1° CORSO NAZIONALE DI AGGIORNAMENTO

Roma,
9-11 novembre 2012

Malattia di Cushing: gestione delle recidive

Moderatori
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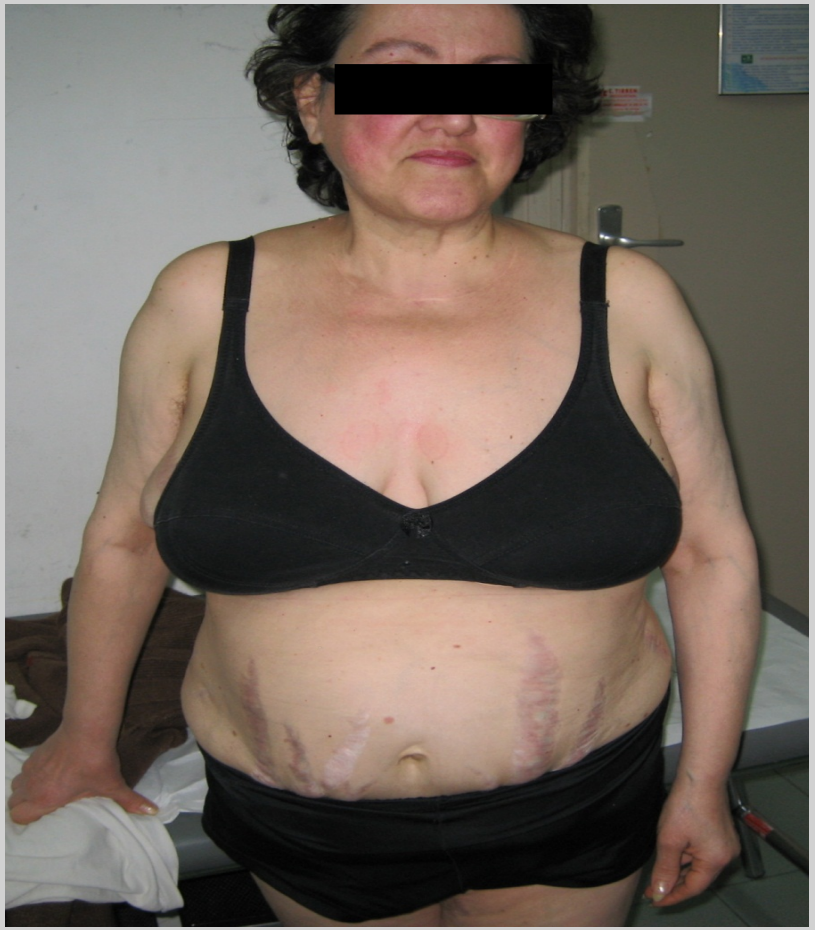
Rosario Pivonello

- Caso clinico
  R. Pivonello
- Rischio di recidiva
  G. Arnaldi
- Difficoltà diagnostiche
  A. Pia
- Opzioni terapeutiche
  M.C. Zatelli
- Take-home messages
  G. Reimondo

Caratteristiche cliniche

Donna, 40 anni,
2 gravidanze a termine

- Incremento ponderale
- Astenia
- Irsutismo
- Alopecia
- *Striae rubrae*
- Ipertensione arteriosa in buon compenso farmacologico
- Dislipidemia mista
- Diabete mellito di recente insorgenza ed in solo trattamento alimentare
- Osteopenia di grado severo

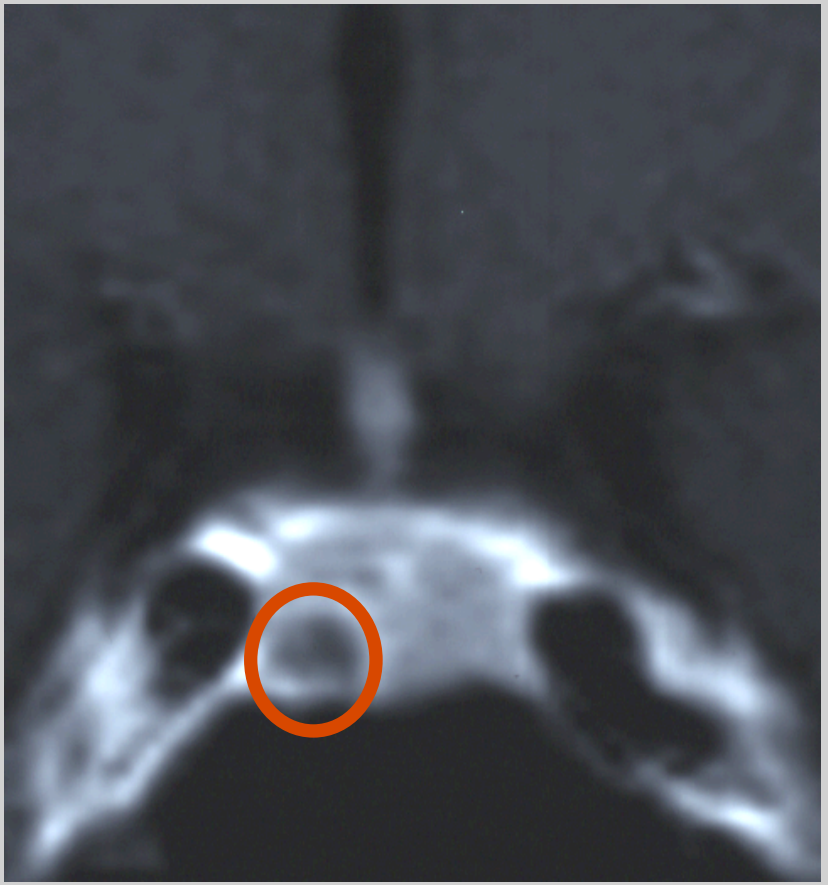


Diagnosi

CLU: 1560 µg/24h
ACTH: 65 pg/ml
Cortisolo sierico: 306 ng/ml

DMX 2 mg
CLU: 644 µg/24h
Cortisolo sierico: 237 ng/ml

RMN
Adenoma ipofisario
Ø = 4 mm



Diagnosi

CRH test
Cortisolo T0: 240 ng/ml
Cortisolo T30: 380 ng/ml

DMX 8 mg
CLU: 250 µg/24h
Cortisolo sierico: 123 ng/ml

Diagnosi:
Malattia di Cushing

Terapia di prima linea

Neurochirurgia: adenomectomia trans-sfenoidale

Dopo 7 giorni

Cortisolo sierico < 18 ng/ml → Cortone Acetato 37,5 mg/die

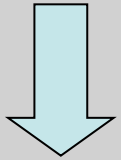
Tre mesi dopo

Baseline Cortisolo sierico = 56 ng/mL

DMX 2 mg Cortisolo sierico <18 ng/mL

ACTH test

Cortisolo basale: 78 ng/ml
Cortisolo T60: 230 ng/ml



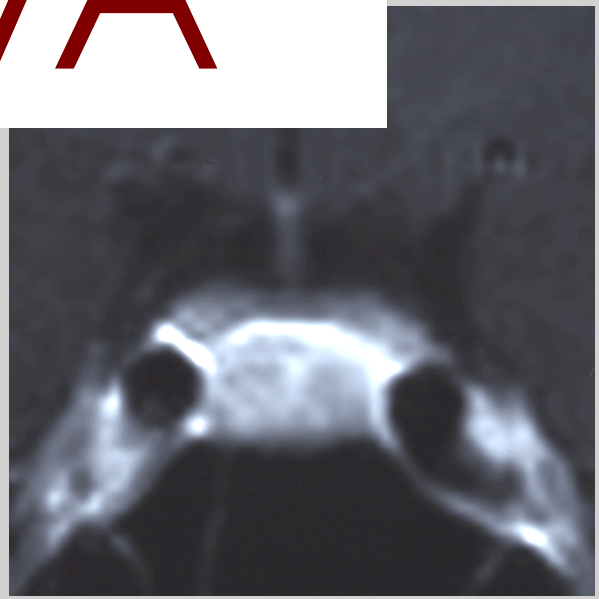
Sospensione del Cortone Acetato

Due anni dopo…

Ipertensione arteriosa in inadeguato compenso farmacologico;
Diabete mellito scompensato;
Osteopo

RECIDIVA

CLU: 840 µg/24h
ACTH: 120 pg/ml
Cortisolo: 250 ng/ml
RMN: no adenoma



Quale Terapia di seconda linea?

