NEN PRECEPTORSHIP
LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

5/6 Aprile 2018 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

IEO
Istituto Europeo di Oncologia

Possible, probable and confirmed NET diagnosis

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Pituitary Unit
NET Multidisciplinary Group

Istituto Clinico Humanitas
Department of Biomedical Sciences
Humanitas University

European Commission

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European ENETS Neuroendocrine Tumor Society

SG, Donna, 72 anni, Pensionata

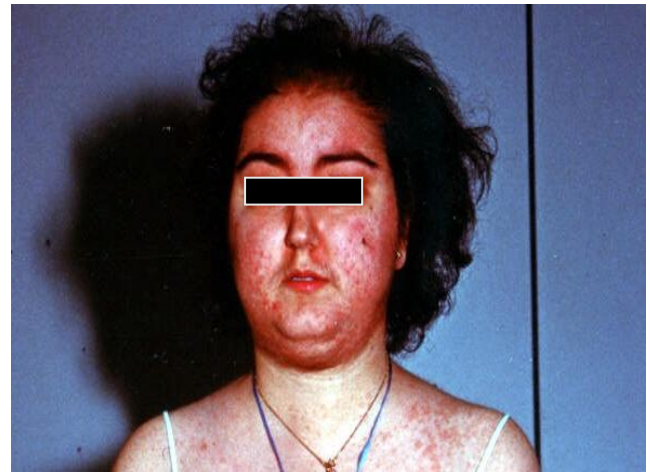
Anamnesi patologica remota: ipertensione arteriosa, dislipidemia

Anamnesi patologica prossima:

Nel maggio del 2016 giunge presso l'ambulatorio di cardiologia di Humanitas per **scarso controllo pressorio** nonostante l'adeguamento della terapia medica, edemi agli arti inferiori e dispnea.

Incremento ponderale di 4 kg nel giro di un mese.

ESAME OBIETTIVO



Altezza 161 cm, peso 67 Kg (+4kg)
PA: 190/100 mmHg, FC:90 R b/min
Facies lunare
Pletora
Edemi arti inferiori: segno della fovea +++

- G.R. = 4,5 X 10^6
- G.B = 12.460 (neu 85%)
- MCV = 84.5 fl
- PLT = 250.00
- ALT = 29
- AST = 28
- GGT = 35
- Glicemia = 78

- Bilirubina = 0.61
- LDH = 422
- Sodio = 140
- Potassio = 2,9 mEq/L
- Calcio = 2.29
- Creatinina = 0.6
- PCR = 6.29

Possible, probable and confirmed Cushing's syndrome

Possible?

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

[a] Features are listed in random order.

[b] Cushing's syndrome is more likely if onset of the feature is at a younger age.

Endocrine Society, Guidelines JCEM, 2008

Probable?

