (4.0%)	1 (2.5%)	
Somatotroph (n=16)	14 (11.2%)	2 (5.0%)	
Immunonegative (n=24)	21 (16.8%)	3 (7.5%)	
Lactotroph (n=40)	25 (20.0%)	15 (37.5%)	
Thyreotroph (n=4)	4 (3.2%)	0 (0.0%)	
Ki-67 (n=131)			0.84
<3% (n=23)	18 (19%)	5 (15%)	
≥3% (n=62)	46 (47%)	16 (47%)	
≥10% (n=46)	33 (34%)	13 (38%)	
Mitotic count (n=61)			0.030
<2/10HPF (n=17	15 (37%)	2 (10%)	
>2/10HPF (n=44)	26 (63%)	18 (90%)	
p53 immunodetection (n=71)			0.63
Negative (n=18)	13 (27%)	5 (22%)	
Positive (n=53)	35 (73%)	18 (78%)	
MGMT (n=65)			0.96
IHC low (n=41)	30 (63%)	11 (65%)	
IHC int (n=7)	5 (10%)	2 (12%)	
IHC high (n=17)	13 (27%)	4 (24%)	
Number of surgeries (n=147)			0.81
0 (n=5)	4 (3.6%)	1 (2.8%)	
1 (n=27)	21 (18.9%)	6 (16.7%)	
2 or 3 (n=73)	55 (49.5%)	18 (50.0%)	
≥ 4 (n=42)	31 (27.9%)	11 (30.5%)	
Number of radiotherapy courses (n=147)			0.014
0 (n=13	12 (10.7%)	1 (2.9%)	
1 (n=90)	71 (63.4%)	19 (54.3%)	
2 (n=41)	29 (25.9%)	12 (34.3%)	
3 or 4 (n=3)	0 (0.0%)	3 (8.6%)	



ITALIAN CHAPTER

Aggressive pituitary tumours and carcinomas: two sides of the same coin?

Jacqueline Trouillas[1], Pia Burman[2,3], Ann McCormack[4,5], Stephan Petersenn[6], Vera Popovic[7], Olaf Dekkers[8] and **Gerald Raverot[1,9]**

MRI	Pathology	Grade #	Surgery and/or medical treatment	± Radiation therapy		Clinical classification	
Non invasive (60-65%)*	Non proliferative	1a	Cured			Adenoma	
	Proliferative	1b	Cured or remission				
Invasive (35-40%)*	Non proliferative	2a	Persistent disease	→	Controlled	Invasive PitNET	
	Proliferative	2b (10%)*	Persistent disease	→	Recurrence Progression	Aggressive Pituitary tumour: Invasive PitNET with malignant potential	Temozolomide
		3		→	Metastasis	Pituitary carcinoma (0.2%)*	

Adenomi corticotropi silenti

Clinical Endocrinology (2010) 72, 648–653 doi: 10.1111/j.1365-2265.2009.036

ORIGINAL ARTICLE

corticotroph adenomas have unique recurrence
cteristics compared with other nonfunctioning pituitary
omas

ng Cho*, Sur

Table 3. Comparison of preoperative tumour characterisrics, ratio of complete resection and adjuvant treatment according to ACTH immunoreactivity

	SCAs (n = 28)	Non-SCAs (n = 134)	P-value
Follow-up period, mean in years (range)	5·2 (1·0-16·0)	4·2 (0.5-16·1)	0·255
Tumour size (cm)	2·8 ± 0·8	3·0 ± 0·9	0·320
Modified Hardy criteria*†			
Grade 2	16 (57·1)	87 (64·9)	0·077
Grade 3	11 (39·3)	47 (35·1)	
Grade 4	1 (3·6)	0 (0)	
Radiologic tumour characteristics (sella MRI)			
Solid tumour	10 (35·7)	88 (65·7)	0·003
Cystic change	8 (28·6)	30 (22·4)	0·483
Intratumoural hemorrhage	10 (35·7)	16 (11·9)	0·004
Complete resection*	10 (35·7)	48 (35·8)	1·000
Postoperative residual tumour size (cm)	1·5 ± 0·9	1·6 ± 0·9	0·520
Adjuvant treatment*‡	6/18 (33·3)	20/86 (23·3)	0·380
Conventional radiotherapy	4 (22·2)	11 (12·8)	0·288
Gamma knife surgery	2 (11·1)	11 (12·8)	1·000
Latency time between operation and adjuvant treatment, mean in months (range)	8·9 (0·9–13·7)	9·3 (1·2–25·4)	0·895

Table 5. Comparison of recurrence characteristics according to age at diagnosis

	SCAs (n = 28)	Non-SCAs (n = 134)	P-value
Recurrence			
≤ 30 years	4/6 (66·7)	5/10 (50)	0·633
>30 years	3/22 (13·6)	31/124 (25)	0·245
Multiple recurrences > 2 times			
≤ 30 years	4/4 (100)	0/5 (0)	0·008
>30 years	0/3 (0)	1/31 (3·2)	1·000
Late recurrence > 5 years			
≤ 30 years	3/4 (75)	0/5 (0)	0·048
>30 years	1/3 (33·3)	6/31 (19·4)	0·511

Data are No. of patients (%).

Conclusion The overall recurrence rate was similar between SCAs and non-SCAs. However, young patients with SCAs had a higher frequency of multiple and late recurrences, which showed more aggressive tumour behaviour. Therefore, we suggest that patients with SCAs, especially patients diagnosed at a young age, require careful long-term monitoring.

Adenomi corticotropi silenti

Clinical Endocrinology (2003) 58, 59–64

Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently

K. J. Bradley, J. A. H. Wass and H. E. Turner
Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and, Metabolism, Radcliffe Infirmary, Oxford, UK

ITALIAN CHAPTER

atteggiamento più aggressivo

Table 1 Comparison of NFAs according to ACTH immunoreactivity

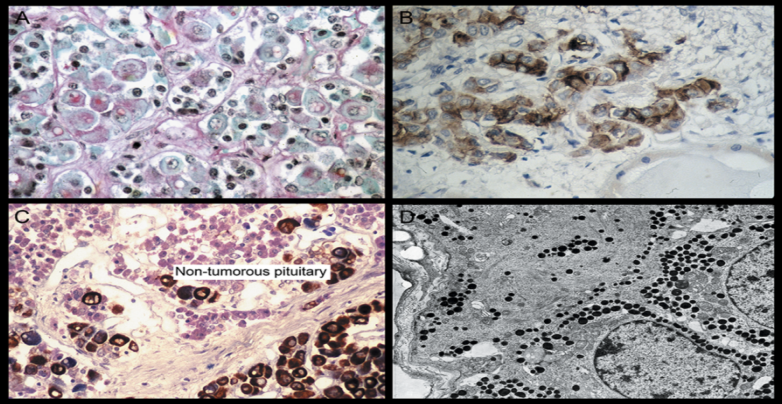
	ACTH immunopositive NFAs	ACTH immunonegative NFAs
Total recurrence rate No. of patients (%) ($P = 0{\cdot}9$)	9/28 (32%)	20/60 (33%)
Recurrence rate in patients without postoperative radiotherapy No. of patients (%) ($P = 0{\cdot}9$)	8/23 (35%)	20/60 (33%)
Recurrence rate in patients without post-operative radiotherapy and excluding those followed-up for less than 1 year No. of patients (%) ($P = 0{\cdot}6$)	8/20 (40%)	20/60 (33%)
Follow-up period Mean in years (range)	7·4 (0·5–26·9)	6·3 (1–14)
Time to tumour regrowth Mean in years (range)	5·8 (1–16)	5·4 (2–14)

Adenomi a cellule di Crooke

ITALIAN CHAPTER

Sex, %	
Female	74.6
Male	23.6
Age, y, range (mean)	16-81 (42.4)
Clinical presentation, %	
Cushing disease	75.6
Silent ACTH adenoma	24.4
Size, %	
Macroadenomas	77.2
Microadenomas	22.8
Invasion to the cavernous or sphenoid sinuses (MRI), %	
Invasive	79.2
Noninvasive	20.8
Morphology	Chromophobic or acidophilic cells; Crooke's hyaline change in >50% of cells; ACTH positive at the cell periphery; LMWK, Cam 5.2 with intense ringlike pattern; dense perinuclear keratin at EM

[a]MRI, magnetic resonance imaging; ACTH, adrenocorticotropic hormone; LMWK, low molecular weight keratin; EM, electron microscopy.



Ialinosi massiva

Reference	No. of Cases	Female, %	Age, y	CS Invasion, n/N (%)[b]	Initial Remission, n/N (%)	Recurrence,[c] n/N (%)	Long-Term Remission, n/N (%)
Blevins et al[27] (1998)	21	90	Mean, 37	6/21 (28)	14/21 (67)	5/14 (36)	9/21 (42.8)
Cannavo et al[28] (2003)	26	65.3	42.5 ± 12.7	8/26 (30.7)	8/26 (30.7)	1/8 (12.5)	9/26 (34.6)
Woo et al[28] (2005)	16	77.83	47.3 ± 13.4	7/18 (39)	2/16 (12.5)	NA	5/14 (35.7)
Kakade et al[30] (2014)	40	60	26.7 ± 9.3	25/40 (62.5)	16/40 (40)	4/16 (25)	27/40 (67.5)
This review (2014)	80	74	Mean 41	38/48 (79.2)	NA	20/30 (66)	NA

[a]CS, cavernous sinus; NA, not available.
[b]Difference statistically significant ($P = .0001$) (2-tailed Fisher exact test).
[c]Difference not statistically significant ($P = .26$) (2-tailed Fisher exact test).

Neurosurgery 2015, 76 (5): 616-622

Carcinomi corticotropi

Alcuni di questi adenomi corticotropi mostrano un aumento della deposizione di collagene, le cosiddette cellule di Crooke, che possono essere un marker di comportamento potenzialmente aggressivo

In circa il 25% dei casi, i carcinomi corticotropi si sviluppano a partire dai tumori corticotropi “silenti”, in cui il tumore secerne precursori dell’ACTH, dosabili in circolo ma che non si legano e non attivano il recettore del’ACTH

Prolattinomi nel maschio

- Più frequenti nel sesso maschile (33 vs 5%)
- Invasivi
- Elevati livelli di Ki-67
- Caratteristiche istologiche di aggressività (50%)

Table 1. *Relationships between clinical and pathological parameters in prolactinomas*

	Ki-67 LI (%)	PCNA LI (%)	Mitotic count (nb)	Cellular atypia[1] (n)
Gender				
– Females	0.7 ± 0.3 [0.0]	3.2 ± 0.3 [2.6]	1 ± 0 [0]	3/37
– Males	2.1 ± 0.8 [0.9]*	6.9 ± 1.6 [4.6]	2 ± 1 [1]	12/36**
Age	r = 0.22	r = 0.09	r = 0.13	r = 0.04
Prolactin	r = 0.07	r = −0.08	r = −0.10	r = 0.09
Tumour diameter	r = 0.27*	r = 0.22	r = 0.17	r = 0.50**
Invasion of cavernous sinus				
– No	0.7 ± 0.2 [0.0]	3.9 ± 1.0 [2.8]	1 ± 0 [0]	4/42
– Yes	2.3 ± 0.9 [0.9]*	6.4 ± 1.5 [4.5]	2 ± 1 [1]	11/31**
Bromocriptine resistance				
– No	0.7 ± 0.2 [0.0]	3.8 ± 0.8 [2.6]	1 ± 0 [0]	8/59
– Yes	4.2 ± 2.0 [1.9]**	10.0 ± 2.7 [8.3]*	4 ± 1 [3]**	7/14**
Tumour staging	r = 0.29*	r = 0.25*	r = 0.30**	r = 0.36**

Table 2. *Clinical and pathological characteristics of prolactinomas, as a function of tumoral behavior*

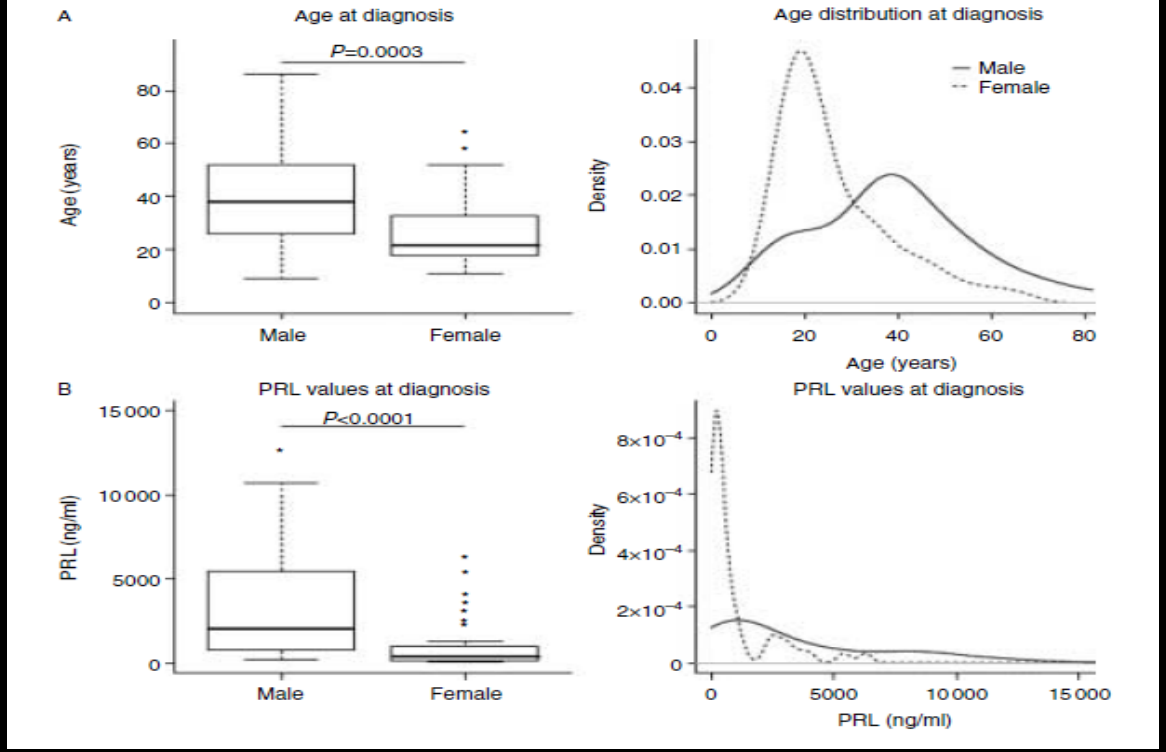
Characteristic	Stage				P value*
	Non-invasive microadenomas	Non-invasive macroadenomas	Invasive tumours	Aggressive tumours	
N	24	19	19	12	
Male sex, n	1 (4%)	9 (47%)	15 (79%)	11 (92%)	<0.001
Ki67 LI (%)	0.8 ± 0.4 [0.0]	0.6 ± 0.3 [0.0]	0.8 ± 0.2 [0.4]	4.8 ± 2.3 [1.9]	0.034
PCNA LI (%)	2.6 ± 0.7 [0.0]	5.6 ± 1.9 [3.5]	3.8 ± 1.1 [2.5]	10.6 ± 3.2 [8.3]	0.071
Mitotic count (nb)	1 ± 0 [0]	1 ± 0 [0]	1 ± 0 [0]	5 ± 2 [3]	0.001
Cellular atypia, n	1/23 (4%)	3/19 (16%)	5/19 (26%)	6/12 (50%)	0.013

European Journal of Endocrinology (2012) **167** 651–662 ISSN 0804-4643

CLINICAL STUDY

Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients

Laurent Vroonen[1,*], Marie-Lise Jaffrain-Rea[2,3,*], Patrick Petrossians[1,*], Gianluca Tamagno[1,4], Philippe Chanson[5,6,7], Lucio Vilar[8], Françoise Borson-Chazot[9,10], Luciana A Naves[11], Thierry Brue[12], Blandine Gatta[13], Brigitte Delemer[14], Enrica Ciccarelli[15], Paolo Beck-Peccoz[16], Philippe Caron[17], Adrian F Daly[1] and Albert Beckers[1]



54% donne

Uomini più vecchi delle donne

Livelli di PRL alla diagnosi maggiori negli uomini

Macroadenomi 86% (più frequenti negli uomini)

Mortalità 4.3%, da carcinoma ipofisario o complicanze neurologiche di massa ipofisaria in rapida espansione

Resistenza secondaria ai dopaminergici

In alcuni casi, lo sviluppo di resistenza ai dopaminergici dipende dall'inizio di terapia sostitutiva gonadica

Gli estrogeni diminuiscono l'effetto dei dopaminergici per azione su:

- trascrizione del gene per PRL
- attività mitotica
- apoptosi
- Numero dei recettori D2 sulla cellula lattotropa

In rari casi questo può corrispondere alla trasformazione maligna di un prolattinoma

GHomi sparsamente granulati

È possibile riconoscere gli adenomi sparsamente granulati prima dell'intervento?