Neurosurgery
Transsphenoidal adenomectomy

relapse

relapse

Bilateral adrenalectomy ⟷ Pituitary radiotherapy

Quale Terapia di seconda linea?

1. Re-intervento chirurgico
2. Surrenalectomia bilaterale
3. Radioterapia
4. Terapia medica

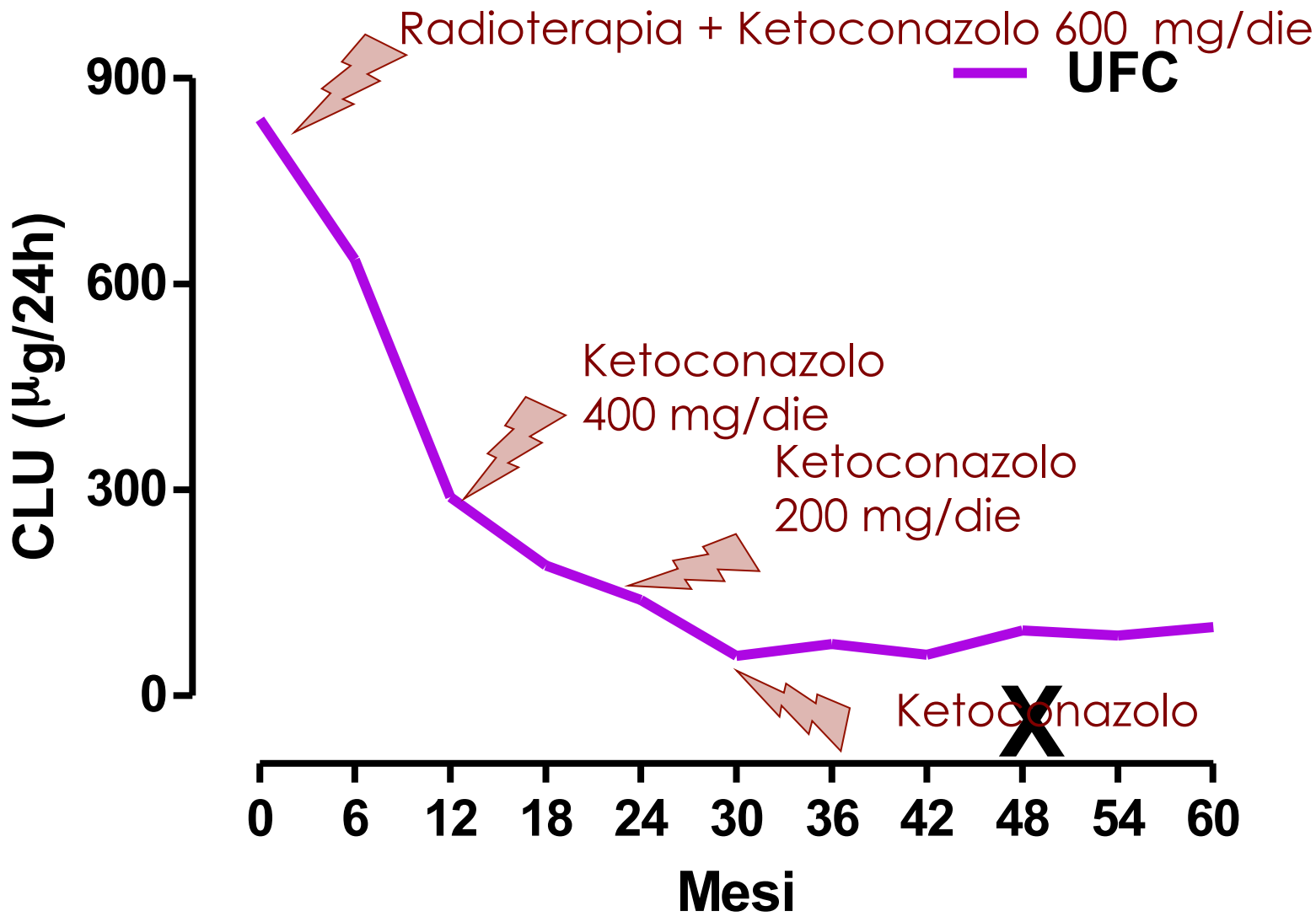
Quale Terapia di seconda linea?

Radioterapia con acceleratore lineare
Dose: 50 Gray distribuiti in 25 applicazioni

Nel frattempo

Ketoconazolo 600 mg/die

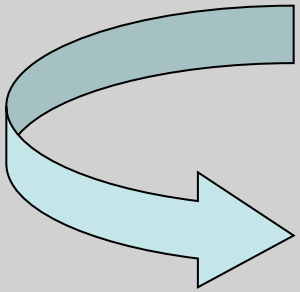
Terapia di seconda linea



Funzione ipofisaria residua

Ipogonadismo secondario

Ipotiroidismo secondario



Eutirox 75 mg/die

Miglioramento del controllo di ipertensione e diabete

Radiotherapy and Radiosurgery for Cushing's Disease

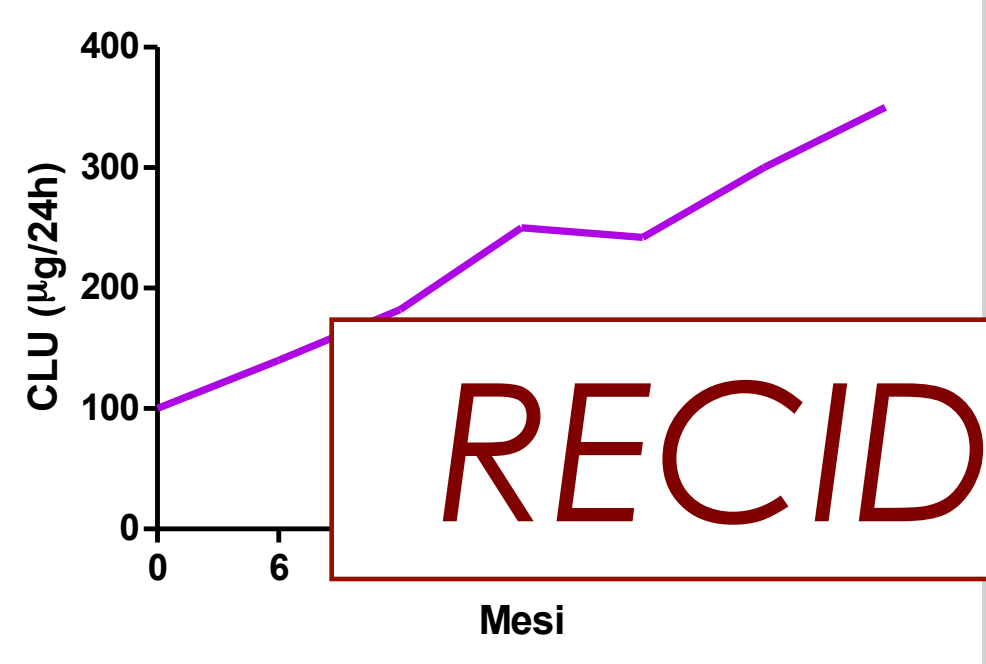
Arq Bras Endocrinol Metab 2007;51/8

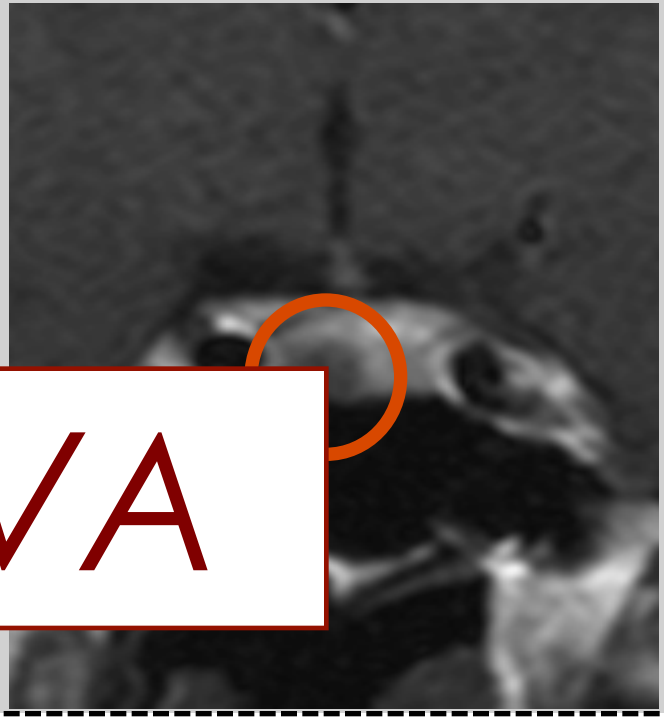
GIUSEPPE MINNITI
MICHAEL BRADA

Table 2. Results of radiosurgery (SRS) for Cushing's disease.