Pseudo-Cushing
Obesity
Hypertension
Depression
Diabetes
Osteoporosis

Possible, probable and confirmed Cushing's syndrome

Overt Cushing's syndrome
1-3/milion/year

Diabetes Mellitus

3-5% in uncontrolled patients

5% in hospitalized patients

1% in adult patients with newly diagnosed diabetes mellitus

Hypertension

1% (2% including subclinical) in hypertensive outpatient patients

Osteoporosis and vertebral fracture

9% of older patients

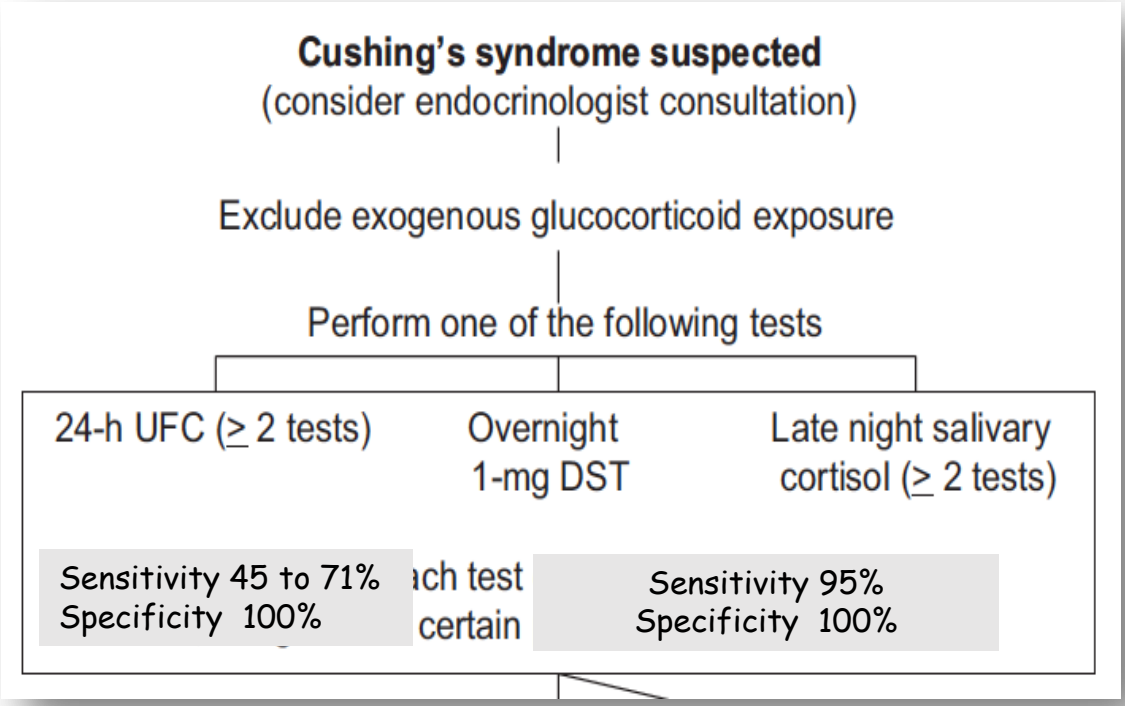
Hirsutism

0.3% in retrospective study

Obesity, diabetes and hypertension and/or hirsutism

5.8% in general endocrine outpatient evaluation

Confirmed?



ACTH: **53,5** pg/mL (v.n.5-50)

Cortisolo: **28** µg/dL (v.n.5-25)

Aldosterone: 4,9 ng/dL

Renina: 5,1 mU/l

ARR: 0,96* (v.n. <3,2)

TSH: 1,15 mU/l

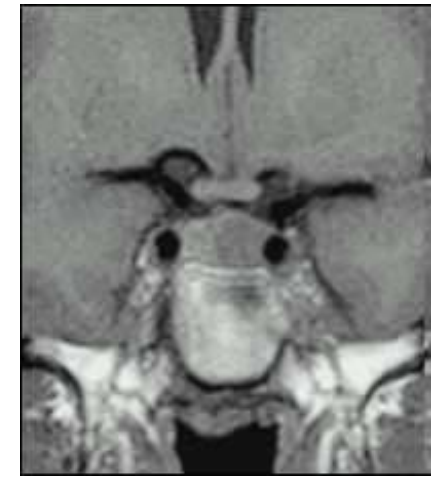
Test di Nugent 1 mg: mancata soppressione del cortisolo (26,4 µg/dL) (vn: < 1.8)