Imaging

Clinical Endocrinology (2012) 77, 72–78 doi: 10.1111/j.1365-2265.2011.04286.x

ORIGINAL ARTICLE

Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly

Groups, baseline	Hypointense	Isointense	Hyperintense	*P*
n (*n* = 45)	12	15	18	
Age at diagnosis (years)	54·5 (44·5–63)	46 (37–60)	46·5 (30·5–56·5)	0·20
Women/men	5/7	7/8	9/9	0·90
Serum GH (μg/l)*	17·5 (6·1–35)	9·3 (6·0–33·5)	4·1 (1·5–8·3)	0·025

Groups	Hypointense	Isointense	Hyperintense	*P*
Preoperative SA treatment; *n* = 25	7	9	9	
Time to evaluation (days)	174 (160–180)	172 (159–178)	160 (104–188)	0·82
IGF-1 below ULN (no. of patients)	4 of 7	2 of 9	1 of 9	0·059**
IGF-1 reduction (%)*	51 (49–70)	36 (19–74)	13 (1–42)	0·031
GH reduction (%)*	86 (72–94)	78 (62–85)	46 (1–70)	0·015

(TG; *n* = 14)				
Sparsely granulated (SG; *n* = 8)	0	0	8	
Total, *n* = 34	10	11	13	

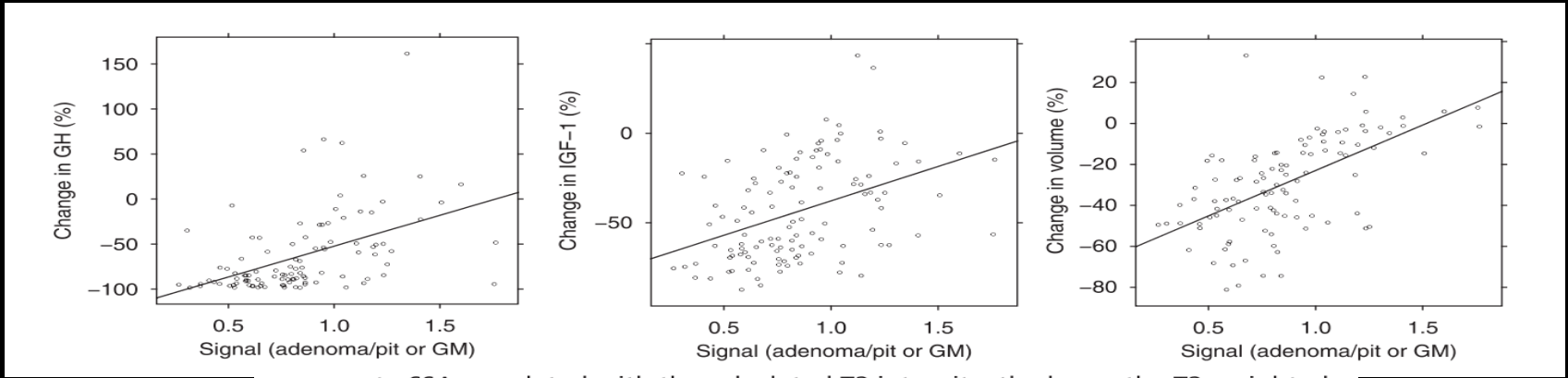
GHomi sparsamente granulati

Research | I Potorac et al. | T2 weighted MRI in acromegaly | 23:11 | 871–881

T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly

Table 1 Baseline and post-treatment characteristics of the different T2-weighted signal groups of adenomas.

	Hypo T2	Hyper T2	Iso T2	*P*
Gender (M:F)	47:37	4:15	7:10	0.018
Age at diagnosis (years)	50.5	51	55	NS
GH nadir (ng/mL) at diagnosis	10.6	3.0	3.8	0.003
IGF-1% at diagnosis	346.1%	184.5%	295.0%	<0.0001
Adenoma volume at diagnosis (mm^3)	863	3235	2444	<0.0001
Random GH reduction (%)	88.0%	36.1%	23.8%	<0.0001
IGF-1% reduction (%)	59.1%	33.2%	19.8%	0.0003
Volume reduction (%)	37.8%	3.0%	8.0%	<0.0001



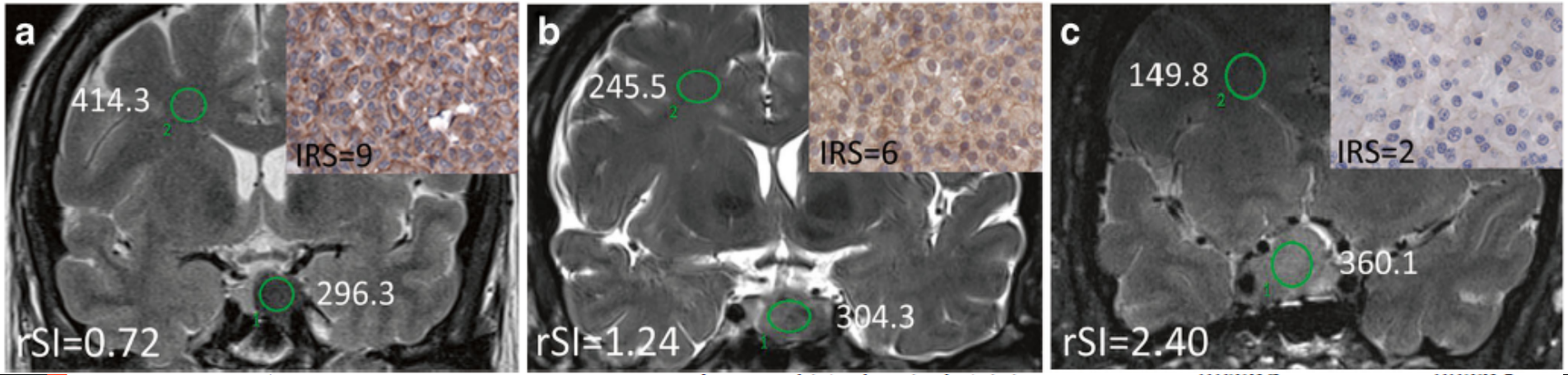
response to SSA correlated with the calculated T2 intensity: the lower the T2-weighted intensity, the greater the decrease in random GH ($P<0.0001$, $r=0.22$), IGF-1 ($P<0.0001$, $r=0.14$) and adenoma volume ($P<0.0001$, $r=0.33$). The T2-weighted signal intensity of GH-secreting adenomas at diagnosis correlates with hormone reduction and tumor shrinkage in response to primary SSA treatment in acromegaly. This study supports its use as a generally available predictive tool at diagnosis that could help to guide subsequent treatment choices in acromegaly.

Imaging

Neuroradiology (2016) 58:1057–1065
DOI 10.1007/s00234-016-1728-4

DIAGNOSTIC NEURORADIOLOGY

Predictive value of T2 relative signal intensity for response to somatostatin analogs in newly diagnosed acromegaly



Biochemical sensitivity‡	0.103	0.001*
Tumor size sensitivity‡	0.765	0.335

† Values were compared by Spearman's rank correlation test
‡ Values were compared by Mann–Whitney *U*-test
*$P < 0.05$ was considered significant

Immunohistochemical staining	SSTR2	SSTR5
rSI on T1 †	0.602	0.383
rSI on T2 †	0.716	0.042*

† Values were compared by Spearman's rank correlation test
*$P < 0.05$ was considered significant

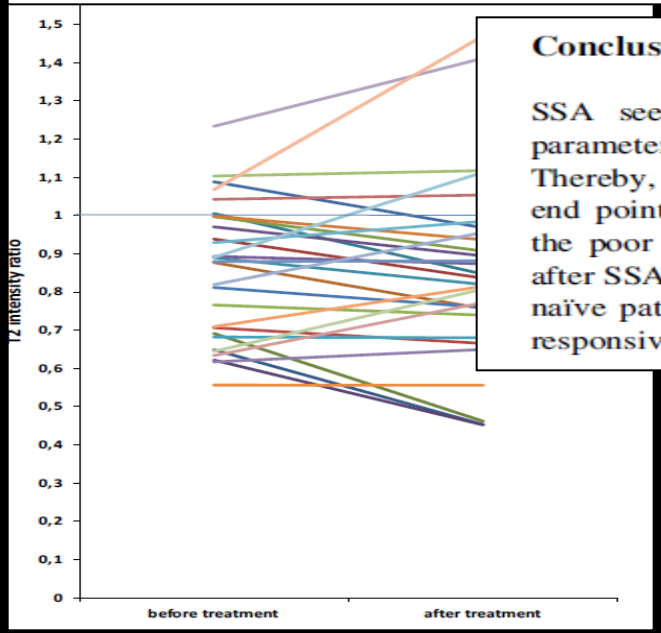
rSI = relative signal intensity

Imaging

Endocrine (2016) 53:327–330
DOI 10.1007/s12020-015-0816-2

RESEARCH LETTER

MRI T2 characteristics in somatotroph adenomas following somatostatin analog treatment in acromegaly



Conclusion

SSA seem to increase the variability of T2 derived parameters, but does not uniformly affect T2 intensity. Thereby, the strengths of the associations to therapeutic end points and histological subtypes are reduced. Due to the poor agreement of T2 intensity measures before and after SSA treatment, only T2 weighted MRI from treatment naïve patients should be assessed as potential marker for responsiveness.

…nasto invariato

…SSA correlava
…: GH, IGF-1, GH

- T2ir dopo terapia con SSA correlava con l'effetto anti-secretorio ma non con riduzione del volume tumorale e sottotipo istologico

2.1 Diagnosis of an aggressive pituitary tumour

R 2.1.1 *We suggest the diagnosis of an aggressive pituitary tumour be considered in patients with a radiologically invasive tumour AND unusually rapid growth rate, or clinically relevant tumour growth despite optimal standard therapies (surgery, radiotherapy and conventional medical treatments).*

R 2.1.4 *In patients with aggressive pituitary tumours, and either site-specific symptoms or discordant biochemical and radiological findings, we recommend screening for metastatic disease.*

2.2 Potential predictors of aggressiveness in pituitary tumours

R 2.2.1 *We recommend all pituitary tumours should undergo histopathological analysis, which should include at a minimum immunodetection of pituitary hormones and Ki-67 index evaluation.* (+000)

R 2.2.2 *We suggest interpretation of histopathological results in the clinical context of the individual patient.* (+000)

R 2.2.3 *In patients with aggressive pituitary tumours, germline genetic testing should be considered based on young age at presentation or family history of pituitary or endocrine neoplasia, as recommended for patients with non-aggressive pituitary tumours.* (+000)

R 2.1.4 *In patients with aggressive pituitary tumours, and either site-specific symptoms or discordant biochemical and radiological findings, we recommend screening for metastatic disease.*

Given that aggressive pituitary tumours often progress and occasionally metastasize insidiously over several years, attention should be paid, and appropriate structural (MRI & CT) and/or functional (FDG- and/or SSTR-PET) imaging studies be considered, in the setting of site specific symptoms (neck/back pain or neurological complaints), and/or where laboratory measures are discordant with known visible extent of disease. Common sites for metastatic disease include craniospinal deposits, neck lymphatic chains and less commonly liver, bone and lung.

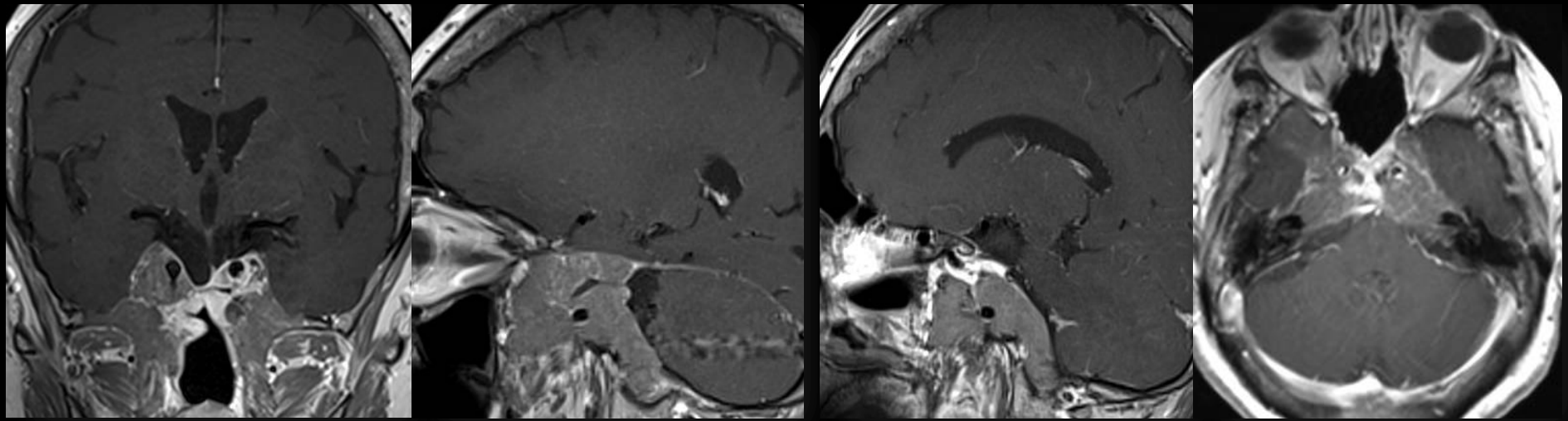
Natascia vs Mario

Chi dei 2 vi sembra più a rischio?

Avete cambiato idea e perché?

E sulla base di quale criterio?

Natascia: follow-up



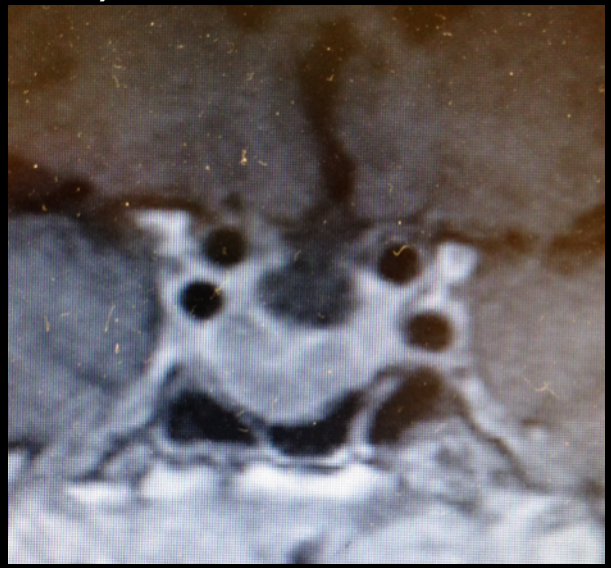
Dopo 4 anni

Voluminosa ripresa tumorale, interessante estesamente il basicranio, con erosione del clivus fino alla giunzione cranio-vertebrale

Mario: follow-up

2001 (dopo 4 anni dalla diagnosi)

- On Cab 2 mg/settimana: PRL 154 ng/mL
- RM: parziale ricrescita intra-sellare

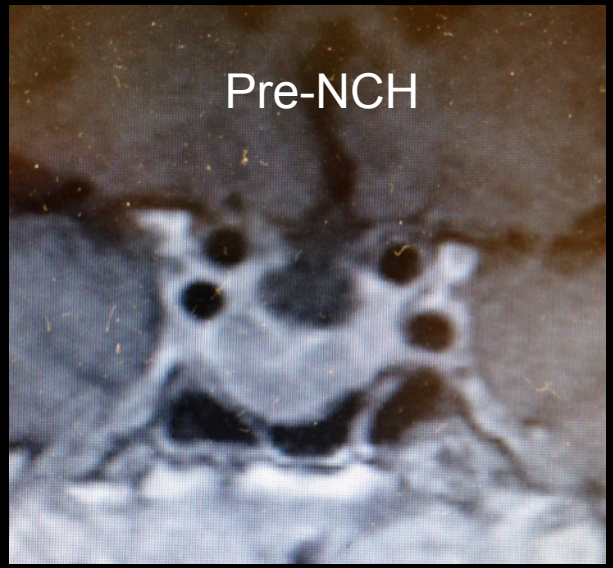


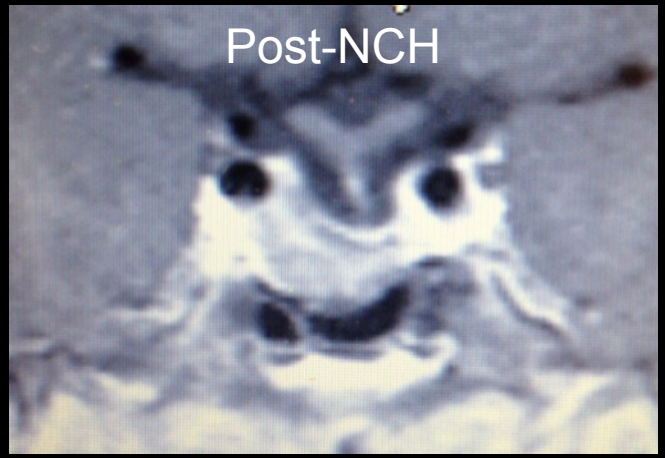
Aumenta Cabergolina
fino a 3.5 mg/settimana

PRL aumenta progressivamente fino a 500 ng/mL
senza ulteriore crescita tumorale

Mario: follow-up

- 2003: NCH TNS
- Istologia: adenoma, immunoistochimica positiva per PRL, Ki-67 2%
- Post-op: PRL 33 ng/mL, persistenza di residuo intra-sellare





Riprende Cab (fino 3.5 mg/settimana) senza variazioni tumorali

Quesiti per il NCH

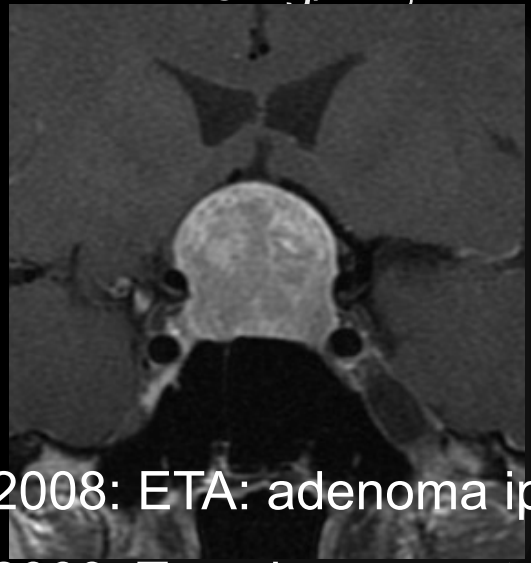
- Operare tutti, operare sempre, operare subito?
- Quanto è necessario essere aggressivi con i “cattivi”?
- Quante volte si può/deve reintervenire?
- Quanto conta il “manico”?