Authors	patients	follow-up	control rate	hormone normalization	late toxicity (%)	
	(n)	median (months)	(%)	(%)	visual	hypopituitarism
Dagerbald 1986 (27)	29	6 years	76	48	NA	55
Kim et al., 1999 (28)	8	26	100	60	NA	NA
Hayashi et al., 1999 (29)	10	> 6	100	10	0	5
Inoue et al., 1999 (30)	3	> 24	100	100	0	0
Izawa et al., 2000 (31)	12	> 6	100	17	NA	0
Hoybye et al., 2001 (32)	18	17 years	100	83	0	66
Kobayashi et al., 2002 (33)	20	60	100	35	NA	NA
Pollock et al., 2002 (34)	9	36	85	35	35	8
Choi et al., 2003 (35)	9	43	100	55	0	0
Devin et al., 2004 (36)	35	35	91	49	0	40
Castinetti et al., 2007 (37)	40	54	100	42	2,5	15
Jagannathan et al, 2007 (38)	90	45	96	54	5	22
Total	**280**	**45**	**94**	**48**	**2**	**24**

Tre anni dopo la cura



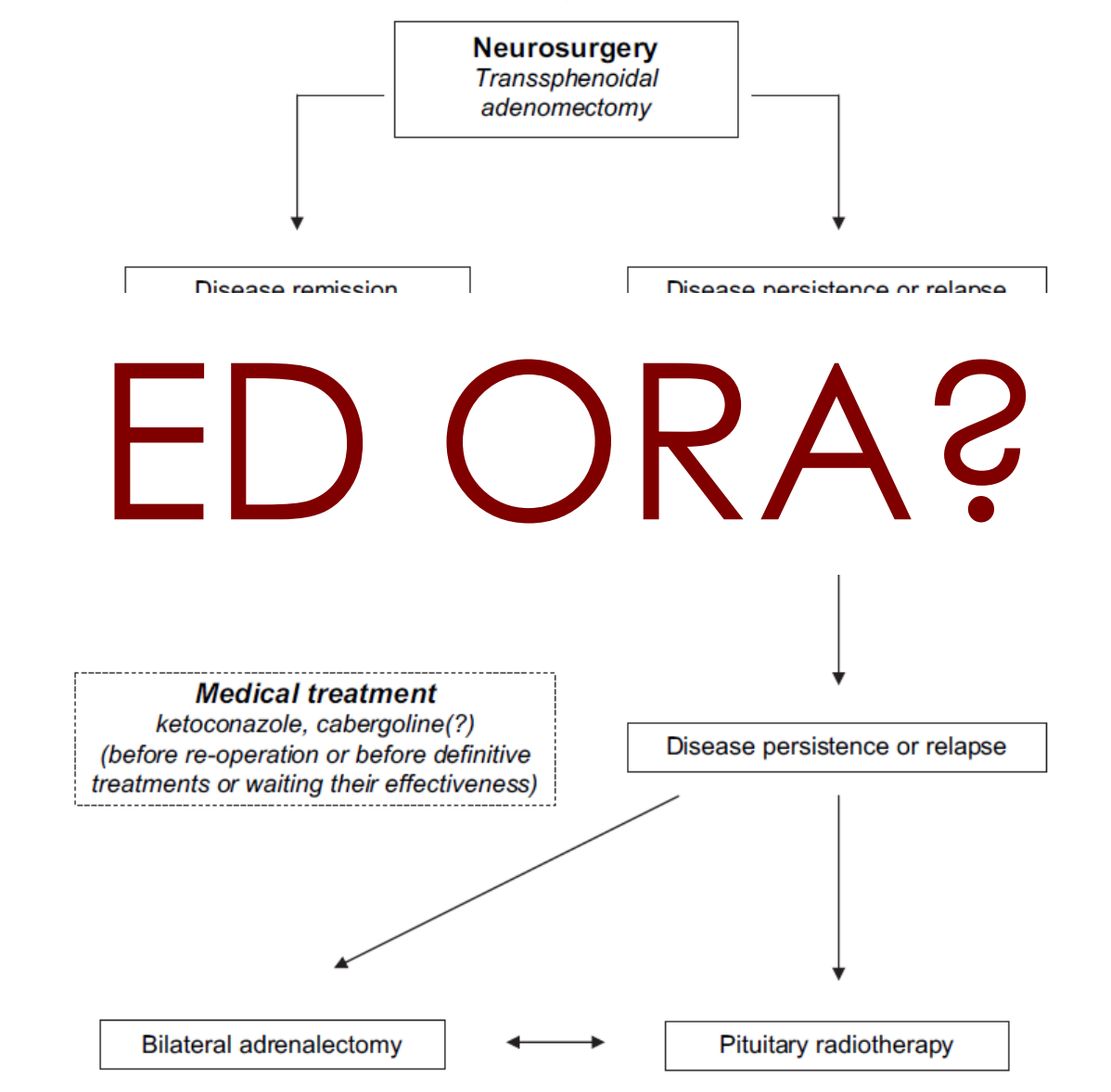


RECIDIVA

CLU: 576 µg/24h
RMN: Adenoma Ø = 6 mm

Osteoporosi severa
Peggioramento controllo ipertensione e diabete

Quale Terapia di terza linea?



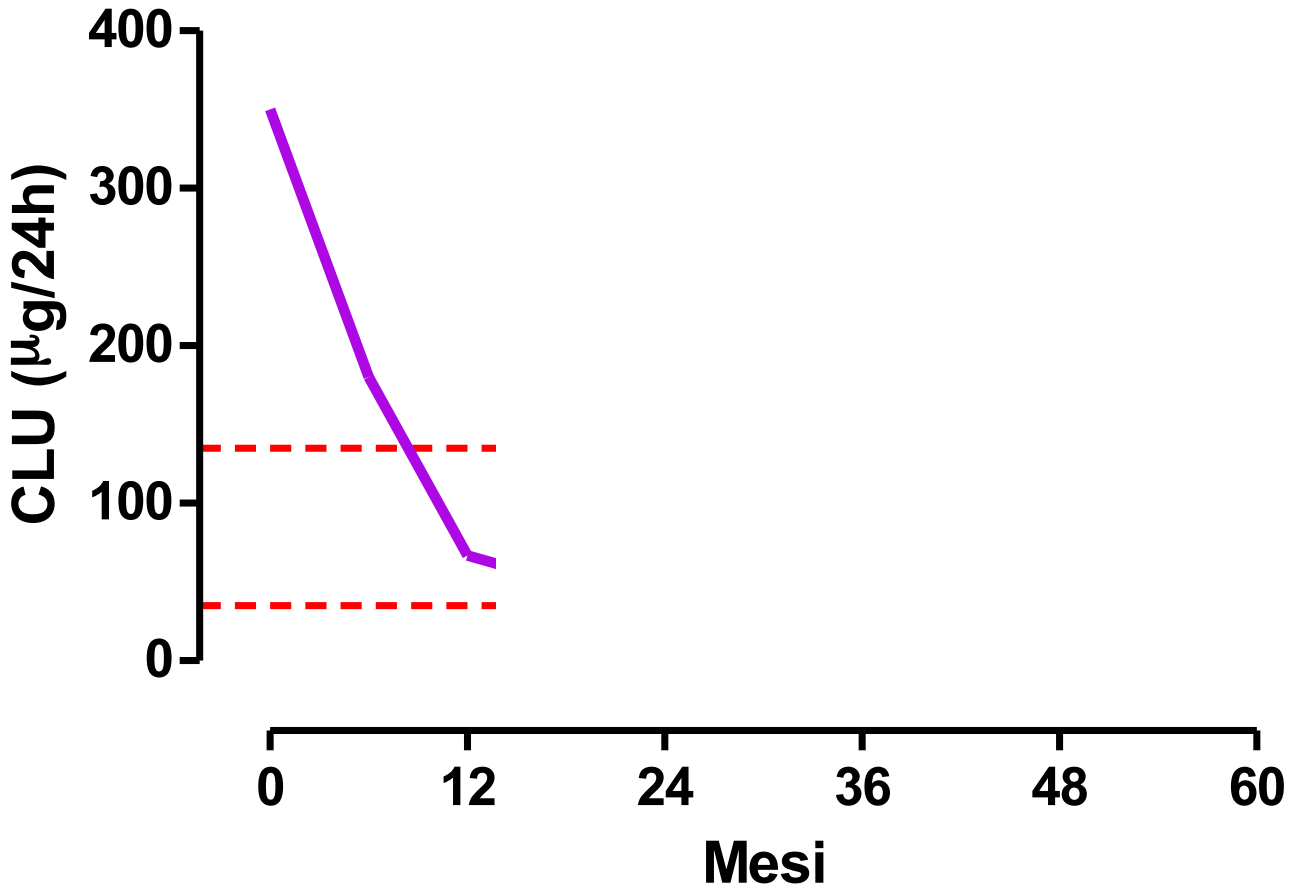
Quale Terapia di terza linea?