Endocrine Society, Guidelines JCEM, 2008

ACTH-Dipendent Cushing's syndrome…

Cushing's Disease

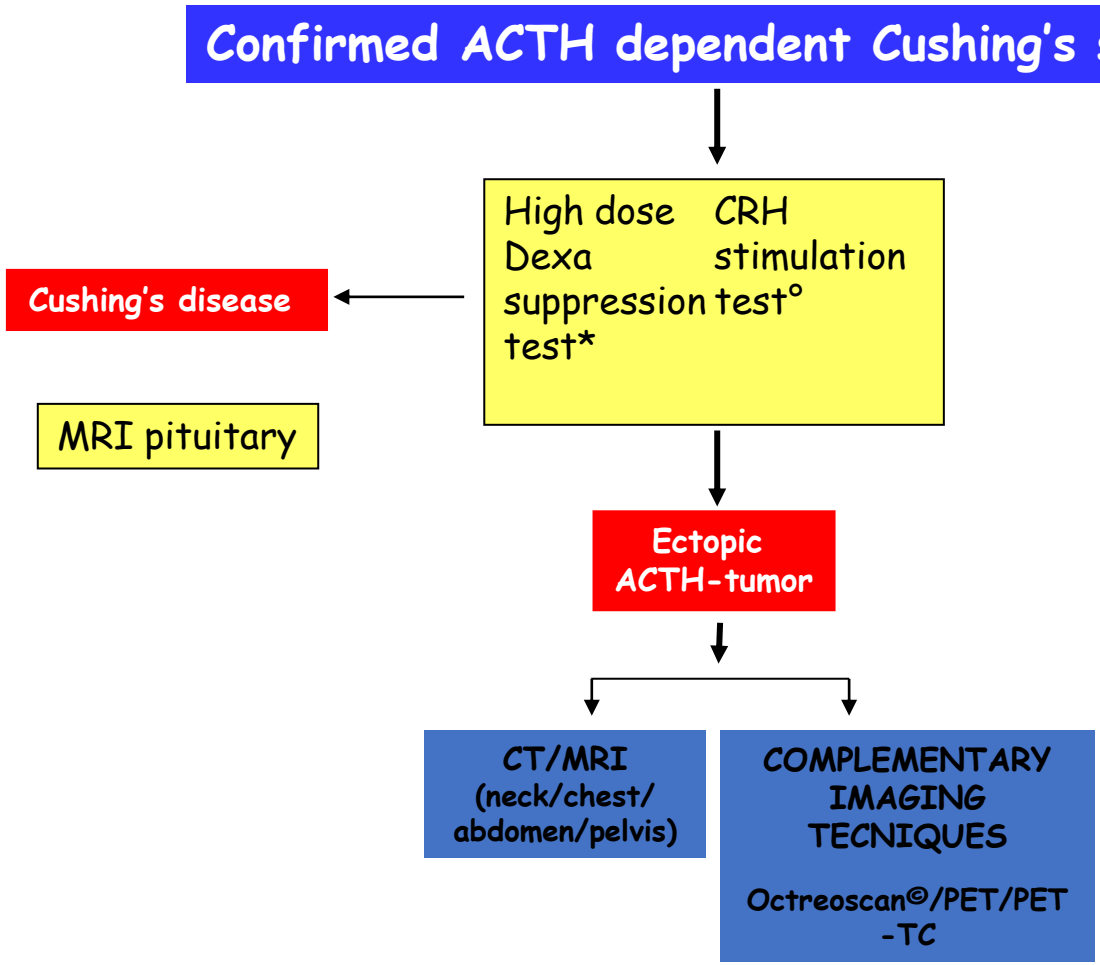
85-90%



Ectopic ACTH

10-15%

ACTH-Dipendent Cushing's syndrome…

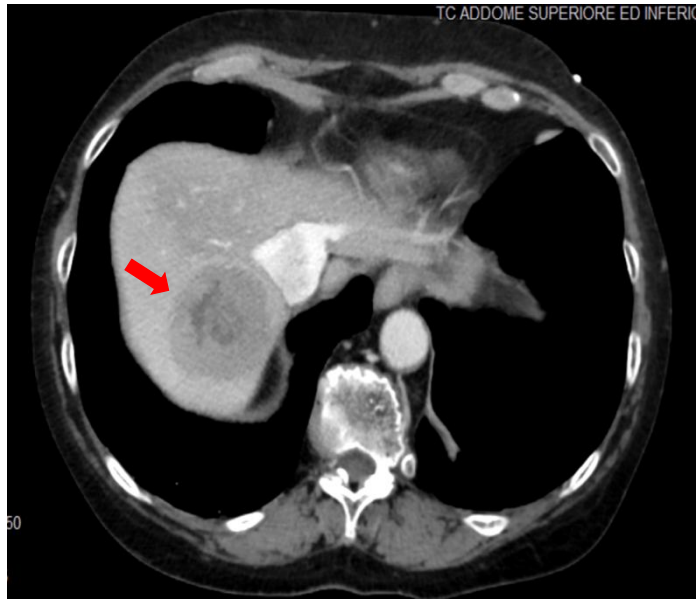


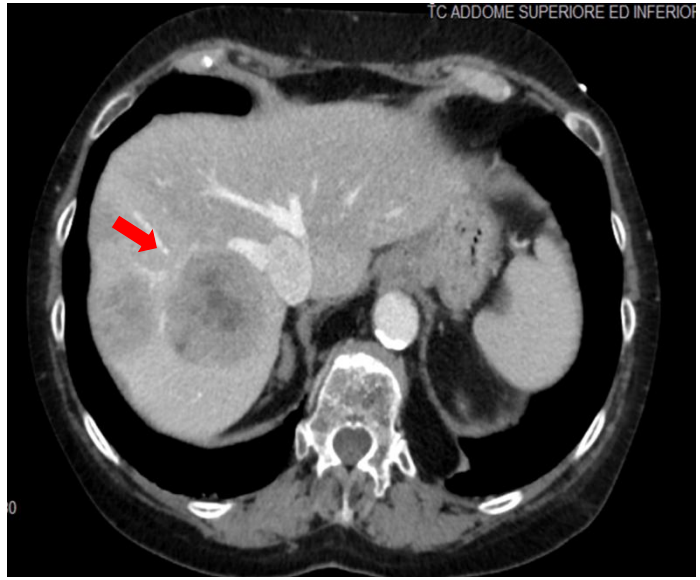
Test con desametasone ad alte dosi 8 mg: mancata soppressione del cortisolo: 20 µg/dL

CRH test: mancata risposta dell'ACTH allo stimolo

Endocrine Society, Guidelines JCEM, 2008

* Sensibilità 89% Specificità 100%
° Sensibilità 85% Specificità 95%





Possible, probable and confirmed NET

Possible? YES

Probable? YES

Confirmed?

Possible, probable and confirmed NET

Confirmed?