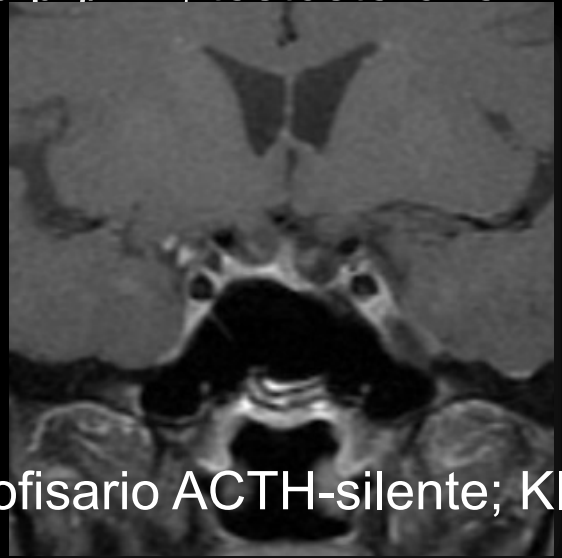
Operare tutti, sempre, subito?

C.S. maschio 48 aa

Calo della libido, iposurrenalismo, disturbi visivi

PRL 12.5 ng/mL; FT4 6 pg/mL; testosterone 1.07 ng/mL





2008: ETA: adenoma ipofisario ACTH-silente; KI

2009: Terapia con cortone acetato e testosterone

2010: Clinicamente stabile. Recidiva alla RM di c

J Neurosurg 114:336–344, 2011

Atypical pituitary adenomas: incidence, clinical characteristics, and implications

Clinical article

GABRIEL ZADA, M.D.,[1] WHITNEY W. WOODMANSEE, M.D.,[2] SHAKTI RAMKISSOON, M.D., PH.D.,[3] JORDAN AMADIO, M.D.,[1] VANIA NOSE, M.D., PH.D.,[3] AND EDWARD R. LAWS JR., M.D.[1]

Department of [1]Neurosurgery and [3]Pathology, and [2]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Object. The 2004 WHO classification of pituitary adenomas now includes an "atypical" variant, defined as follows: MIB-1 proliferative index greater than 3%, excessive p53 immunoreactivity, and increased mitotic activity. The authors review the incidence of this atypical histopathological subtype and its correlation with tumor subtype, invasion, and surgical features.

Methods. The records of 121 consecutive patients who underwent transsphenoidal surgery for pituitary adenomas during an 18-month period were retrospectively reviewed for evidence of atypical adenomas.

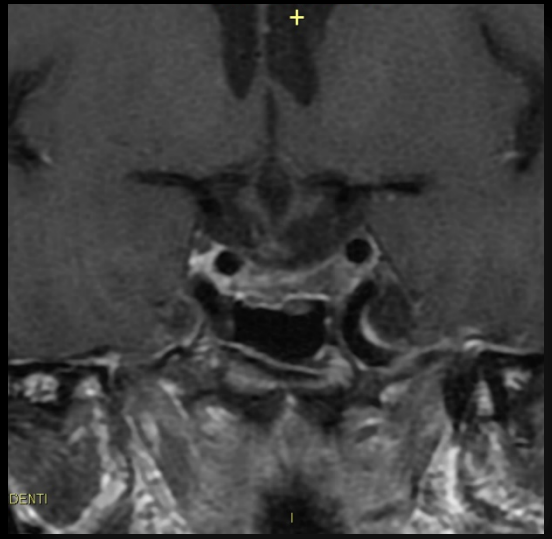
Results. Eighteen adenomas (15%) met the criteria for atypical lesions; 17 (94%) of the 18 were macroadenomas. On imaging, 15 (83%) demonstrated imaging evidence of surrounding invasion, compared with 45% of typical adenomas ($p = 0.002$). Atypical tumors occurred in 12 female (67%) and 6 male (33%) patients. Patient age ranged from 6 to 70 years (mean 48 years). Nine patients (50%) had hormonally active tumors, and 9 had nonfunctional lesions. Four (22%) of the 18 patients presented to us with recurrent tumors. Immunohistochemical analysis demonstrated the following tumor subtypes: GH-secreting adenoma with plurihormonal staining (5 patients [28%]); null-cell adenoma (5 patients [28%]); silent ACTH tumor (3 patients [17%]), ACTH-staining tumor with Cushing's disease (2 patients [11%]), prolactinoma (2 patients [11%]), and silent FSH-staining tumor (1 patient [6%]). The MIB-1 labeling index ranged from 3% to 20% (mean 7%).

Conclusions. Atypical tumors were identified in 15% of resected pituitary adenomas, and they tended to be aggressive, invasive macroadenomas. More longitudinal follow-up is required to determine whether surgical outcomes, potential for recurrence, or metastasis of atypical adenomas vary significantly from their typical counterparts.

(DOI: 10.3171/2010.8.JNS10290)

KEY WORDS • pituitary adenoma • transsphenoidal • atypical • tumor biology • Ki 67 • MIB-1 • p53 • carcinoma

2011: Reintervento endoscopico endonasale con asportazione radicale della neoplasia



Controllo precoce post-op

LITERATURE REVIEW

CrossMark

Endoscopic Endonasal Versus Microscopic Transsphenoidal Surgery for Recurrent and/or Residual Pituitary Adenomas

Yoshua Esquenazi[1], Walid I. Essayed[2], Harminder Singh[2,5], Elizabeth Mauer[6], Mudassir Ahmed[2], Paul J. Christos[5], Theodore H. Schwartz[2-4]

Key words
- Endonasal endoscopic
- Microscopic
- Pituitary adenoma
- Pituitary surgery
- Recurrent
- Skull base
- Transsphenoidal

Abbreviations and Acronyms
CS: Cavernous sinus
CSF: Cerebrospinal fluid
DI: Diabetes insipidus
GTR: Gross total resection

From the [1]Vivian L. Smith Department of Neurosurgery, The University of Texas Health Science Center at Houston, Houston, Texas; Departments of [2]Neurosurgery, [3]Otolaryngology and [4]Neuroscience, Weill Cornell Medical College, Cornell University, New York-Presbyterian Hospital, New York, New York; [5]Department of Neurological Surgery, Stanford University School of Medicine, Stanford, California; and [6]Healthcare Policy and Research, Division of Biostatistics and Epidemiology, Weill Cornell Medical College, New York, New York, USA

To whom correspondence should be addressed: Yoshua Esquenazi, M.D. [E-mail: Yoshua.EsquenaziLevy@uth.tmc.edu]

Yoshua Esquenazi and Walid I. Essayed contributed equally to the manuscript.

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Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

OBJECTIVE: Surgery for recurrent/residual pituitary adenomas is increasingly being performed through endoscopic surgery. Whether this new technology has altered the indications and outcomes of surgery is unknown. We conducted a systematic review and meta-analysis of published studies to compare the indications and outcomes between microscopic and endoscopic approaches.

METHODS: A PubMed search was conducted (1985–2015) to identify surgical series of endoscopic endonasal and microscopic transsphenoidal resection of residual or recurrent pituitary adenomas. Data were extracted regarding tumor characteristics, surgical treatment, extent of resection, endocrine remission, visual outcome, and complications.

RESULTS: Twenty-one studies met inclusion criteria. A total of 292 patients were in the endoscopic group, and 648 patients were in the microscopic group. Endoscopic cases were more likely nonfunctional ($P < 0.001$) macroadenomas ($P < 0.001$) with higher rates of cavernous sinus invasion ($P = 0.012$). The pooled rate of gross total tumor resection was 53.5% for the endoscopic group and 46.6% for the microscopic group. Endocrine remission was achieved in 53.0% and 46.7% of patients, and visual improvement occurred in 73.2% and 49.6% for the endoscopic and microscopic groups. Cerebrospinal fluid leak and pituitary insufficiency were higher in the endoscopic group.

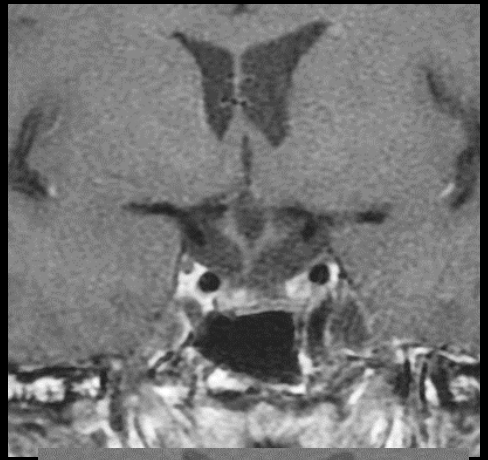
CONCLUSION: This meta-analysis indicates that the use of the endoscope to reoperate on residual or recurrent adenomas has only led to modest increases in resection rates. However, larger more complex cases are being tackled, so direct comparisons are misleading. The most dramatic change has been in visual improvement along with modest increases in risk. Reoperation for recurrent or residual adenomas is a safe and effective treatment option.

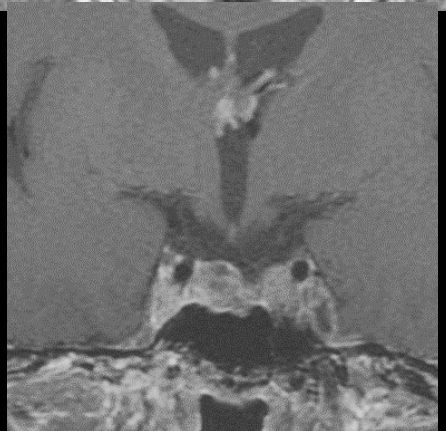
2012: RMN: recidiva seno cavernoso sinistro

Radioterapia conformazionale

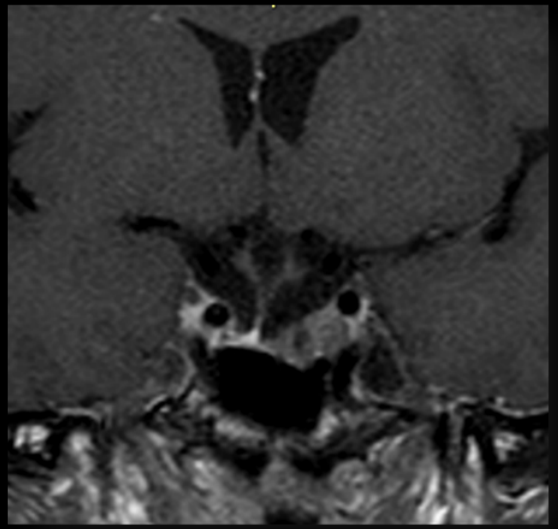
2013: Ipopituitarismo anteriore
RMN: Riduzione del residuo

2014 (dopo sei mesi): trasformazione in morbo di Cushing
RMN: recidiva bilaterale nei due seni cavernosi

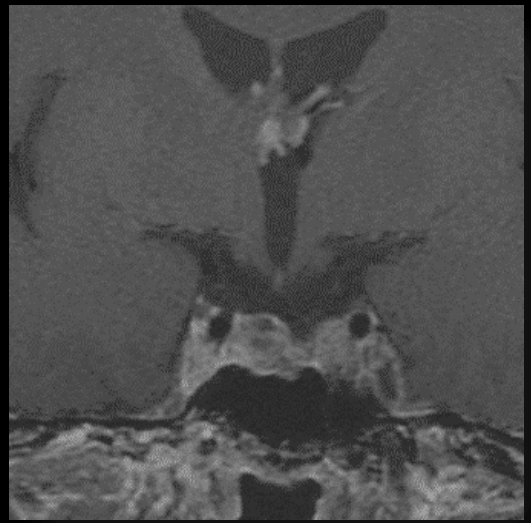




Quante volte si può/deve reintervenire?



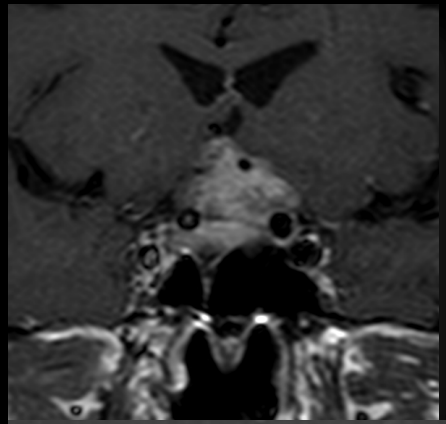
2010
SI

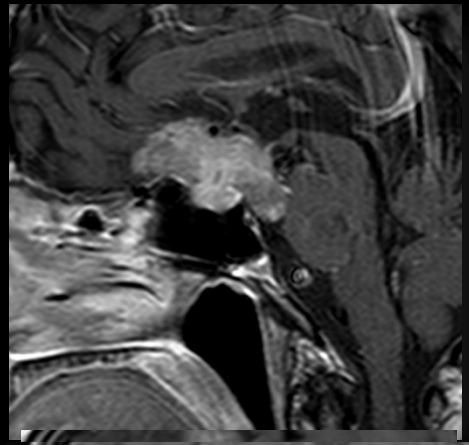


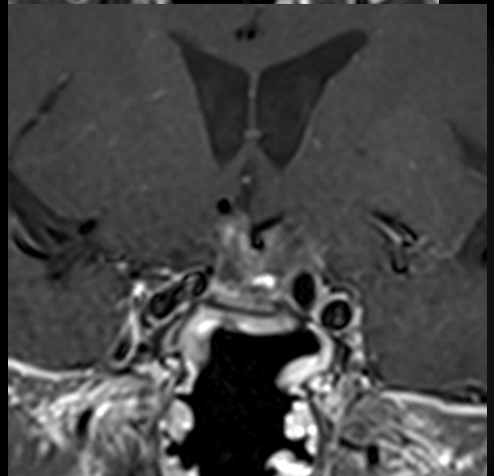
2014
NO

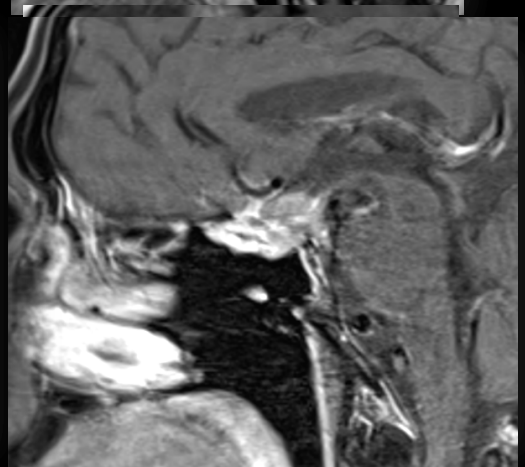
Tutte le volte che si potrà programmare un trattamento successivo

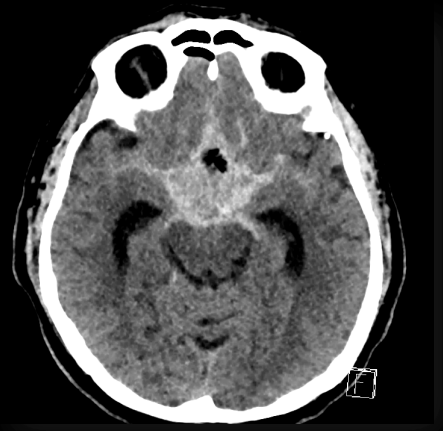
Quanto è necessario essere aggressivi con i cattivi?

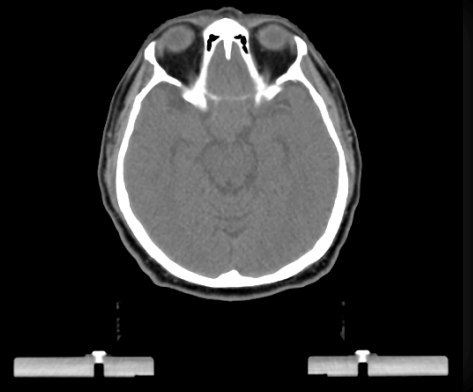












Quanto conta il "manico"?

JNS

CLINICAL ARTICLE

J Neurosurg 124:596–604, 2016

Comparison of outcomes between a less experienced surgeon using a fully endoscopic technique and a very experienced surgeon using a microscopic transsphenoidal technique for pituitary adenoma

Hasan A. Zaidi, MD,[1] Al-Wala Awad, BS,[1] Michael A. Bohl, MD,[1] Kristina Chapple, PhD,[1] Laura Knecht, MD,[2] Heidi Jahnke, BS, MSN,[1] William L. White, MD,[1] Andrew S. Little, MD[1]

[1]Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center; and [2]Department of Internal Medicine, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

CONCLUSIONS A less experienced surgeon using a fully endoscopic technique was able to achieve outcomes similar to those of a very experienced surgeon using a microscopic technique in a cohort of patients with nonfunctioning tumors smaller than 60 cm³. The study raises the provocative notion that certain advantages afforded by the fully endoscopic technique may impact the learning curve in pituitary surgery for nonfunctioning adenomas.

Clinical trial registration no.: NCT01504399 (clinicaltrials.gov)

http://thejns.org/doi/abs/10.3171/2015.4.JNS15102

ORIGINAL ARTICLE

CrossMark

Two-Dimensional High Definition Versus Three-Dimensional Endoscopy in Endonasal Skull Base Surgery: A Comparative Preclinical Study

Vittorio Rampinelli[1], Francesco Doglietto[2], Davide Mattavelli[1], Jimmy Qiu[3], Elena Raffetti[4], Alberto Schreiber[1], Andrea Bolzoni Villaret[1], Walter Kucharczyk[3], Francesco Donato[4], Marco Maria Fontanella[1], Piero Nicolai[2]

CONCLUSIONS: In a preclinical setting for endonasal skull base surgery, 3D technology appears to confer an advantage in terms of time of execution and precision of surgical maneuvers.

Quanto conta il “manico”?