1. Intervento chirurgico
2. Surrenalectomia bilaterale
3. Nuova radioterapia
4. Terapia medica

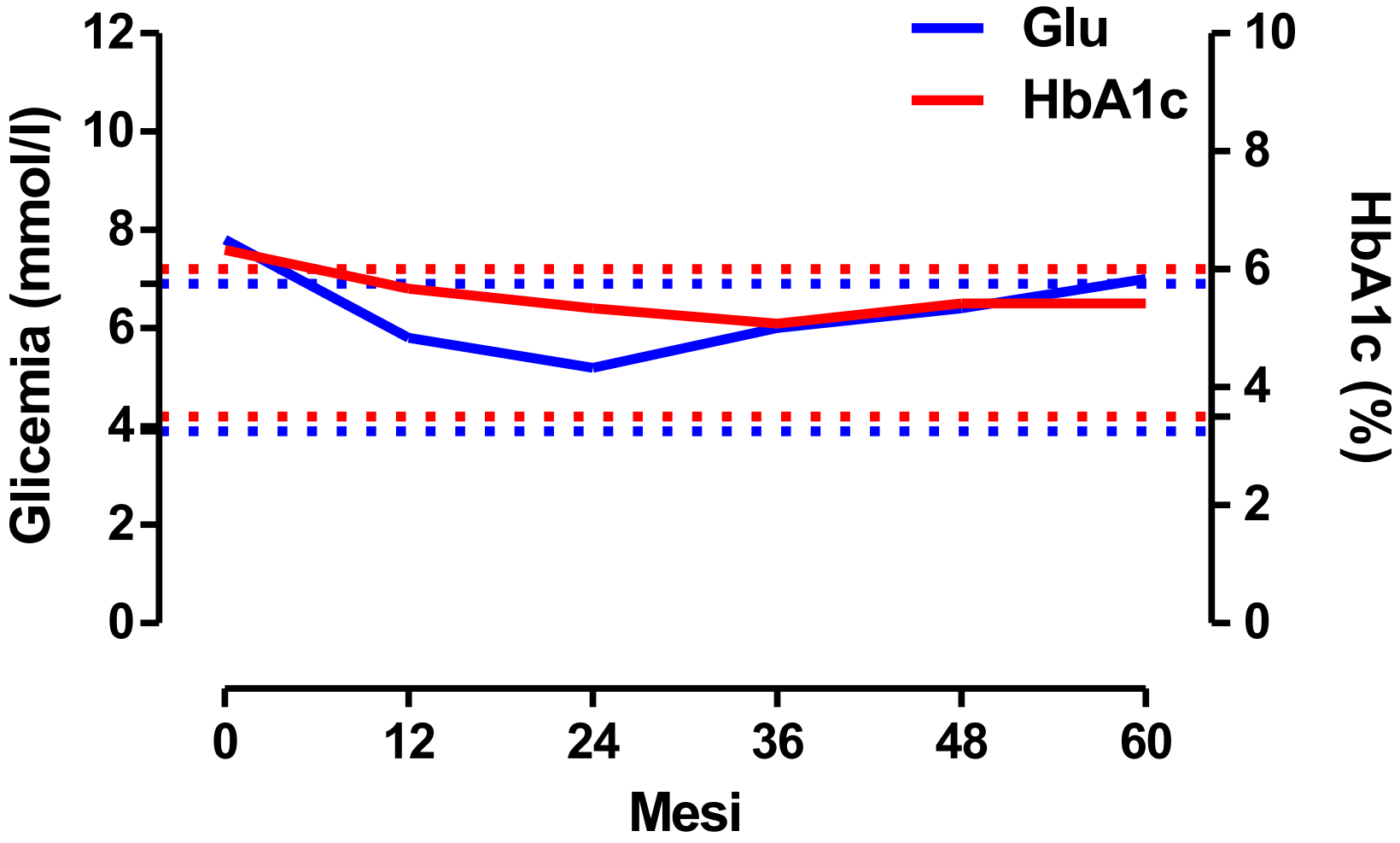
Terapia medica

Terapia medica 1

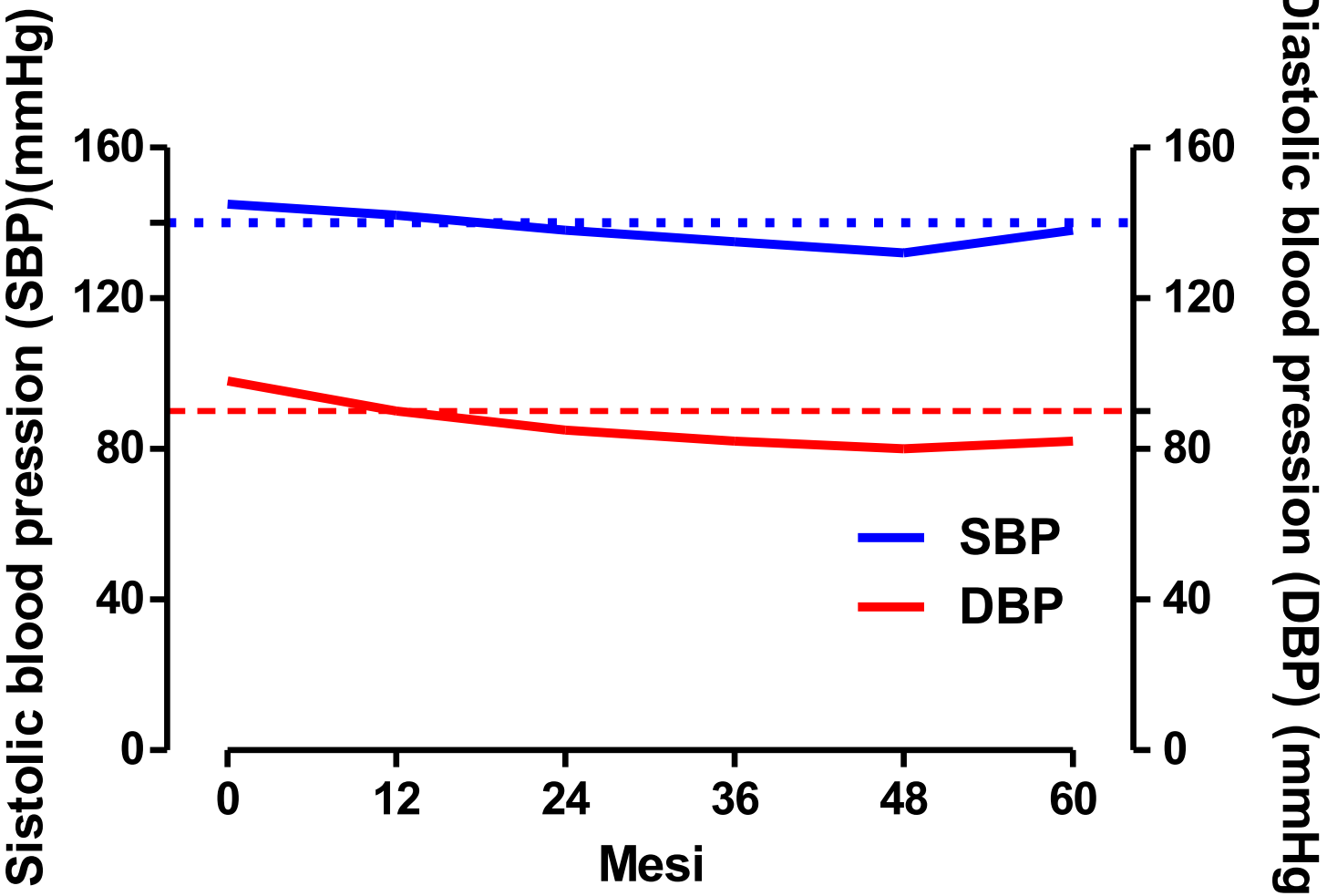
Cabergolina 1-3 mg/settimana



Profilo glicemico

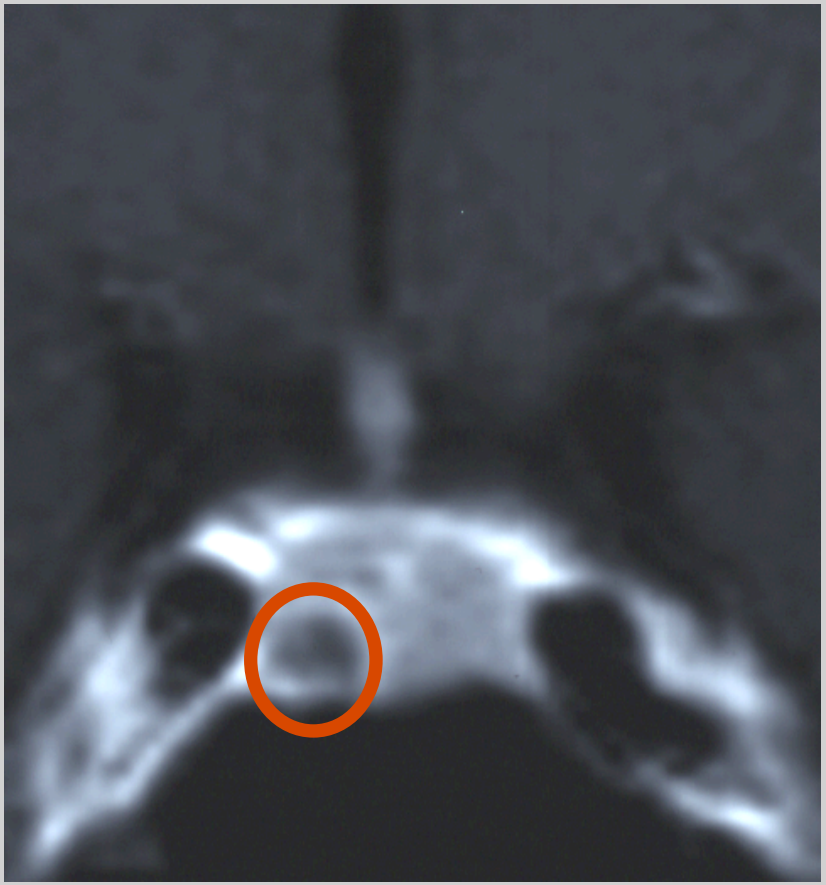


Profilo pressorio



Tumore ipofisario

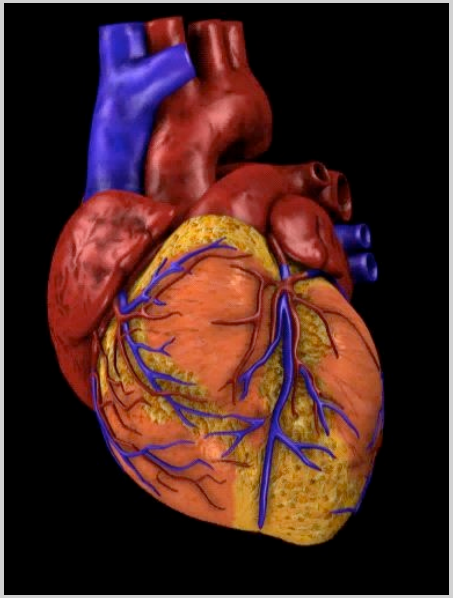