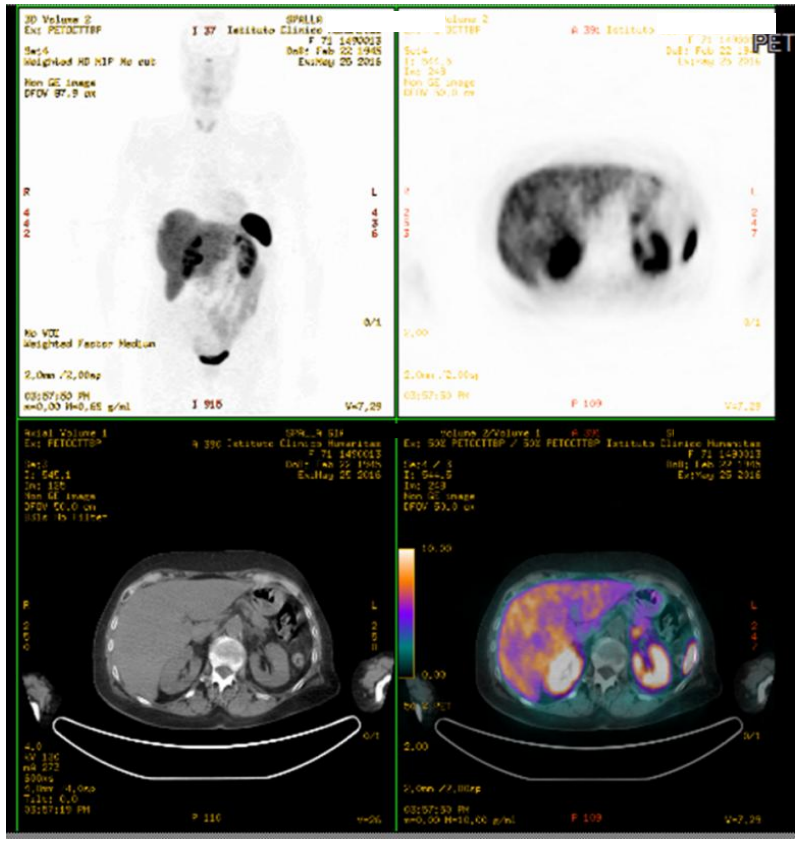
Biopsy

68 Gallium PET

Primary tumor?

Confirmed?

PET con ^{68}Ga



Captazione fisiologica del radiofarmaco

Possible, probable and confirmed NET

Liver biopsy

Proliferazione di elementi epitelioidi ad habitus neuroendocrino, privi di atipie e necrosi
Cromogranina A +
Sinaptofisina +
ACTH +/-
Ki67: 5%

Metastasi di Carcinoma neuroendocrino ben differenziato, G2 (NET G2)

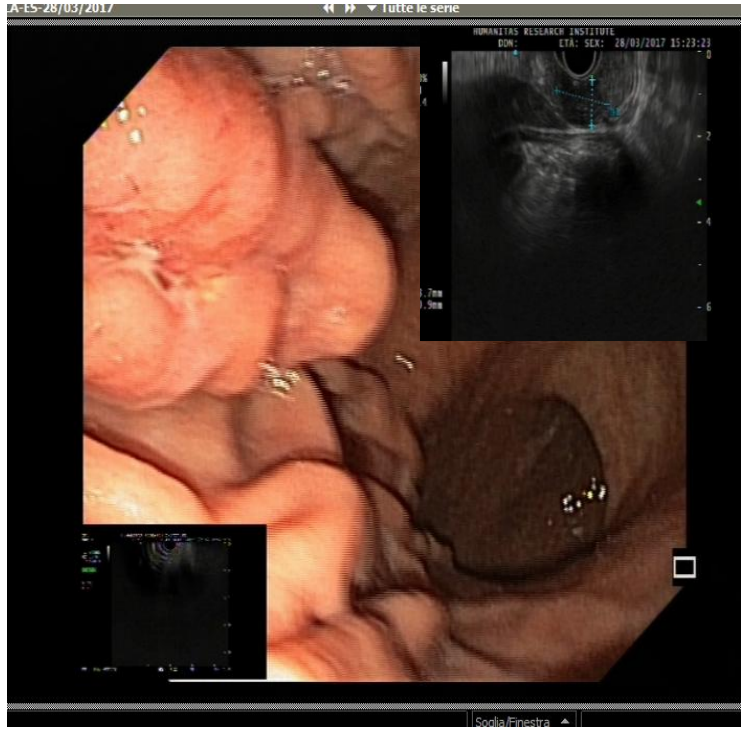
Causes of ectopic ACTH syndrome

Localization	Frequency % (No.)			
	Aniszewski et al., 2001	***Ilias et al., 2005***	***Isidori et al., 2005***	***Salgado et al., 2006***
Bronchial carcinoid	25% (26/106)	40% (35/90)	34% (12/35)	40% (10/25)
Pancreatic carcinoid	16% (17/106)	1% (1/90)	8% (3/35)	12% (3/25)
Small-cell lung cancer	11% (12/106)	3% (3/90)	6% (2/35)	nd
Thymic carcinoid	5% (5/106)	5% (5/90)	6% (2/35)	16% (4/25)
Unknown/occult	7% (7/106)	19% (17/90)	14% (5/35)	8% (2/25)
Other	36% (39/106)	32% (27/90)	32% (11/35)	24% (6/25)

Primary tumor?