Molto, perché il chirurgo esperto è consapevole che non sarà in grado di essere risolutivo

Il chirurgo inesperto seguirà la recidiva anche in zone ritenute più “safe”,

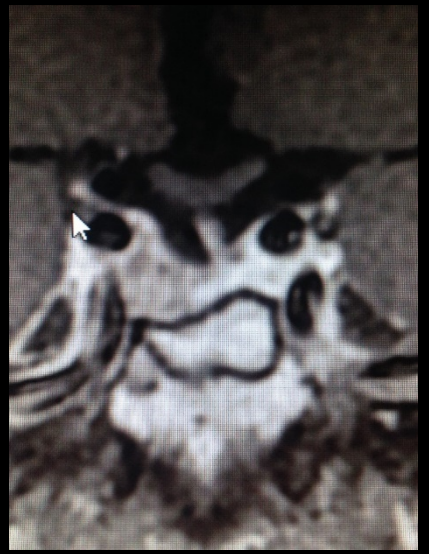
fino alla complicanza grave

Mario: follow-up

- 2005: PRL 200 ng/mL
- 2° intervento NCH TNS
- Istologia sovrapponibile al precedente
- PRL post NCH: 310 ng/mL

Mario: follow-up

- 2006: radioterapia frazionata (dose totale 39.6 Gy)
- PRL: 3 mesi = 87 ng/mL; 12 mesi: 57 ng/mL
- RM: lieve riduzione tumorale



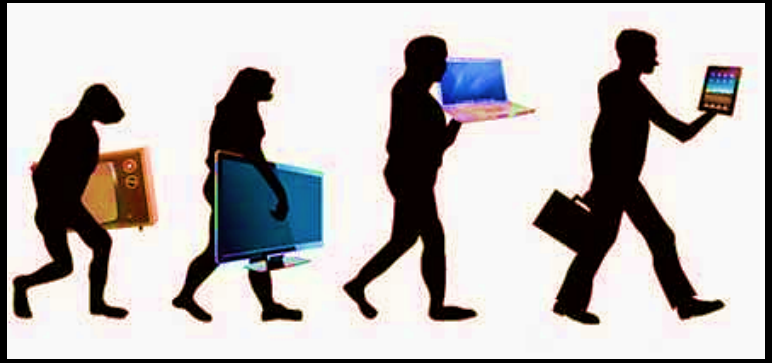
Nei successivi 4 aa (con Cab 1.5 mg/settimana)

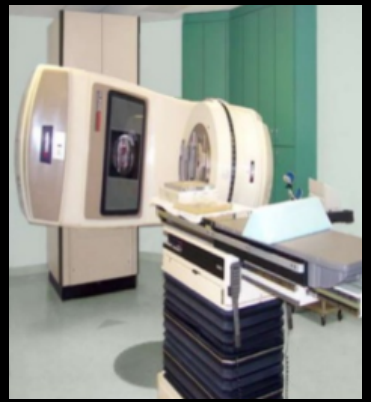
PRL e quadro RM stabili

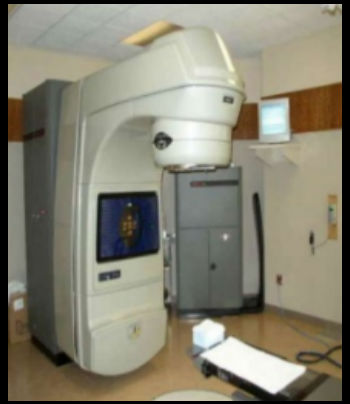
Quesiti per il radioterapista

- Quale terapia radiante e quando?
- Quanto bisogna essere aggressivi con la dose?
- Vale la pena re-irradiare?

Radioterapia oncologica:
cosa è cambiato negli ultimi 50 anni?

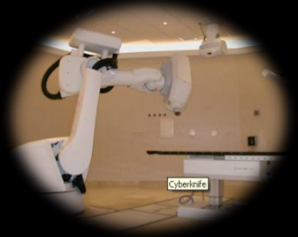


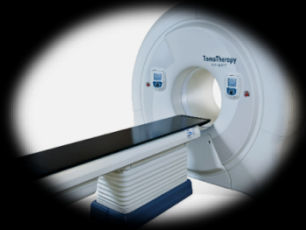


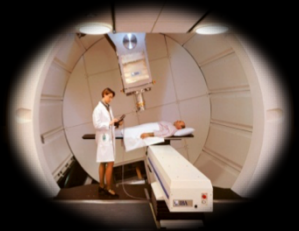


Nuove tecniche

- Radioterapia stereotassica conformazionale (SRT)
- Radiochirurgia stereotassica (SRS)
- Radioterapia a modulazione di intensità (IMRT)
- Tomoterapia
- Radioterapia con particelle





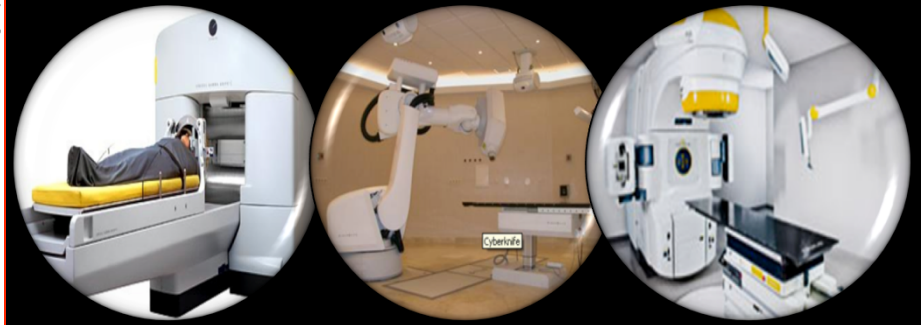


SRS/FSRT per gli adenomi ipofisari

Roma, 8-11 novembre 2018

ITALIAN CHAPTER

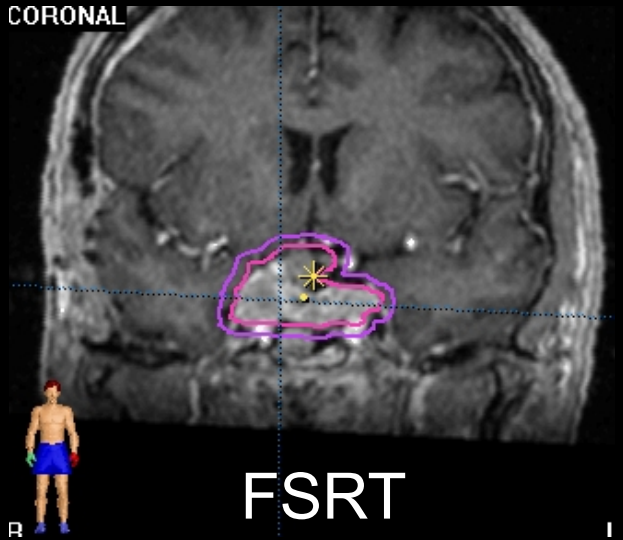
Authors	Patients	Type of SRS	dose (Gy)	Follow-up (months)	Tumor control (%)	Late toxicity (%) visual	hypopituitarism
Feigl et al, 2002 [33]	61	GK	15[a]	55.2	94	NA	40
Sheehan et al, 2002 [58]	42	GK	16[a]	31.2	97.6	2.4	0
Wowra & Stummer, 2002 [59]	30	GK	16[a]	55	93.3 (93 at 5 years)	0	10
Petrovich et al, 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]	100	GK	18.5[a]	44.9	92.2	0	19.7
Voges et al, 2006 [66]	37	LINAC	13.4	56.6	100	1.4	12.3
Liscak et al, 2007 [67]	140	GK	20[a]	60	100	0	2
Pollock et al, 2008 [68]	62	GK	16[a]	64	96.8 (95 at 5 years)	0	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
Wilson et al, 2012 [75]	51	LINAC	14	50	100	0	0
Sheehan et al, 2013 [76]	512	GK	16[a]	36	93.4 (95 at 5 years)	7.9	21
Lee et al, 2014 [77]	41	GK	12[a]	48	92.7 (85 at 10 years)	2.4	24.4
Bir et al, 2015 [78]	57	GK	15[a]	45.5	93 (90 % at 10 years)	0	8.8



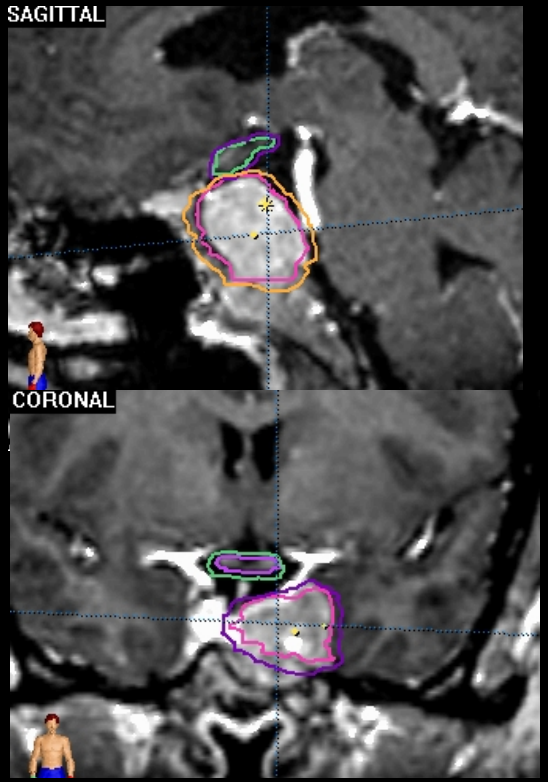
Authors	type of adenoma	Patients	mean dose (Gy)	follow-up (months)	tumor control (%)	late toxicity (%) visual	hypopituitarism
Milker-Zabel et al., 2001	NFA, SA	68	50.4	38	93 at 5 years	7,5	5
Milker-Zabel et al., 2004	GH	20	52.2	26	100 (92**)	0	3
Paek et al., 2005	NFA, SA	68	50	30	98 at 5 years	3	6
Colin 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