Lieve riduzione delle dimensioni del tumore ipofisario

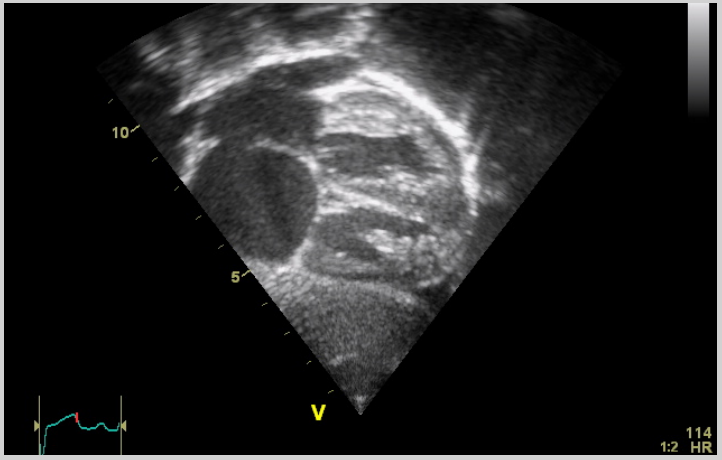


Studio ecocardiografico

Baseline

- ✓ Insufficienza mitralica lieve
- ✓ Insufficienza tricuspidalica lieve





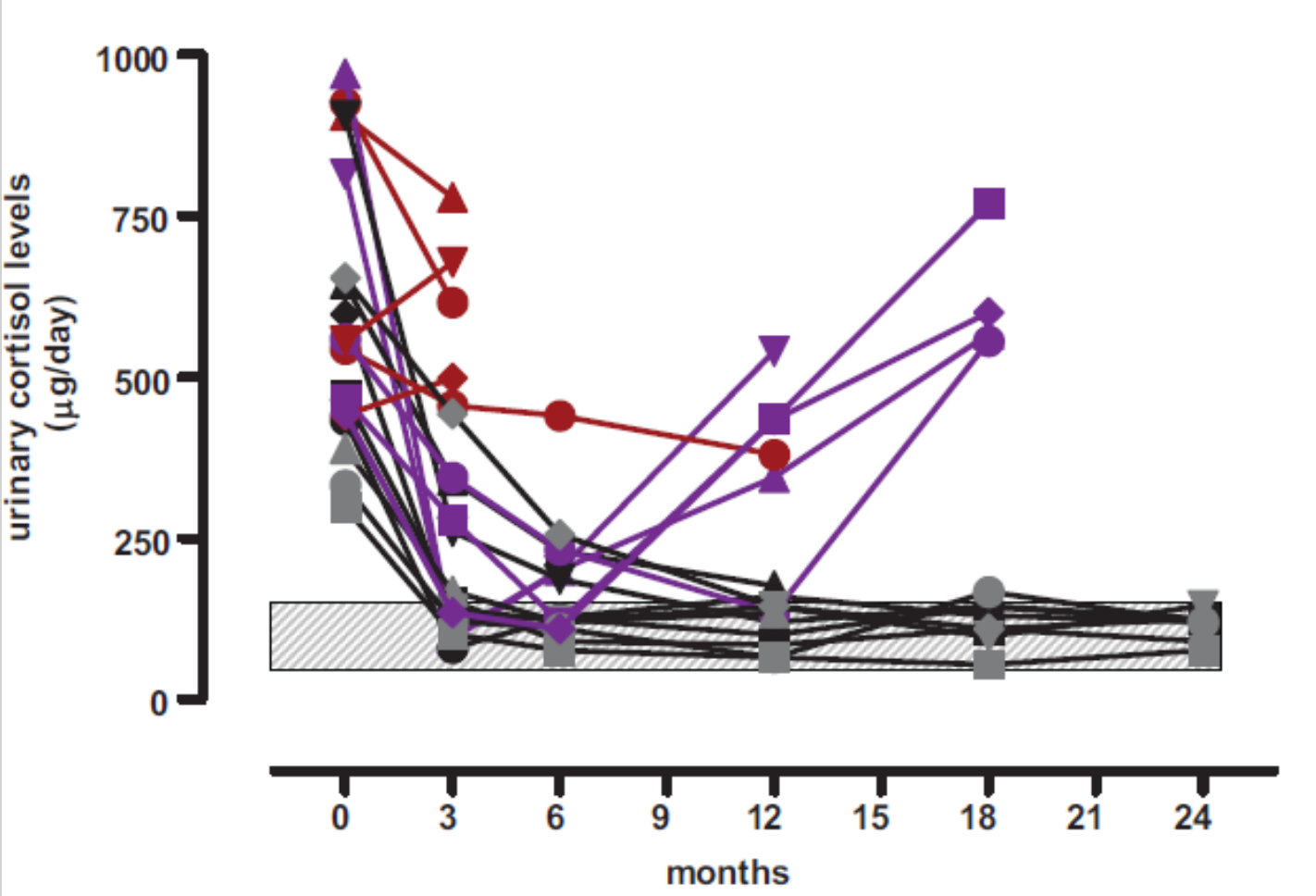
Post-trattamento

- ✓ Insufficienza mitralica lieve
- ✓ Insufficienza tricuspidalica lieve
- ✓ Insufficienza aortica lieve