Possible, probable and confirmed NET

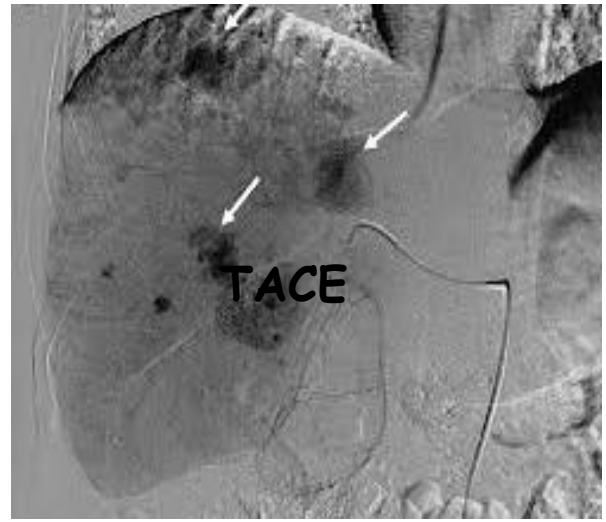
- **COLONSCOPIA → NEGATIVA**
- **EGDS**

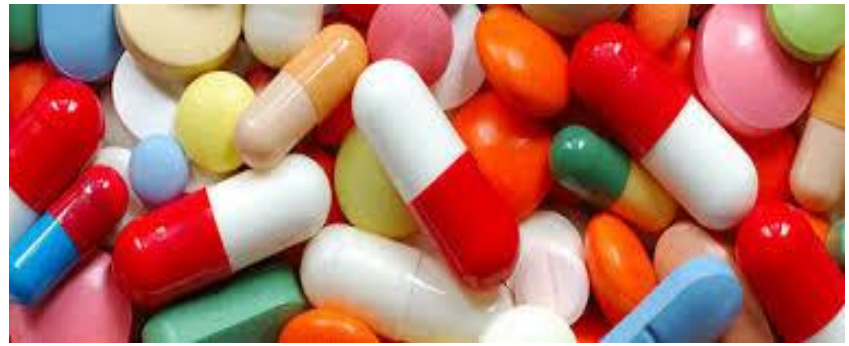


proliferazione, in lamina propria, di nidi di elementi epitelioidi ad habitus neuroendocrino
Cromogranina A +
Sinaptofisina +/-
ACTH +/-
Ki67: 5%

Carcinoma neuroendocrino ben differenziato, G2 (NET G2)

Quale sequenza terapeutica?