Minniti et al, Radiat Oncol 2016, 11: 135

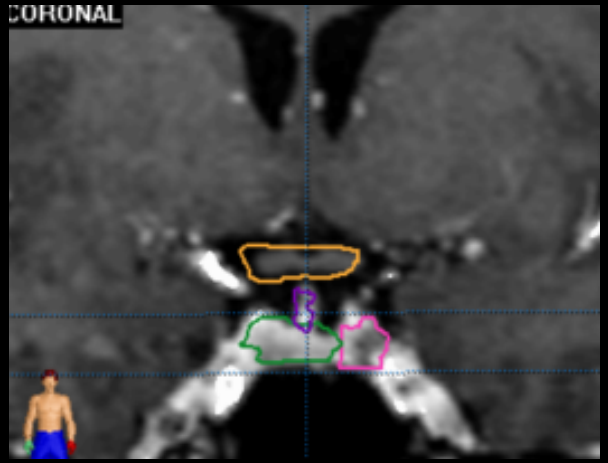
Scelta della tecnica di irradiazione



FSRT

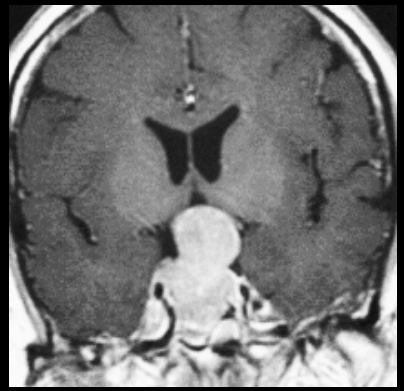


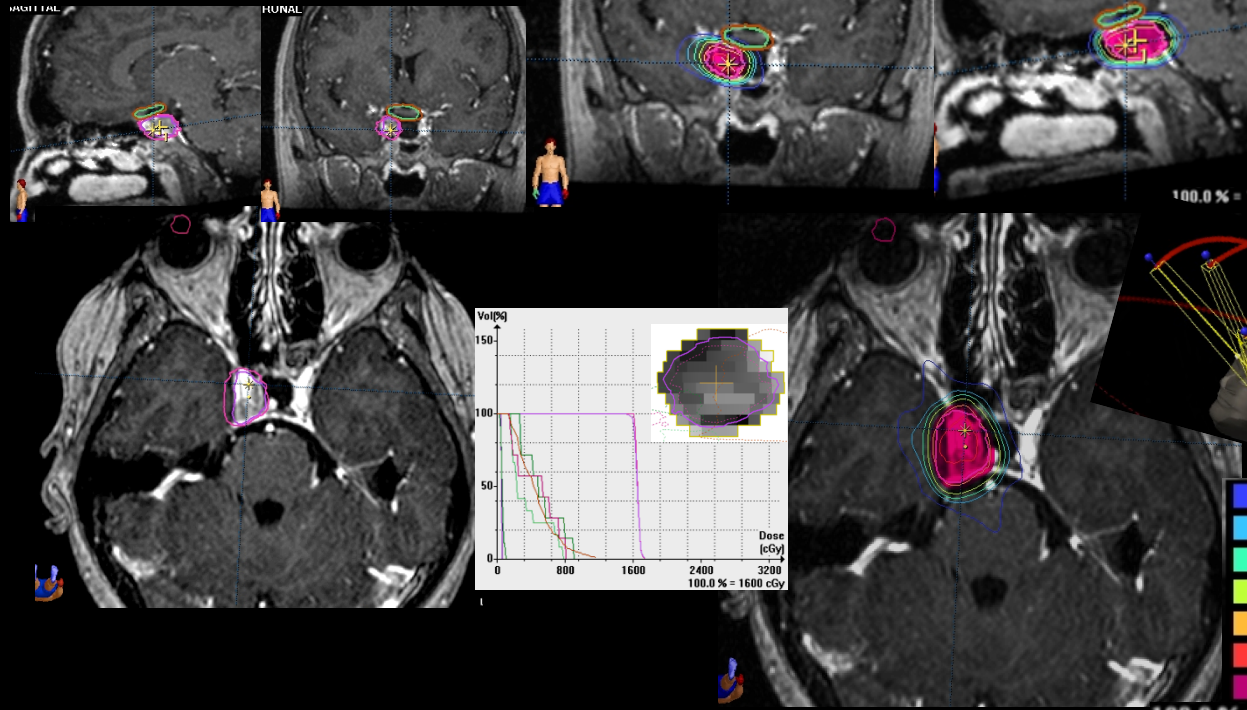
HSRT



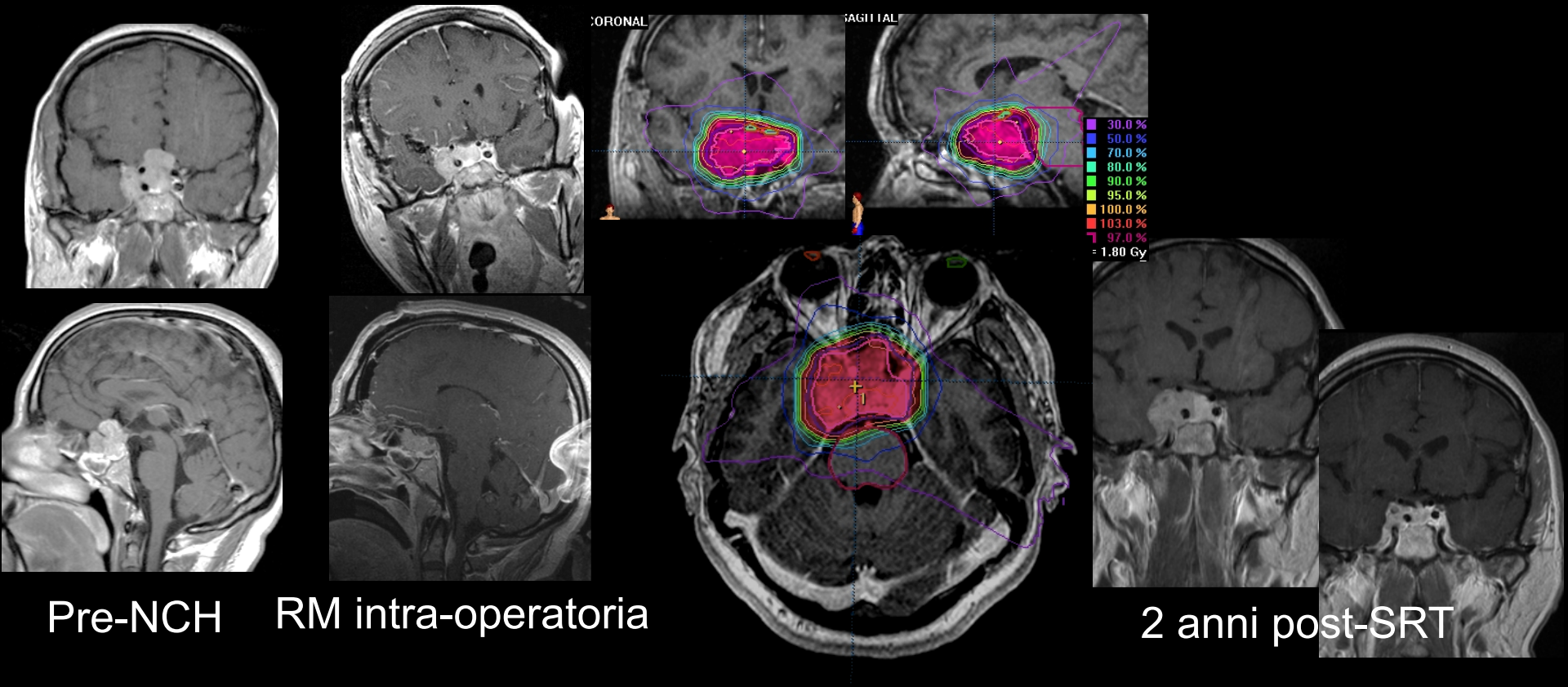
SRS

RS per residui di adenoma ipofisario





FSRT per macroadenoma NF



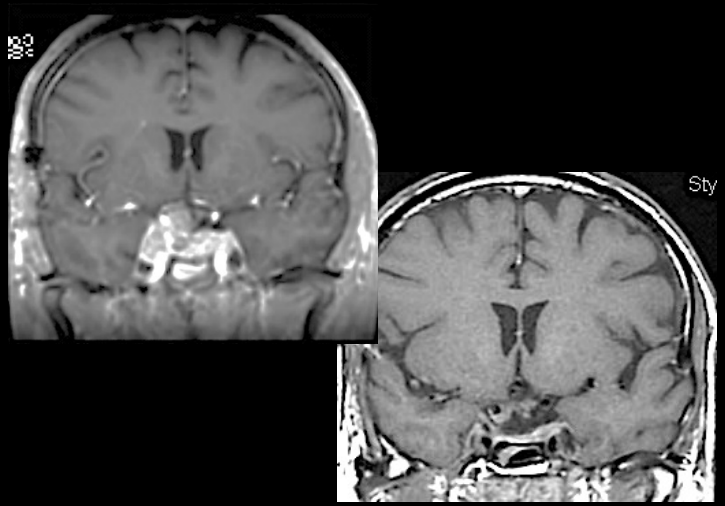
Pre-NCH

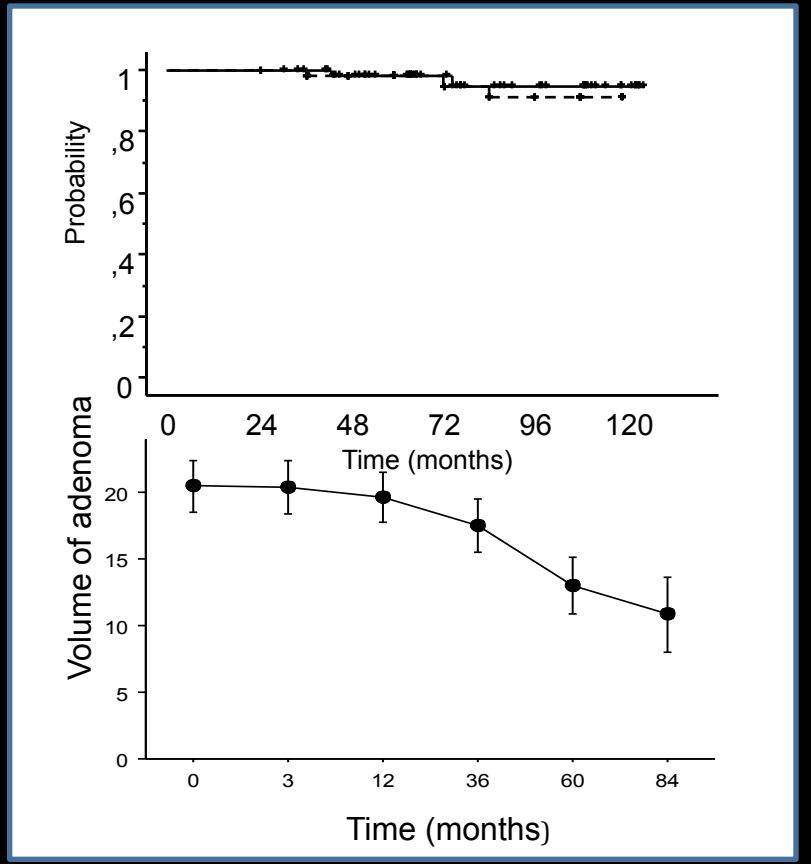
RM intra-operatoria

2 anni post-SRT

SRT per adenomi giganti

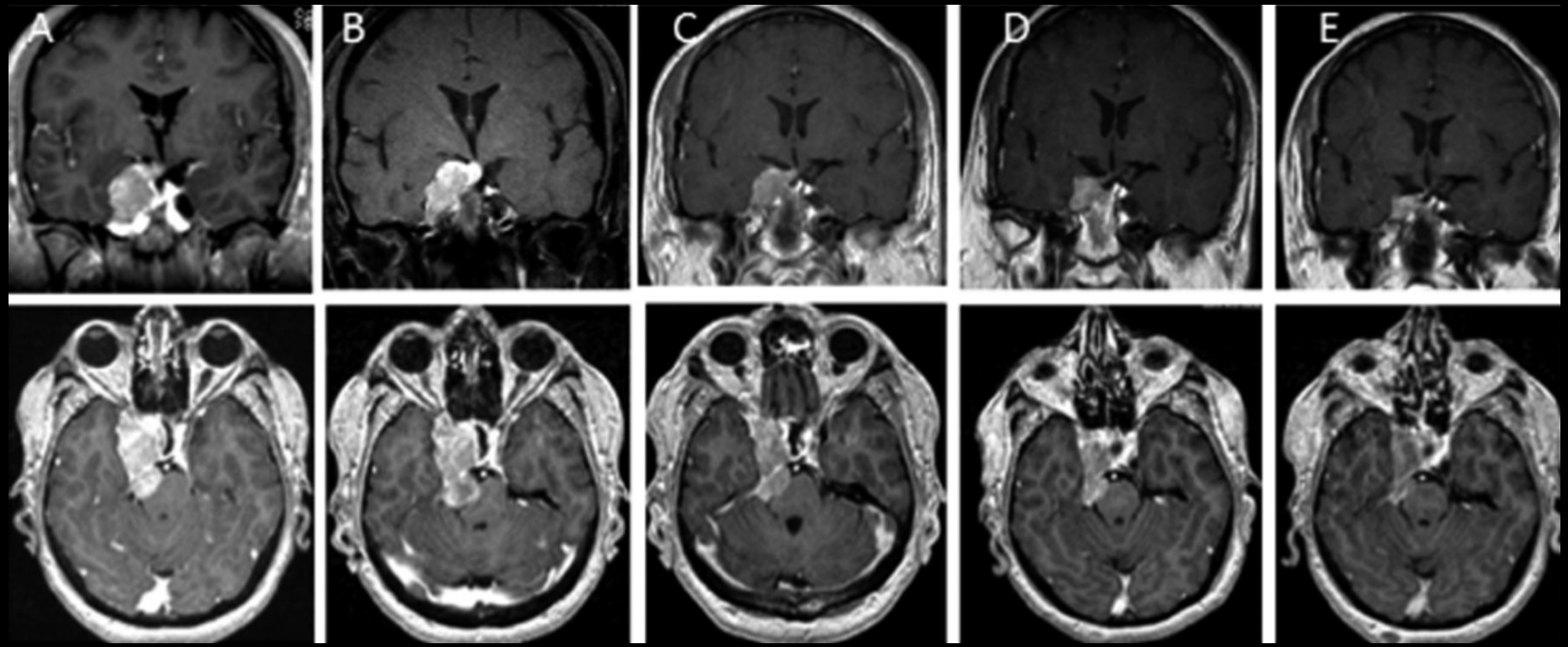
Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response





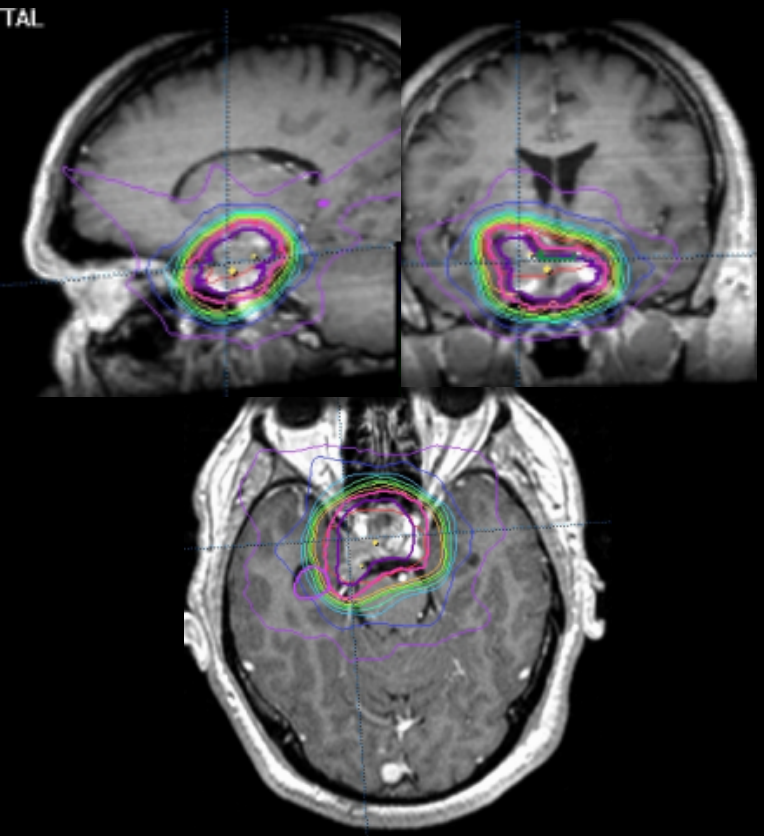
Minniti et al, EJE 2015

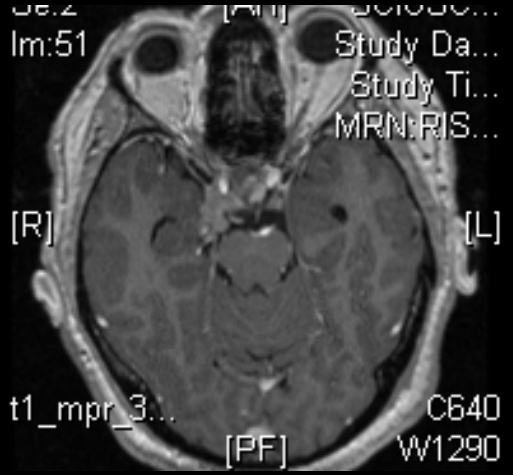
FSRT per macroadenomi



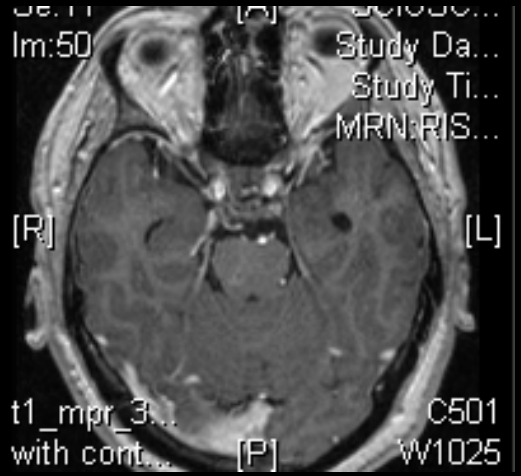
G Minniti et al, Eur J Endocrinol 2015, 172: 433-441

SRT per un PRL-oma



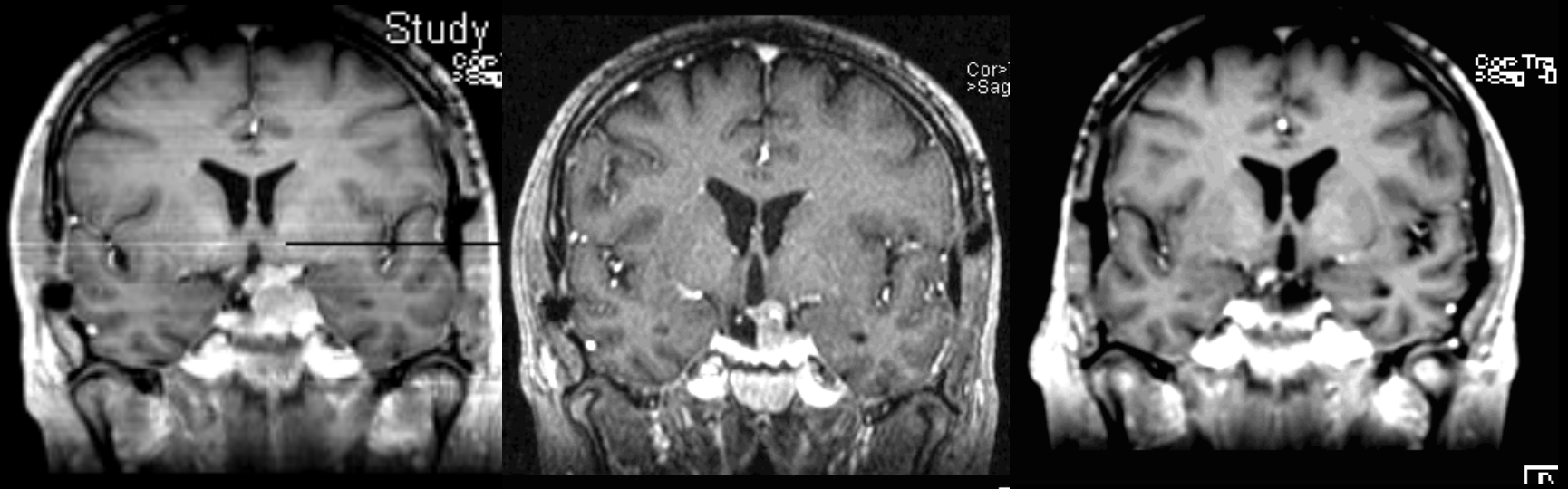


PRL 346 ng/mL



Post RT, 3 aa
PRL 6 ng/mL

Re-irradiazione



Riassumendo

- La radioterapia frazionata è molto efficace nella gestione degli adenomi ipofisari aggressivi e i dati a lungo termine evidenziano il controllo tumorale in oltre l'80% dei casi a 10 anni, con un'incidenza accettabile di complicanze

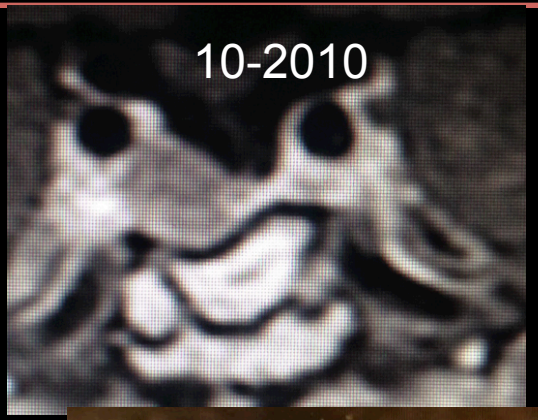
- SRT e SRS danno controllo tumorale a lungo termine sovrapponibile con minor morbilità

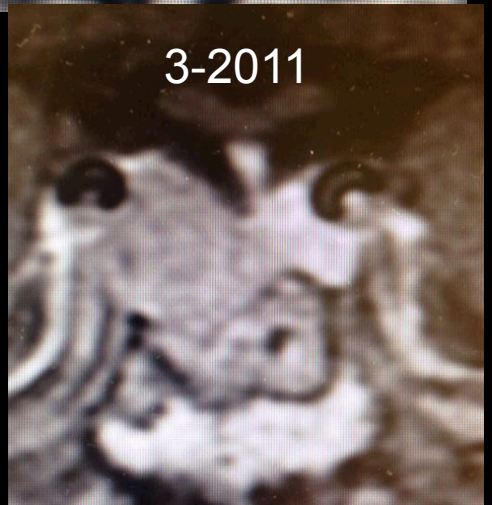
- Anche se SRS rappresenta un'opzione terapeutica attraente per i tumori ipofisari, non è utilizzabile in tutti I casi (dipende dalle dimensioni tumorali)

Mario: 2010-2011

Dopo 5 aa da RT (e 2 pregressi NCH)

- PRL 773 ng/mL
- RM: incremento della lesione
- 3° intervento NCH TNS
- Diagnosi istologica: immunoistochimica positiva per PRL, non mitosi, Ki-67 2%

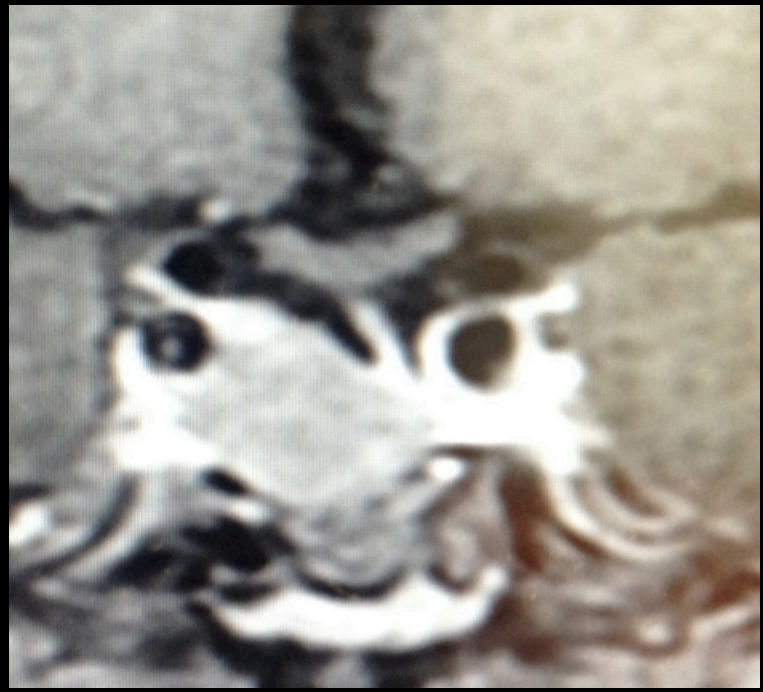




Mario

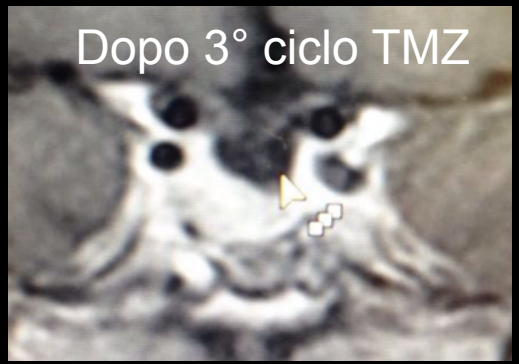
Dopo 3° NCH

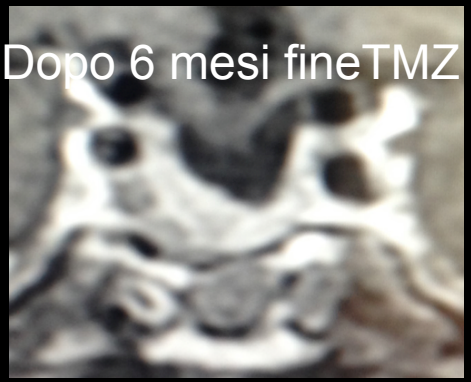
- PRL: 350 ng/mL, a 1 mese 564 ng/mL, a 6 mesi 620 ng/mL
- Campimetria: normale
- RM regione sellare: invariata
- RM total body: non metastasi



Mario: temozolomide

- Continua cabergolina e inizia temozolomide: 200 mg/m^2 per 5 giorni al mese per 6 cicli
- Trattamento ben tollerato (clinica e biochimica)
- Dopo il 3° ciclo: PRL 256 ng/mL, riduzione tumorale
- Dopo 6 mesi da fine TMZ: PRL 76 ng/mL, ulteriore shrinkage





Quesiti per l'endocrinologo

- Terapie "classiche": servono? Quanto insistere?
- Terapie alternative: esistono? Quali sono? Chi le maneggia? Funzionano?
- Come scegliere fra le terapie "non classiche" disponibili?