The Medical Treatment of Cushing's Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery

Rosario Pivonello, Maria Cristina De Martino, Paolo Cappabianca, Monica De Leo, Antongiulio Faggiano, Gaetano Lombardi, Leo J. Hofland, Steven W. J. Lamberts, and Annamaria Colao

J Clin Endocrinol Metab, January 2009, 94(1):223–230



Cabergoline monotherapy in the long-term treatment of Cushing's disease

Ariane Godbout, Marcos Manavela[1], Karina Danilowicz[1], Hugues Beauregard, Oscar Domingo Bruno[1] and André Lacroix

European Journal of Endocrinology (2010) **163** 709–716

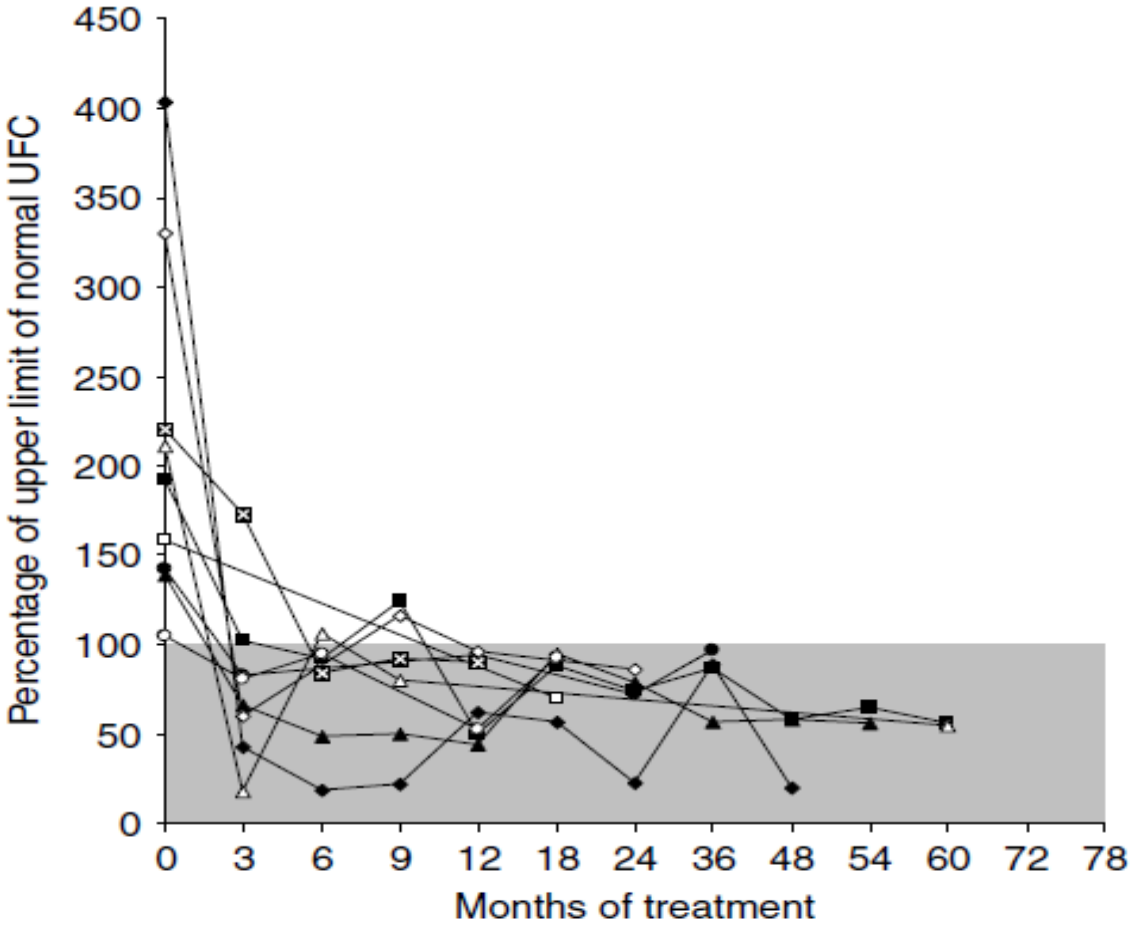


Figure 1 Complete long-term response to cabergoline monotherapy in nine patients with CD.

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease

Renzo Zanettini, M.D., Angelo Antonini, M.D., Gemma Gatto, M.D., Rosa Gentile, M.D., Silvana Tesei, M.D., and Gianni Pezzoli, M.D.

Potential Cardiac Valve Effects of Dopamine Agonists in Hyperprolactinemia

Elena Valassi, Anne Klibanski, and Beverly M. K. Biller

Neuroendocrine Clinical Center, Massachusetts General Hospital and Harvard Medical School Boston, Massachusetts 02114

Conclusions: Although most reports do not show an association between use of dopamine agonists and valvulopathy, caution must be exercised, especially in patients requiring long-term, high-dose medication regimens. Clinicians should recommend the lowest possible doses of dopamine agonists and address the question of echocardiographic monitoring on an individual basis.

Quale Terapia di terza linea?