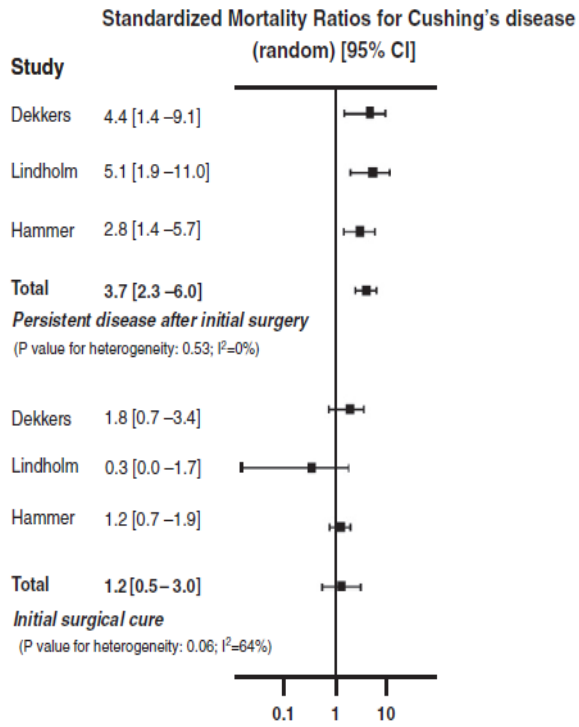


Original article

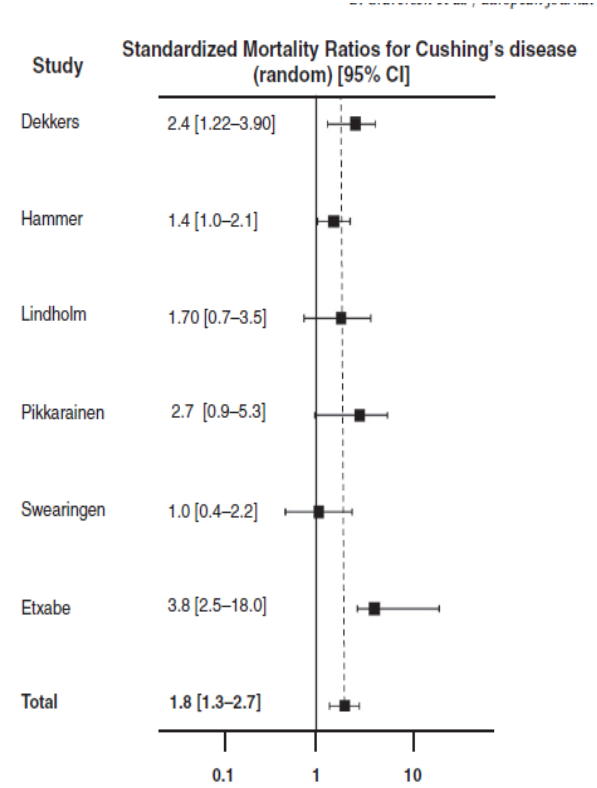
Mortality in Cushing's syndrome: A systematic review and meta-analysis

D. Graversen, P. Vestergaard, K. Stochholm, C.H. Gravholt, J.O.L. Jørgensen *

Department of Endocrinology and Internal Medicine (MEA), Aarhus University Hospital, Aarhus, Denmark



sub-analysis indicated that this excess mortality was confined to patients in whom remission after initial surgery was not achieved. Moreover, our study showed that mortality for patients with a benign cortisol producing adrenal adenoma did not differ significantly from the general population.



In this systematic review we observed a significant 84% increase in overall mortality in patients diagnosed with Cushing's disease compared to the general population matched for age and sex