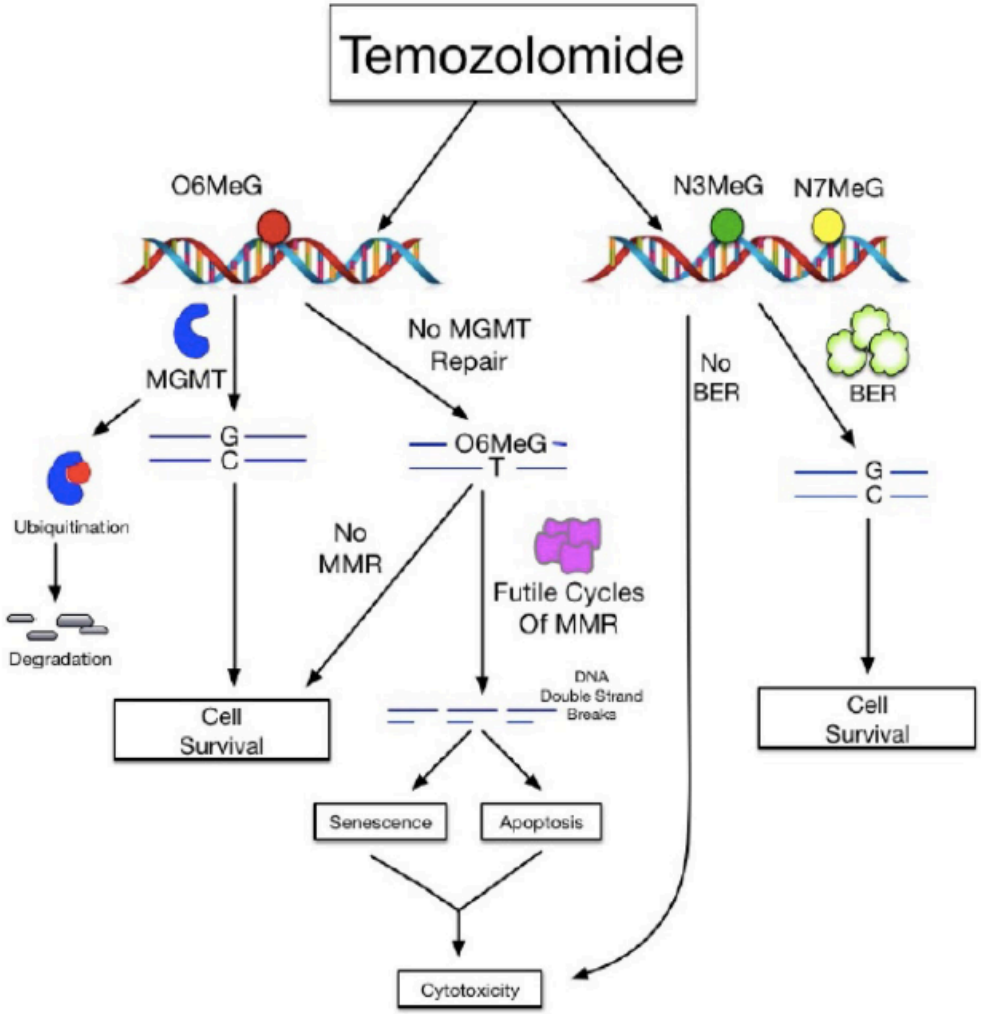
European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas

Gerald Raverot[1,2,3], Pia Burman[4], Ann McCormack[5,6], Anthony Heaney[7], Stephan Petersenn[8], Vera Popovic[9], Jacqueline Trouillas[2,10] and Olaf M Dekkers[11,12] on behalf of The European Society of Endocrinology

European Journal of Endocrinology (2018) **178**, G1–G24

R 3.3.1 We recommend standard medical treatment with maximally tolerated doses in order to control tumour growth, as per current guidelines

- PRLomas: Cabergoline
- GHomas: Somatostatin analogs/Pegvisomant
- ACTH: Pasireotide
- TSH: Somatostatin analogs


Temozolomide
O6MeG
N3MeG
N7MeG
MGMT
No MGMT Repair
No BER
BER
G
C
O6MeG
T
Ubiquitination
Degradation
No MMR
Futile Cycles Of MMR
DNA Double Strand Breaks
Cell Survival
Cell Survival
Senescence
Apoptosis
Cytotoxicity

Temozolomide: quando?

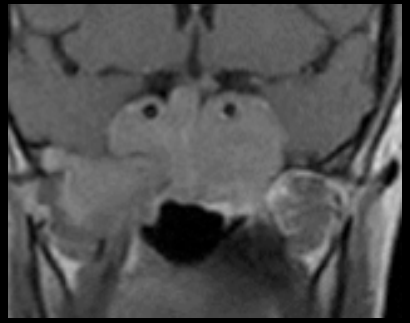
- Invasivi

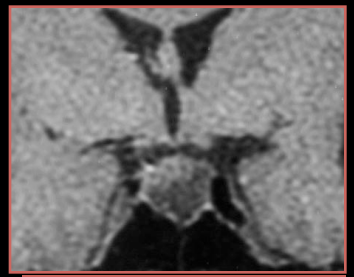
+

- Resistenti

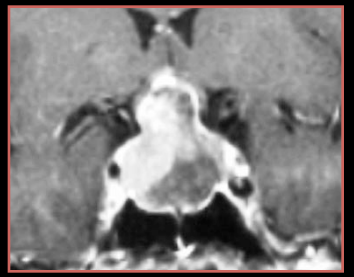
+

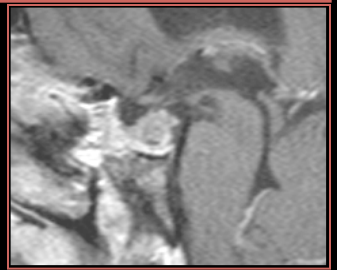
- Crescita veloce



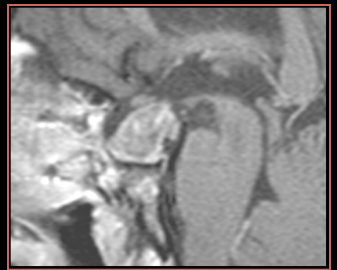


Cab 12 mesi





9 mesi



Temozolomide: quando?

Clinical Practice Guideline | G Raverot and others | Aggressive pituitary tumour guidelines | 178:1 | G1–G24

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

Gerald Raverot[1,2,3], Pia Burman[4], Ann McCormack[5,6], Anthony Heaney[7], Stephan Petersenn[8], Vera Popovic[9], Jacqueline Trouillas[2,10] and Olaf M Dekkers[11,12] on behalf of The European Society of Endocrinology

R 3.4.1 We recommend use of temozolomide monotherapy as first-line chemotherapy for aggressive pituitary tumours and pituitary carcinomas, following documented tumour growth (++00).

TMZ: quando valutare la risposta?

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R 3.4.2 We recommend first evaluation of treatment response after 3 cycles. If radiological progression is demonstrated, temozolomide treatment should be ceased (++00).

TMZ: risposta nei diversi tipi di adenoma

Tumour subtype	TMZ treatment response		
	YES (partial or complete response)	Stable disease	NO (disease progression)
PRL	44 % (12/27)	19 % (5/27)	37 % (10/27)
ACTH	56 % (19/34)	15 % (5/34)	29 % (10/34)
GH	38 % (3/8)	25 % (2/8)	38 % (3/8)
NF	22 % (6/27)	48 % (13/27)	30 % (8/27)
Other	50 % (2/4)	50 % (2/4)	N/A

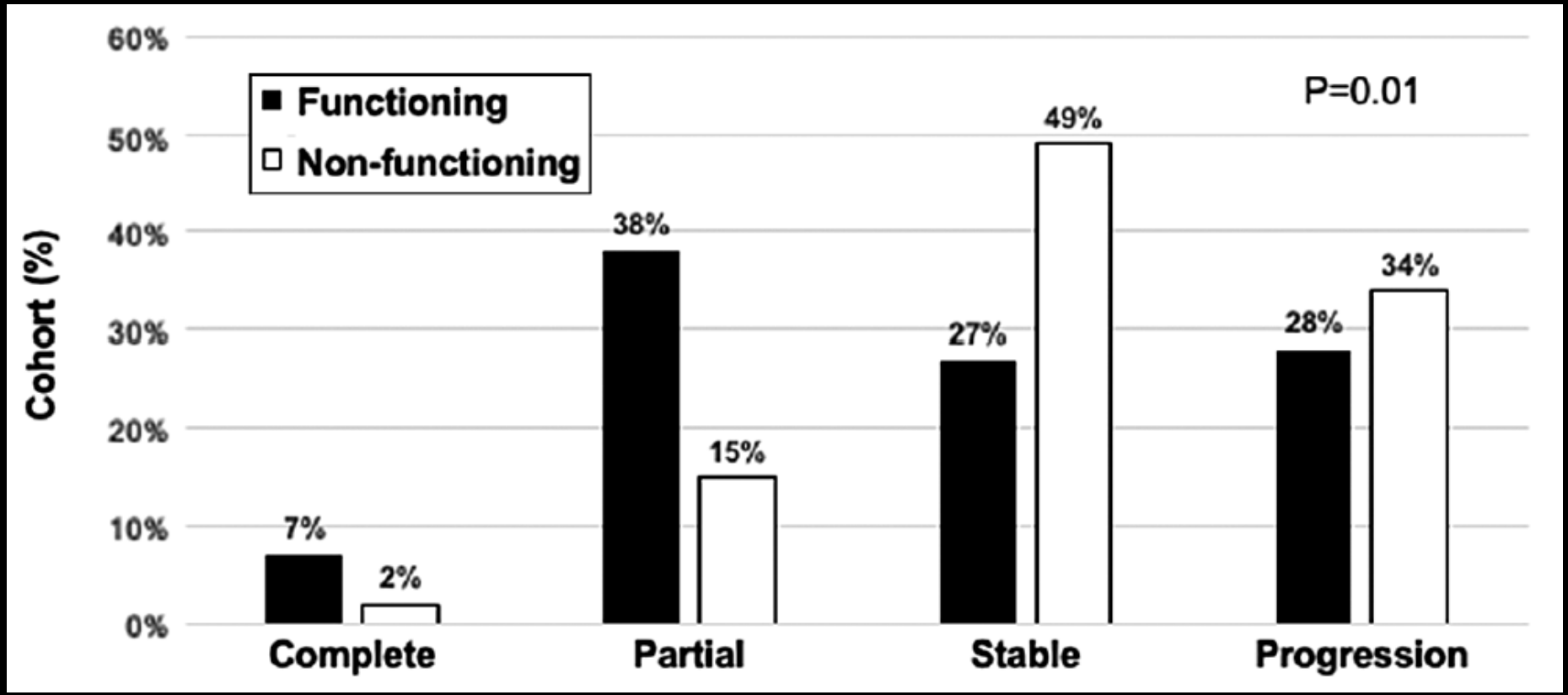
These results are taken from the case series in Table 1

PRL prolactin-secreting, *ACTH* adrenocorticotrophic-secreting; growth hormone-secreting, *NF* non-functioning, *N/A* not applicable

All values have been rounded to 0 dp. Therefore some total percentage values are below/exceed 100 %

Halevy et al, Pituitary 2016

TMZ: risposta nei diversi tipi di adenoma



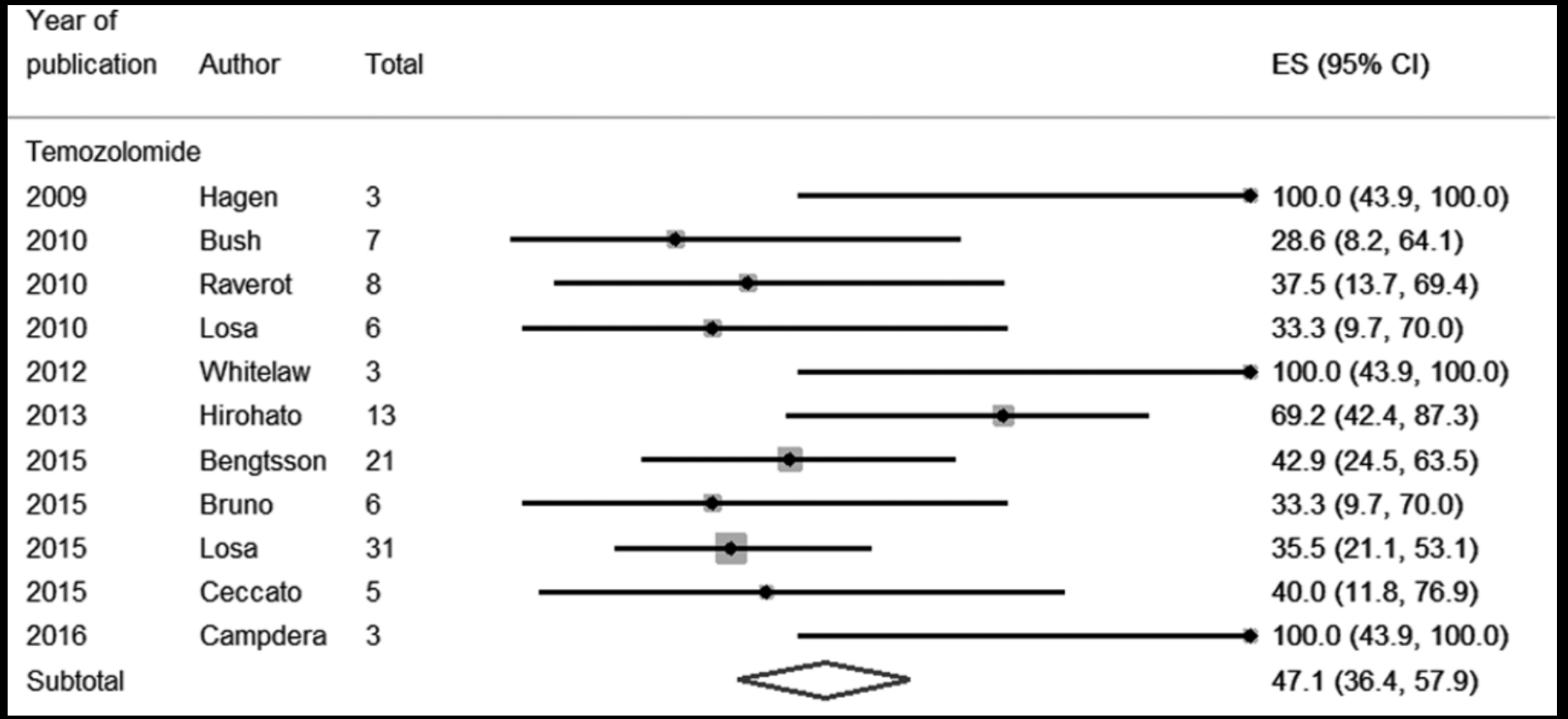
McCormack et al, Eur J Endocrinol 2018, 178: 265

TMZ: risposta nei diversi tipi di adenoma

	Complete regression	Partial regression	Stable disease	Progression	P-Value
Total	9 (6%)	49 (31%)	52 (33%)	47 (30%)	
Patient gender					0.20
Female (n = 55)	6 (11%)	16 (29%)	19 (35%)	14 (25%)	
Male (n = 101)	3 (3%)	32 (32%)	33 (33%)	33 (33%)	
Diagnosis					0.051
Aggressive pituitary tumour (n = 116)	5 (4%)	36 (31%)	45 (39%)	30 (26%)	
Pituitary carcinoma (n = 40)	4 (10%)	13 (33%)	7 (18%)	16 (40%)	
What was the clinical subtype?					0.011
Clinically functioning (n = 94)	6 (6%)	37 (39%)	27 (29%)	24 (26%)	
Initially silent becoming functioning (n = 16)	2 (13%)	5 (31%)	2 (13%)	7 (44%)	
Clinically non-functioning (n = 47)	1 (2%)	7 (15%)	23 (49%)	16 (34%)	

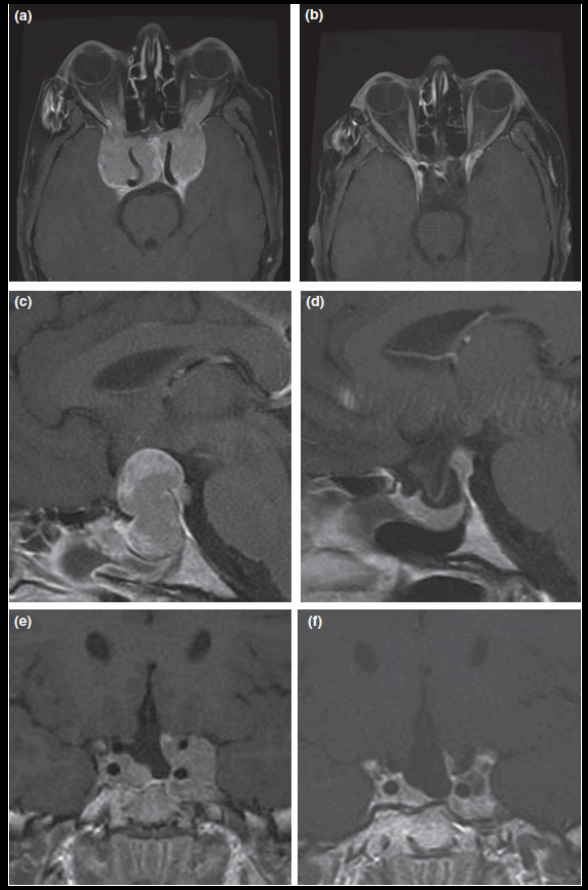
McCormack et al, Eur J Endocrinol 2018, 178: 265

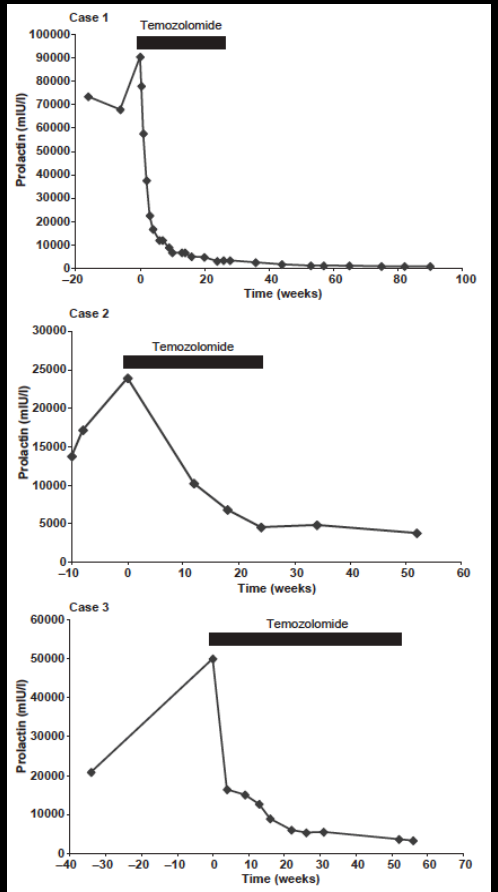
TMZ: efficacia



Raverot et al, Eur J Endocrinol 2018, 178 (1):G1-G24

TMZ: efficacia





Whitelaw et al, Clin Endocrinol 2012, 76: 877

TMZ: quanto continuare?