1. Intervento chirurgico
2. Surrenalectomia bilaterale
3. Nuova radioterapia
4. Terapia medica

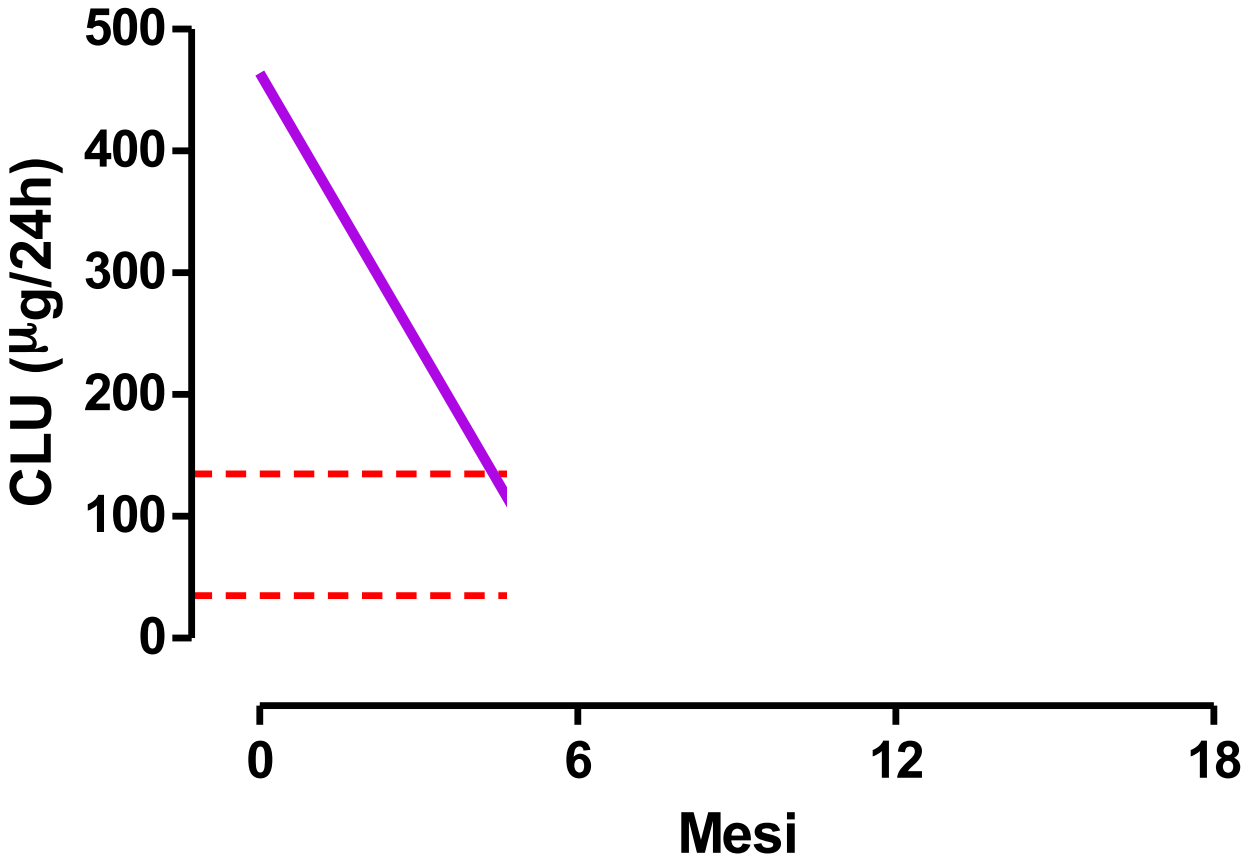
Proposta

Surrenalectomia bilaterale

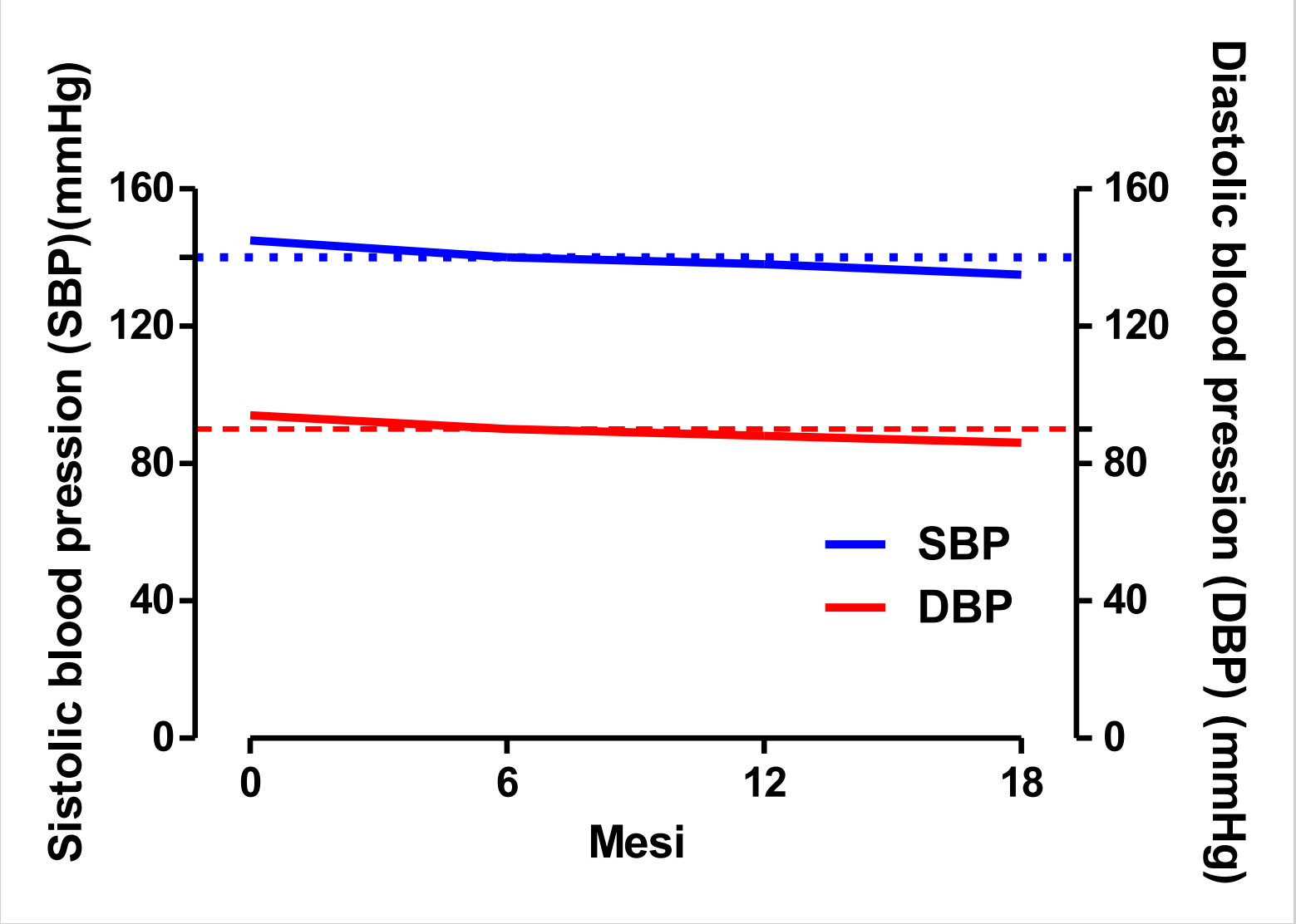
Rifiuto della paziente

Terapia medica 2

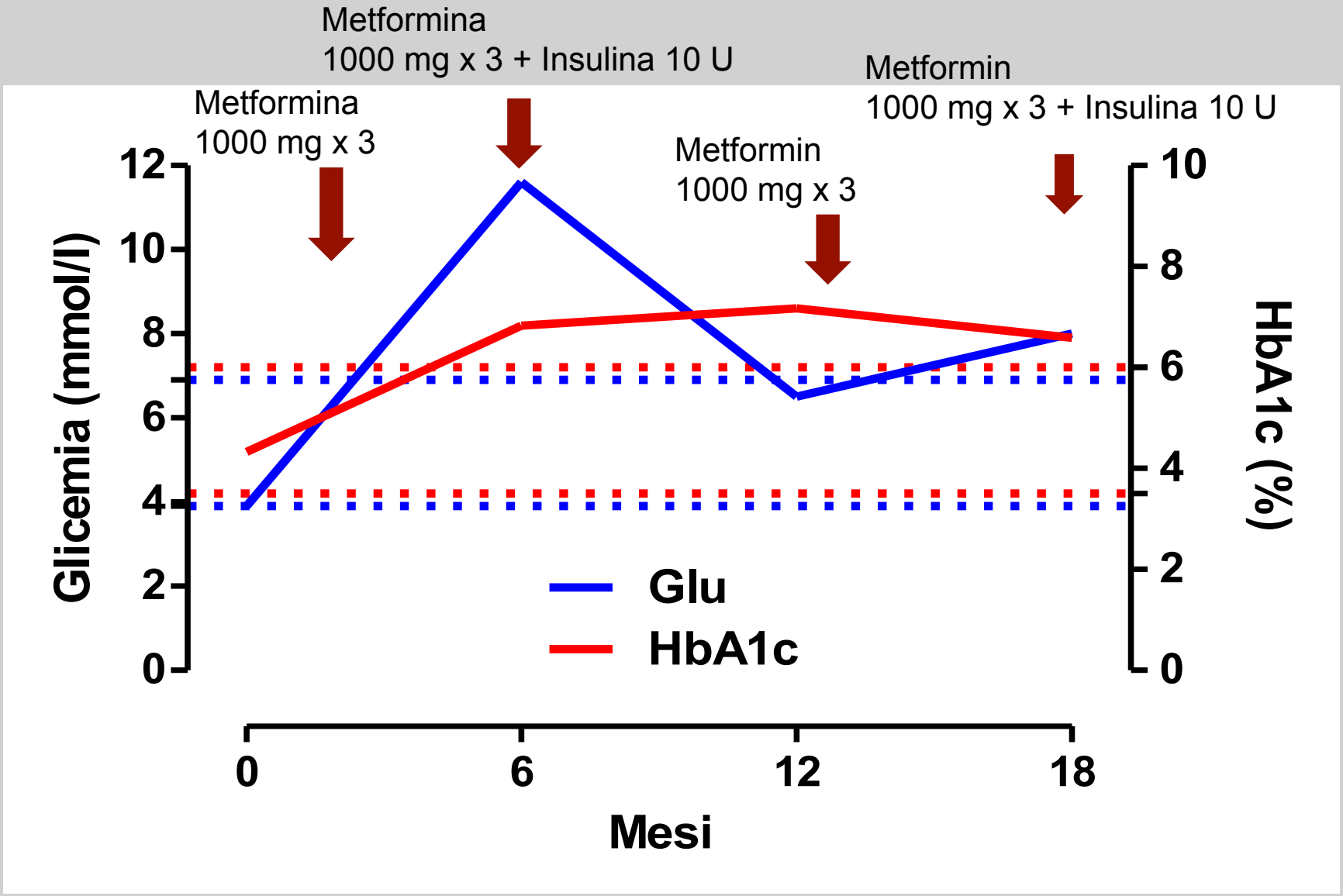
Pasireotide 1800 μg/die



Profilo pressorio



Profilo glicemico



A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D., for the Pasireotide B2305 Study Group*