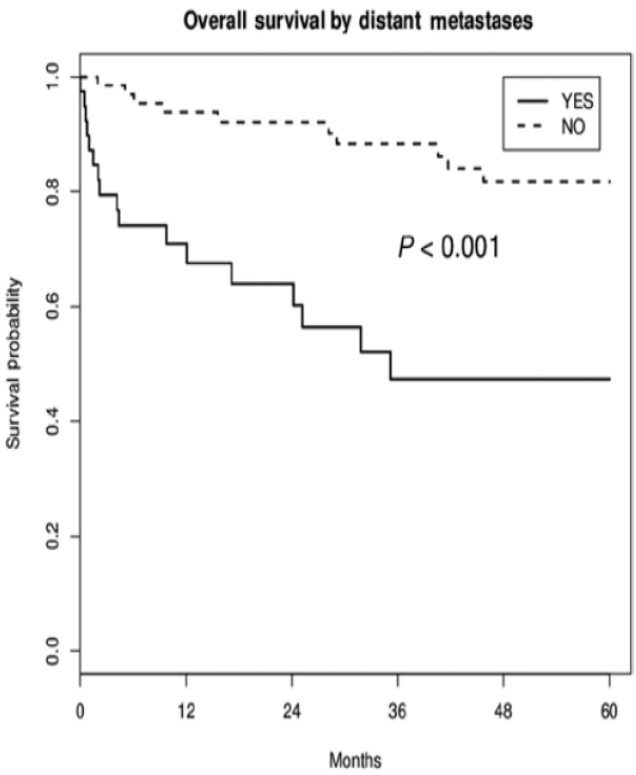
Diabete

Infezioni

Mortalità

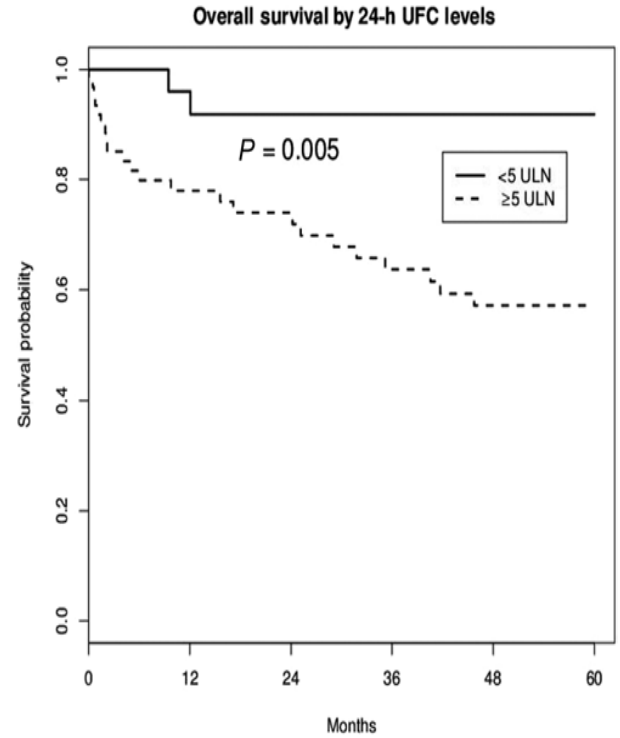
Ipokaliemia

Coagulopatie



Prognostic factors in ectopic Cushing's syndrome due to neuroendocrine tumors: a multicenter study

European Journal of Endocrinology
(2017) **176**, 453–461



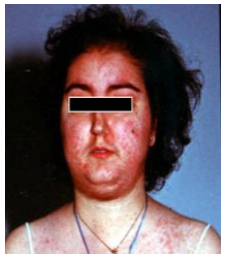
Patients with a higher increase in hormonal levels or a presence of hypokalemia and diabetes mellitus and those who did not perform surgery of the NET had a worse prognosis.

O'Riordain et al. found 5-year survival probability of 39%, with 73% of deaths related directly to metastatic malignant disease

Porterfield et al., in a group of 35 subjects reported 5-year survival probability of 51.3%

Ilias et al. demonstrated that subjects with an unknown/occult source survived longer compared with those with an identified tumour and that amongst those with identified tumour, patients with pulmonary EC (excluding small cell lung cancer) survived longest

Possible, probable and confirmed Cushing's syndrome



Diagnosi biochimica

Maggio '16

Diagnosi radiologica/AP

Giugno'16

Localizzazione primitivo

Terapia medica
Normalizzazione esami

Luglio '16

TAE

Ottobre/dicembre '16

SospensioneTerapia medica
Normalizzazione esami

Febbraio '17

Rimozione
Primitivo

Ottobre '17

Possible, probable and confirmed NET

Grazie a…


HUMANITAS


HUMANITAS


HUMANITAS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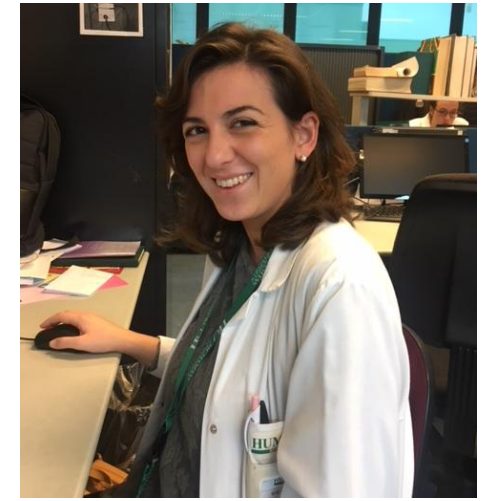

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