Clinical Practice Guideline | G Raverot and others | Aggressive pituitary tumour guidelines | 178:1 | G1–G24

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R 3.4.7 In patients responding to first-line temozolomide, as assessed after 3 cycles, we suggest treatment to be continued for at least 6 months in total, with consideration for longer duration if continued therapeutic benefit is observed (+000).

TMZ: caratteristiche predittive efficacia

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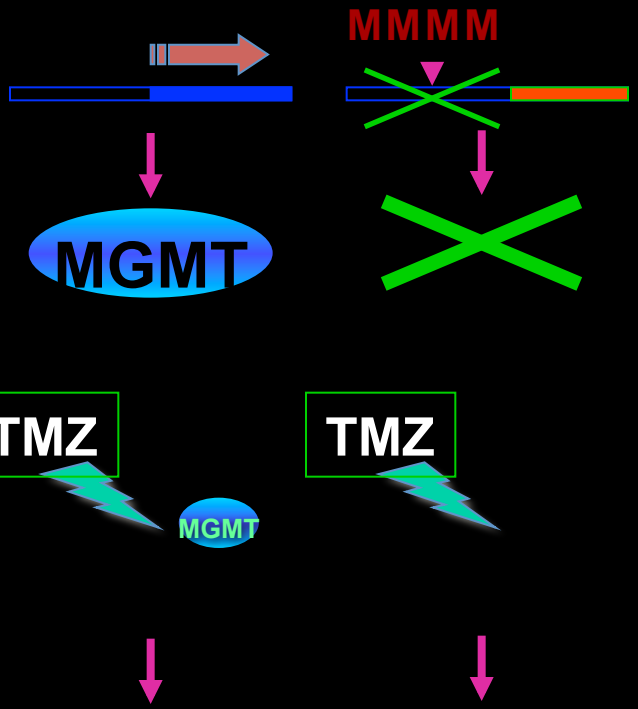
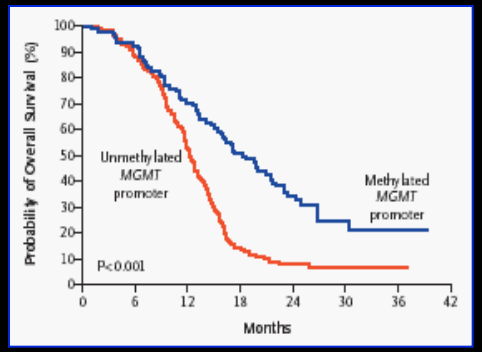
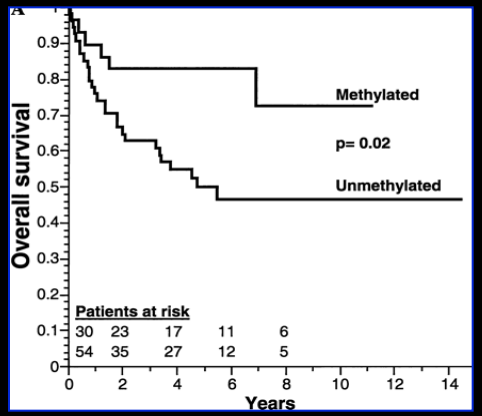
R 3.4.6 We suggest that evaluation of MGMT status by immunohistochemistry by an expert neuropathologist should be performed. High MGMT expression is suggestive of a lack of response; however, there may be exceptions (++00).

TMZ: interazione con MGMT



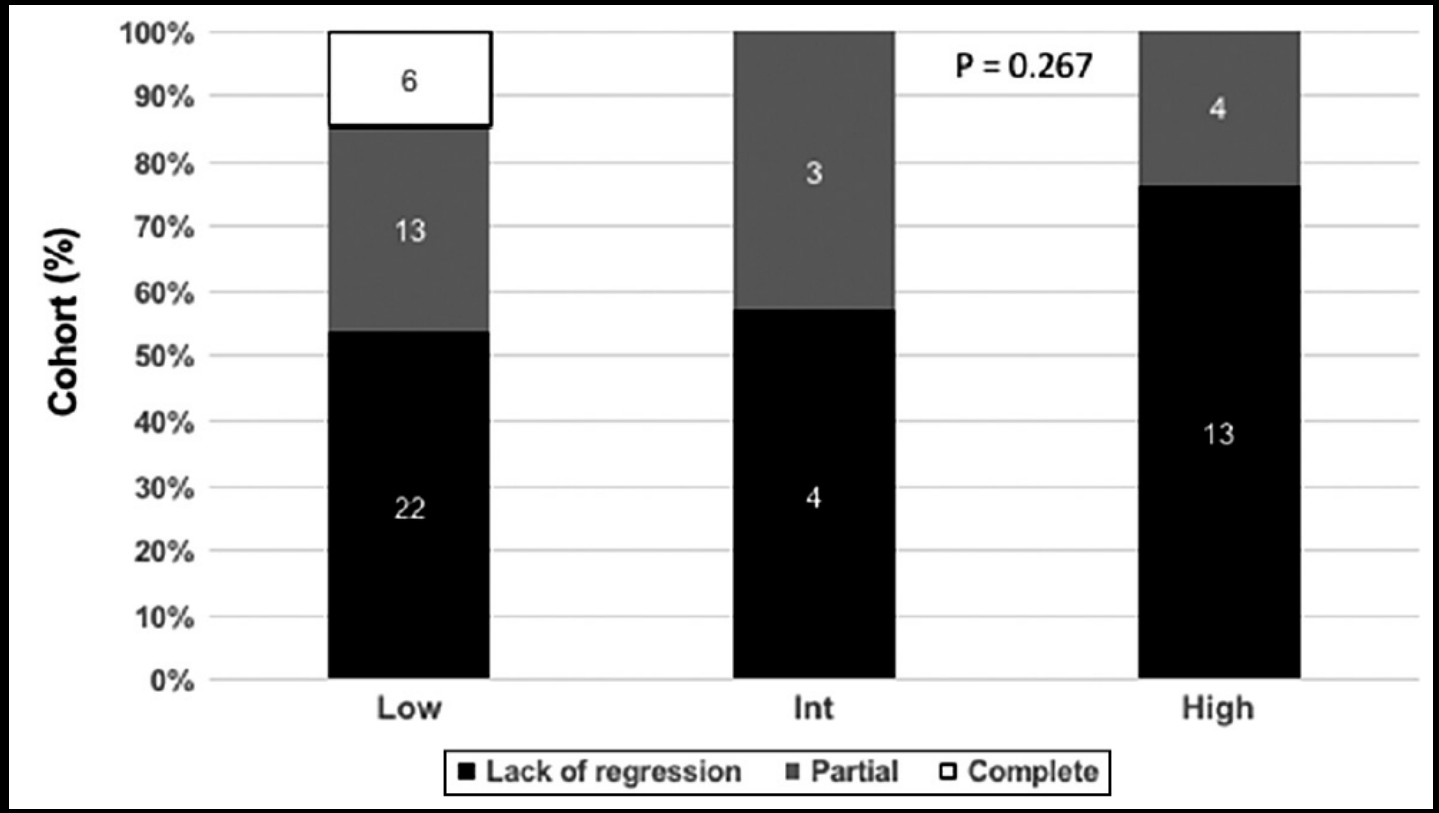


TMZ nei glioblastomi



TMZ nei linfomi SNC

TMZ: interazione con MGMT

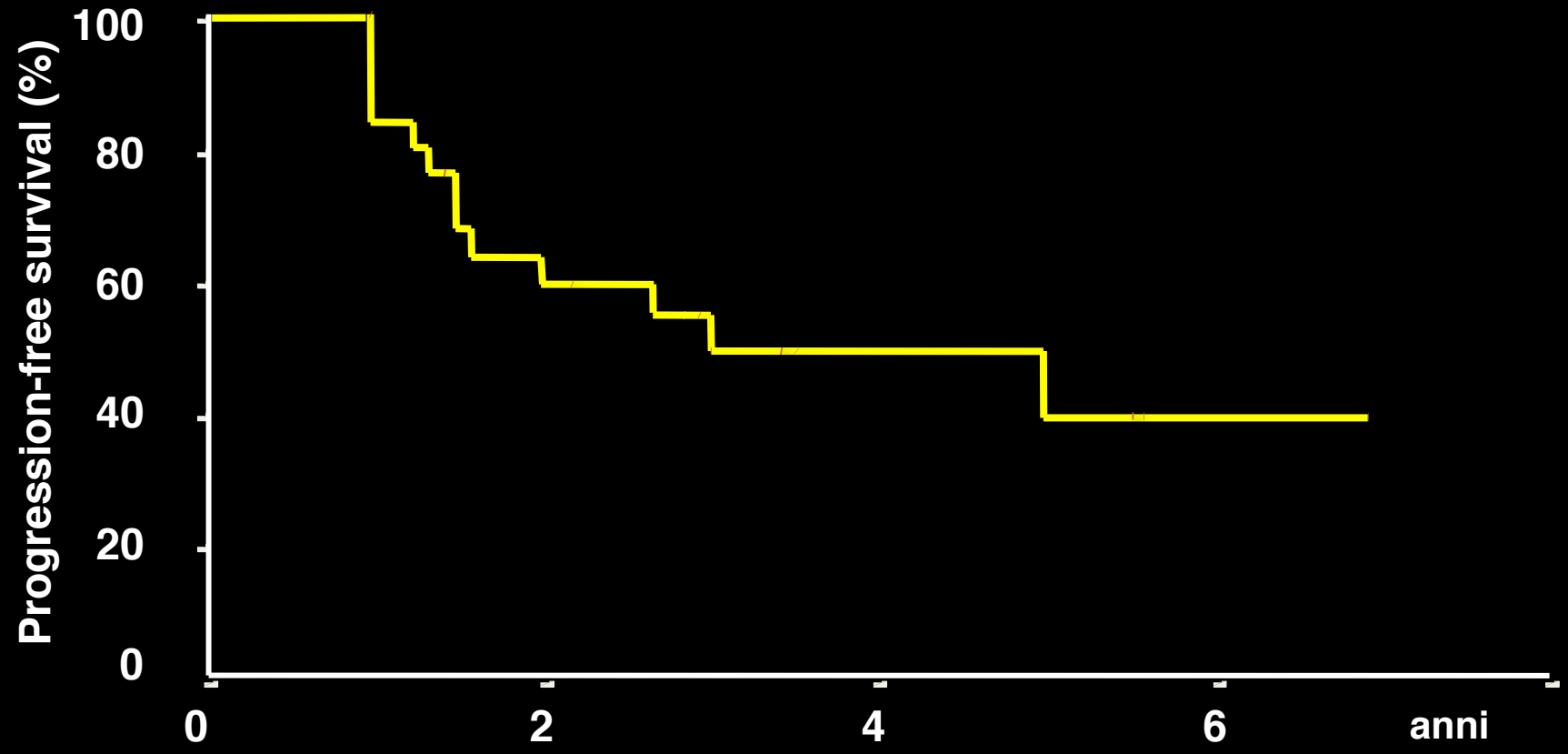


McCormack et al, Eur J Endocrinol 2018, 178: 265

Temozolomide: come?

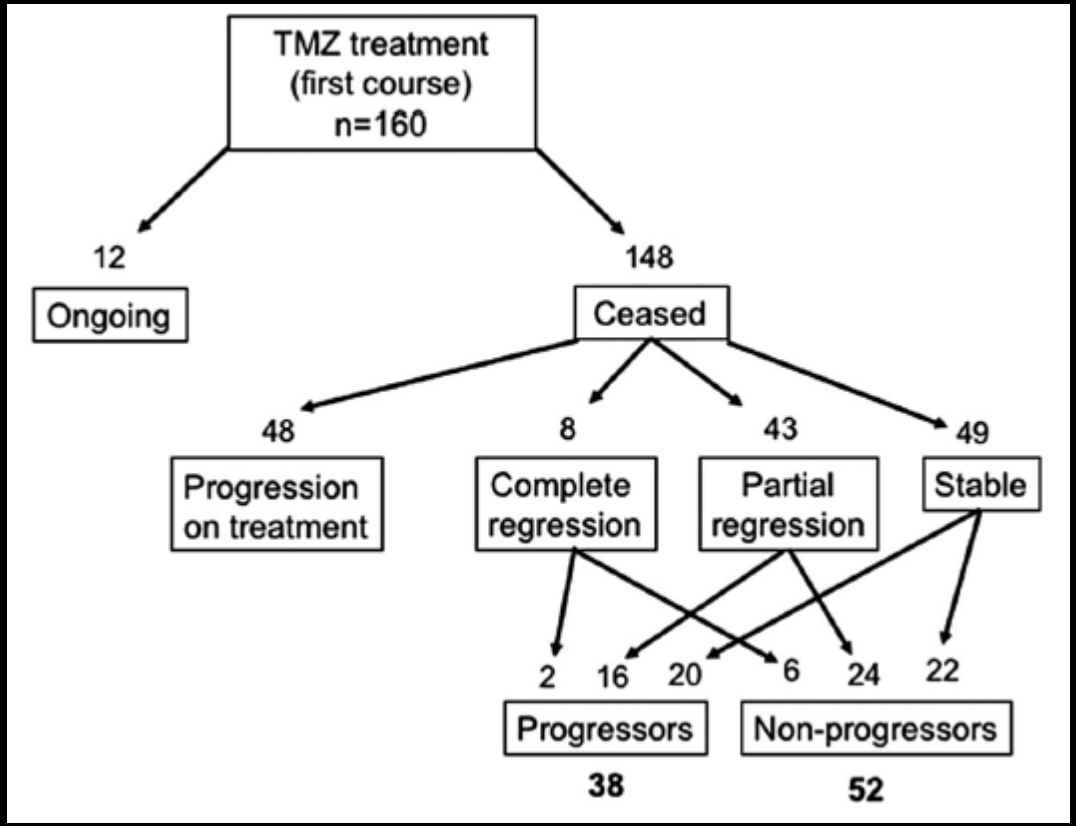
- Chi può prescrivere
- Autorizzazione e rimborsabilità
- Dosaggi e confezioni

TMZ: rischio di recidiva



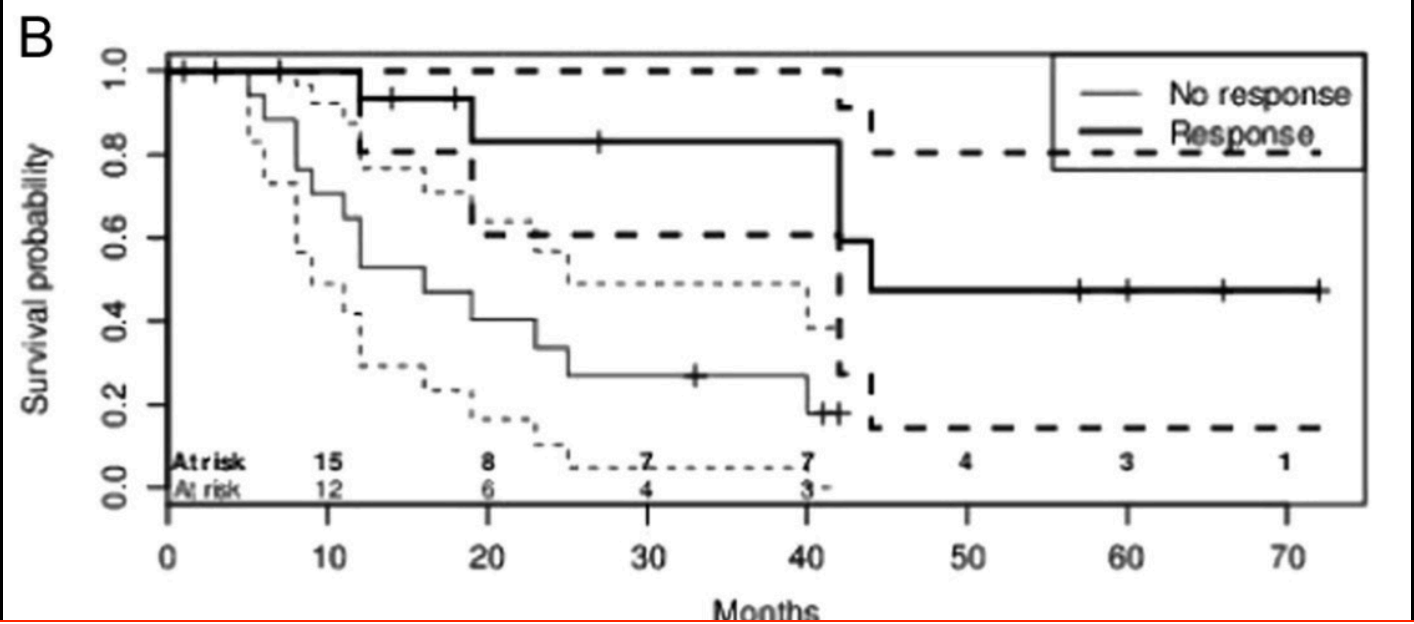
Losa et al, J Neuro-oncol 2016, 126: 519