N ENGL J MED 366;10 NEJM.ORG MARCH 8, 2012

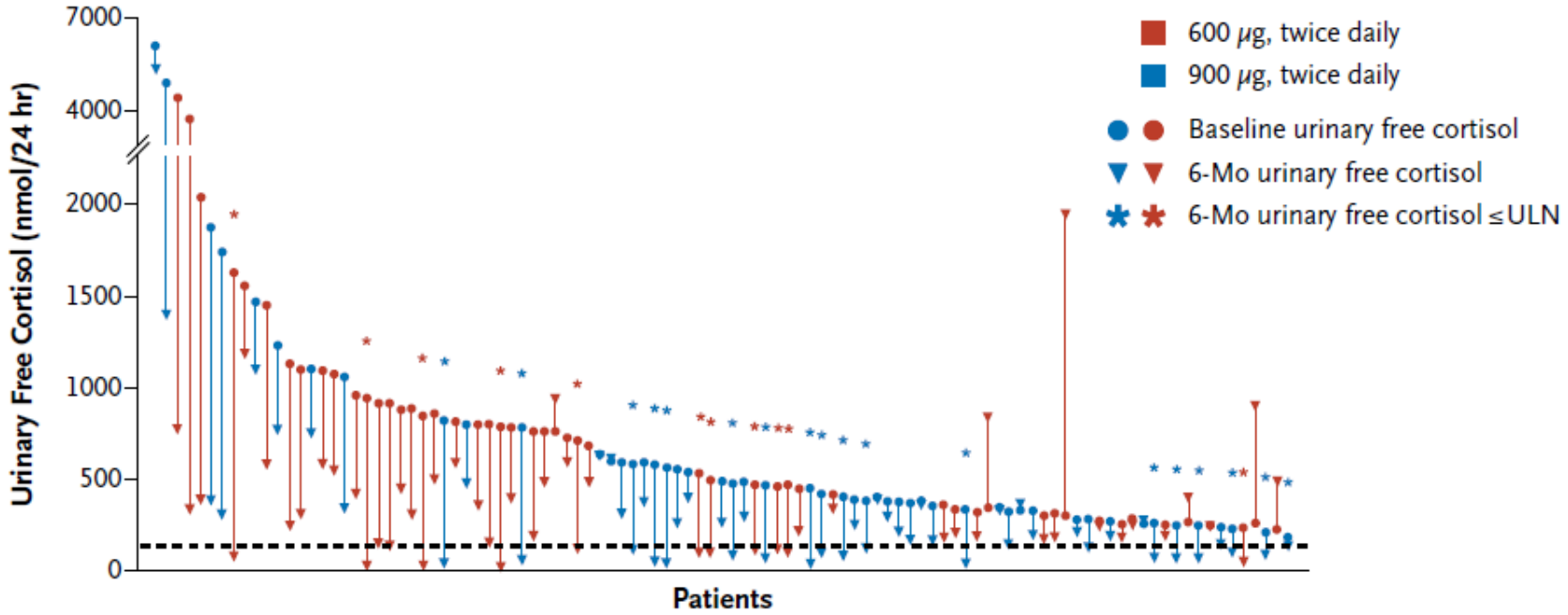


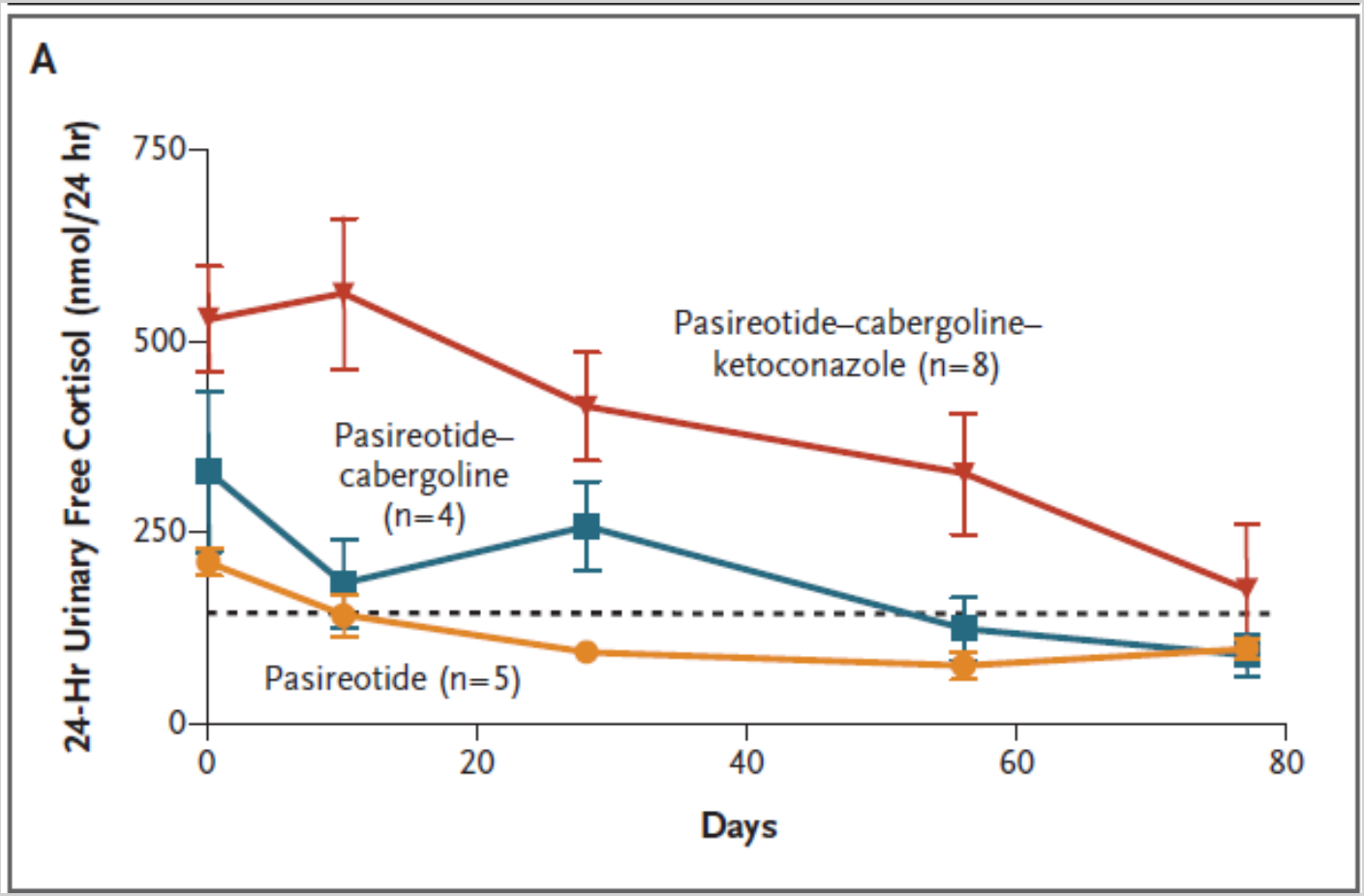
Figure 1. Absolute Change in Urinary Free Cortisol Levels from Baseline to Month 6.

Urinary free cortisol was available at baseline and at month 6 in a total of 103 patients; 61 patients had a reduction of at least 50% in urinary free cortisol levels at month 6. The black dashed line represents the upper limit of the normal range (ULN) (145 nmol per 24 hours [52.5 μg per 24 hours]).

Pasireotide Alone or with Cabergoline and Ketoconazole in Cushing's Disease

Richard A. Feelders, M.D., Ph.D.

N ENGL J MED 362;19 NEJM.ORG MAY 13, 2010



Grazie per l’attenzione