TMZ: rischio di recidiva



McCormack et al, Eur J Endocrinol 2018, 178: 265

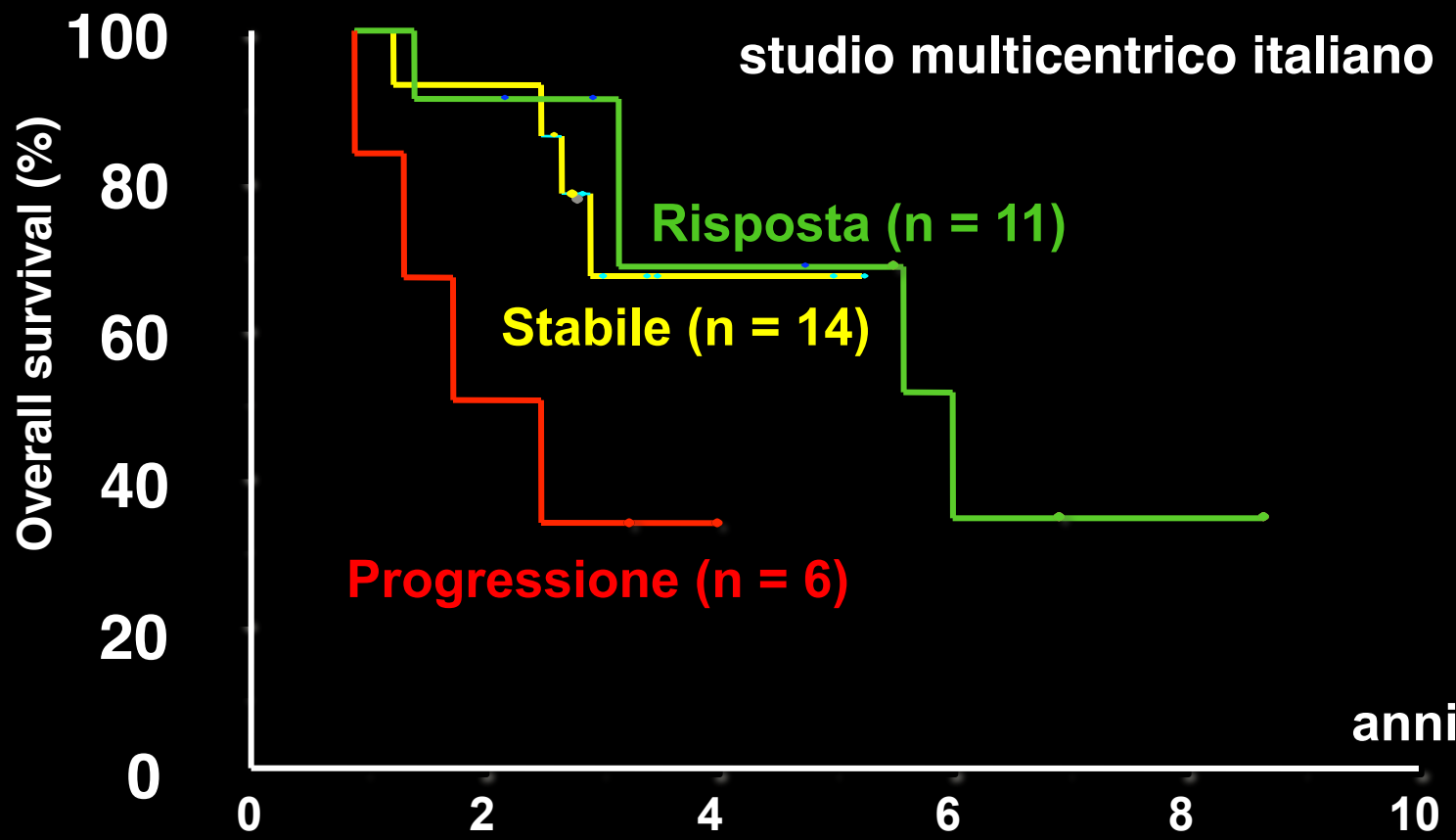
TMZ: effetto su sopravvivenza



In conclusion, we observed a successful treatment in about 50% of patients, associated with an important improvement in survival.

Lasolle et al, Eur J Endocrinol 2017, 176: 769

TMZ: effetto su sopravvivenza



TMZ: sicurezza

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R 3.4.4 We recommend monitoring of haematological parameters, liver function tests and careful clinical observation for potential adverse effects during treatment (+++0).

TMZ: sicurezza

Cause di sospensione del trattamento

Studio multicentrico italiano:

- **2/31 (6.5%)**: per piastrinopenia al 4° e al 5° mese

Losa et al, J Neuro-oncol 2016, 126: 519-525

Studio multicentrico nord-europeo:

- **3/24 (12.5%): 1 per perdita udito al 1° mese**

  1 per astenia al 1° mese, 1 per tossicità epatica al 4° mese

Bengtsson et al, J Clin Endocrinol Metab 2015, 100: 1689-1698

TMZ: sicurezza

Effetti collaterali riportati nella survey ESE:

33/157 (21.0%):

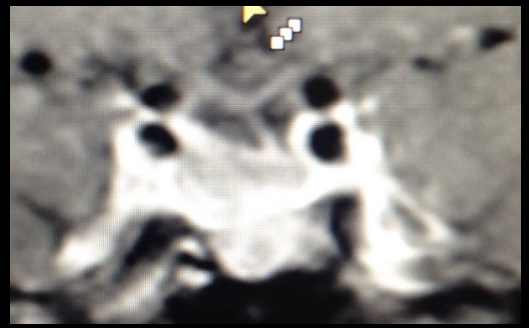
- 7 piastrinopenia
- 2 leucocitopenia
- 5 piastrinopenia + leucocitopenia
- 11 astenia
- 10 nausea/vomito
- 1 deficit uditivo

McCormack et al, Eur J Endocrinol 2018, 178 (3): 265-276

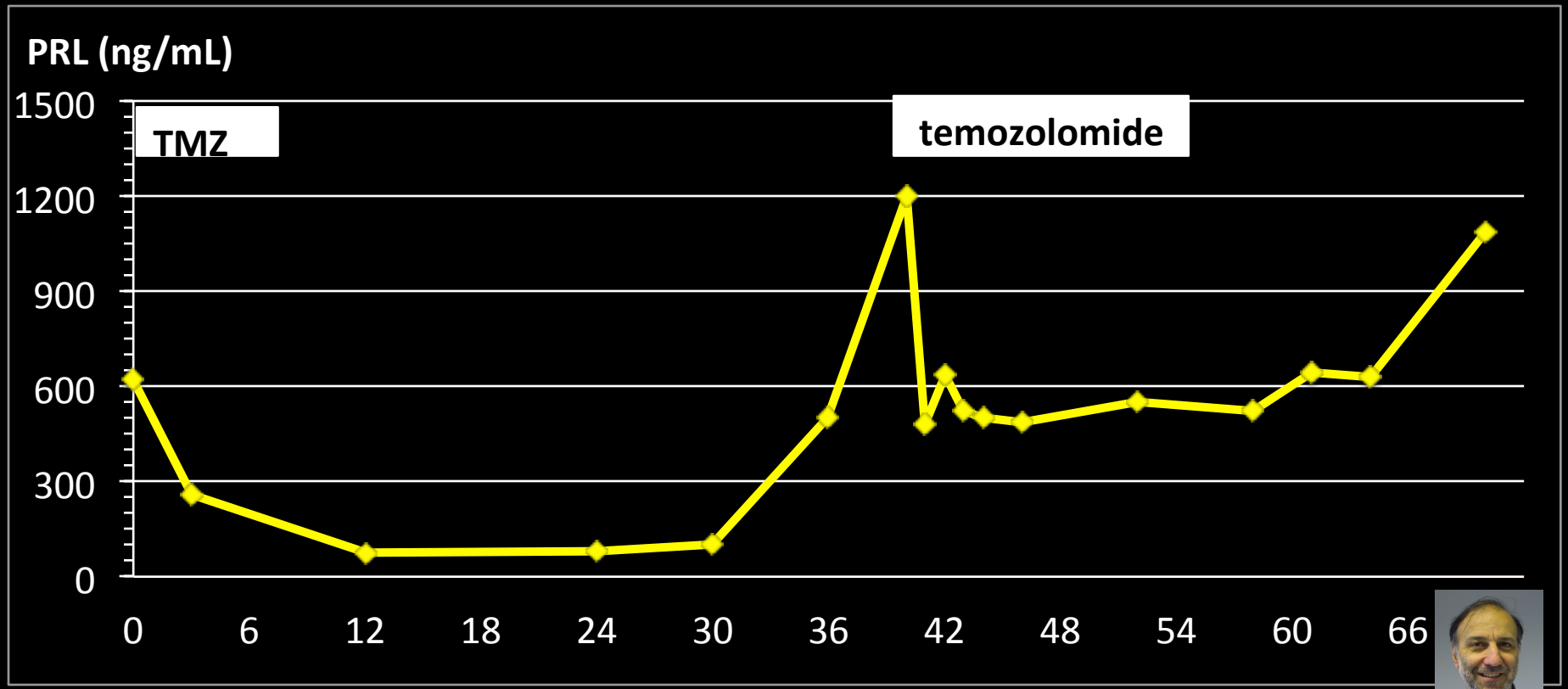
Mario: dopo TMZ

- PRL stabile per 18 mesi, poi ricrescita progressiva fino a 1219 ng/mL
- Ricrescita tumorale intra-sellare

- 2°ciclo TMZ (stesso dosaggio) per 12 mesi
- Risposta PRL e tumore
- Buona tolleranza



Mario: PRL e TMZ



Che fare dopo TMZ?

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R 3.4.9 In patients who develop a recurrence following response to temozolomide treatment, we suggest a second trial of 3 cycles of temozolomide (+000).

(unpublished ESE survey). In 15 patients, TMZ was given as monotherapy, in one patient (134) in combination with other drugs. Partial remission was achieved in 1 of 16 patients, 2 had stable disease and 13 had progression.

Che fare dopo TMZ?

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R 3.4.8 In patients with rapid tumour progression on temozolomide treatment, we suggest a trial with other systemic cytotoxic therapy. Given the variety of chemotherapeutic agents that have been reported, we cannot suggest a particular regimen (+000).

Che fare dopo TMZ?

Agent	Number of cases	Stable	Progression
Cisplatin + etoposide	2		2
Carboplatin + etoposide	3		3
Bevacizumab	3	1	1
Cisplatin + adriblastin	1	1	
Capecitabine	1		1
Cisplatin + capecitabine	1		
Cisplatin + 5FU	1		1
Doxorubicin + 5FU	1		1
Oxaliplatin + 5FU	1		1
Etoposide	2		2
Etoposide +cyclophosphamide	1		1
Everolimus	3		3
Erlotinib	1		1
Lapatinib	2		2
Sunitib	1		1
Radiotherapy	10	4	6

McCormack et al, Eur J Endocrinol 2018,

Take home messages

- I termini aggressivo, invasivo e maligno non sono sinonimi (e atipico deve essere dimenticato)
- Un tumore ipofisario può avere un decorso indolente per anni e poi cambiare: nessuno deve essere perso al follow-up
- Non ci sono elementi clinici, biochimici e radiologici in grado di differenziare in modo attendibile benigno e maligno

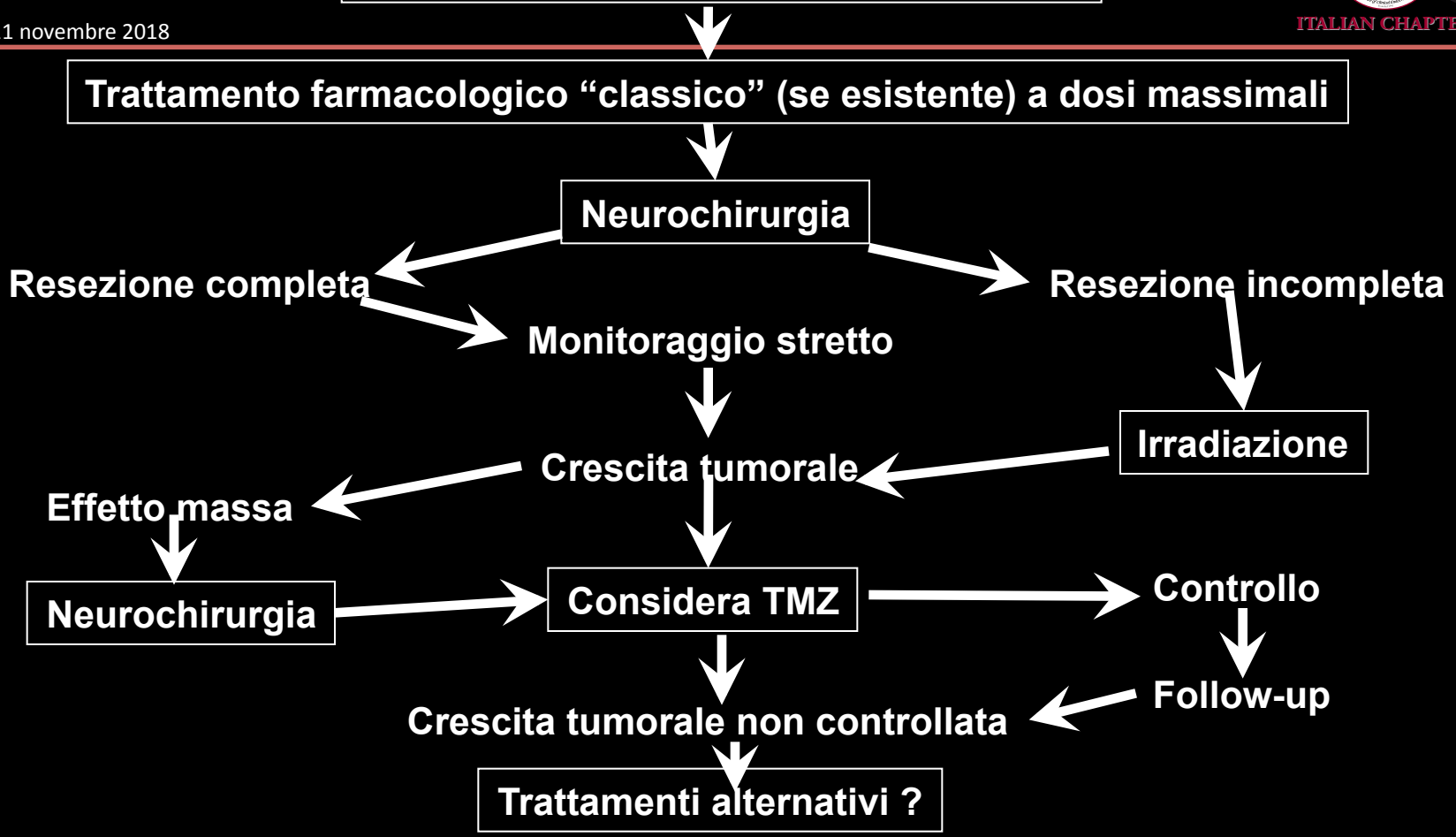
Take home messages-2

- Non ci sono marcatori patologi predittivi in modo attendibile dell'evoluzione a comportamento aggressivo
- Attenzione alle variazioni del pattern secretorio e alla resistenza secondaria
- Sempre approccio e trattamento multi-disciplinare e multi-modale

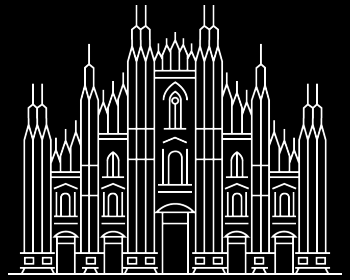
Take home messages- 3

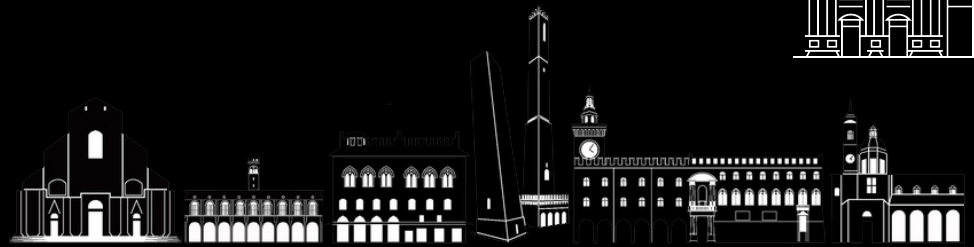
- TMZ è opzione da considerare nei carcinomi e negli adenomi aggressivi non controllabili con le terapie standard (chirurgia, radioterapia, farmaci)
- TMZ può ottenere prolungamento dell'intervallo libero di malattia e della sopravvivenza
- **Non siate "timidi" nell'inviare questi pazienti complessi a centri con esperienza!!**

Tumori ipofisari aggressivi



Grazie





a tutti i relatori e a tutti voi