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

Maria Vittoria Davi'[1,*], Elisa Cosaro[1,*], Serena Piacentini[2,*], Giuseppe Reimondo[3], Nora Albiger[4], Giorgio Arnaldi[5], Antongiulio Faggiano[6,*], Giovanna Mantovani[7], Nicola Fazio[8,*], Alessandro Piovesan[9], Emanuela Arvat[9], Franco Grimaldi[10], Letizia Canu[11], Massimo Mannelli[11], Alberto Giacinto Ambrogio[12,13], Francesca Pecori Giraldi[12,13], Chiara Martini[14], Andrea Lania[15,*], Manuela Albertelli[16], Diego Ferone[17], Maria Chiara Zatelli[18], Davide Campana[19], Annamaria Colao[20,*], Carla Scaroni[4], Massimo Terzolo[3], Laura De Marinis[2,*], Sara Cingarlini[21,*], Rocco Micciolo[22] and **Giuseppe Francia[1,*]**

[1]Section of Endocrinology, Department of Medicine, University of Verona, Verona, Italy, [2]Endocrinology Unit, Catholic University of Sacred Heart, Policlinico A. Gemelli, Rome, Italy, [3]Internal Medicine, Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Italy, [4]Endocrinology Unit, Department of Medicine DIMED, University Hospital, Padua, Italy, [5]Clinica di Endocrinologia e Malattie del Metabolismo Ospedali Riuniti di Ancona, Ancona, Italy, [6]Thyroid and Parathyroid Surgery Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione G. Pascale' IRCCS, Napoli, Italy, [7]Endocrinology and Diabetology Unit, University of Milan, Milan, Italy, [8]Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, IEO, Milan, Italy, [9]Oncological Endocrinology Unit, Department of Medical Sciences, University of Turin, Turin, Italy, [10]Endocrinology, Diabetes, Metabolism and Clinical Nutrition Unit, University-Hospital S. Maria della Misericordia, Udine, Italy, [11]Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence, Florence, Italy, [12]Department of Clinical Sciences & Community Health, University of Milan, Milan, Italy, [13]Neuroendocrine Research Laboratory, Istituto Auxologico Italiano, Milan, Italy, [14]Internal Medicine, Department of Medicine, DIMED, University of Padova, Padova, Italy, [15]Department of Biomedical Sciences, Humanitas University and Endocrinology Unit, Humanitas Research Hospital, Rozzano, Italy, [16]Endocrinology, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy, [17]Endocrinology, Department of Internal Medicine (DiMI), IRCCS, AOU San Martino IST and Center of Excellence for Biomedical Research (CEBR), University of Genoa, Genoa, Italy, [18]Sezione di Endocrinologia e Medicina Interna, Department of Medical Sciences, University of Ferrara, Ferrara, Italy, [19]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, [20]Endocrinology Division, Department of Clinical Medicine and Surgery, Università di Napoli Federico II, Naples, Italy, [21]Oncology, University of Verona, Verona, Italy, and [22]Department of Psychology and Cognitive Sciences, University of Trento, Trento, Italy
*(ENETS Center of excellence)

Correspondence should be addressed to M V Davi'
Email mariavittoria.davi@aovr.veneto.it

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Abstract

Objective: Evidence is limited regarding outcome of patients with ectopic Cushing's syndrome (ECS) due to neuroendocrine tumors (NETs).
Design: We assessed the prognostic factors affecting the survival of patients with NETs and ECS.
Methods: Retrospective analysis of clinicopathological features, severity of hormonal syndrome, treatments from a large cohort of patients with NETs and ECS collected from 17 Italian centers.
Results: Our series included 110 patients, 58.2% female, with mean (±S.D.) age at diagnosis of 49.5 ± 15.9 years. The main sources of ectopic ACTH were bronchial carcinoids (BC) (40.9%), occult tumors (22.7%) and pancreatic (p)NETs (15.5%). Curative surgery was performed in 56.7% (70.2% of BC, 11% of pNETs). Overall survival was significantly higher in BC compared with pNETs and occult tumors ($P=0.033$) and in G1-NETs compared with G2 and G3 ($P=0.007$). Negative predictive factors for survival were severity of hypercortisolism ($P<0.02$), hypokalemia ($P=0.001$), diabetes mellitus ($P=0.0146$) and distant metastases ($P<0.001$). Improved survival was observed in patients who underwent NET removal ($P<0.001$). Adrenalectomy improved short-term survival.

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Conclusions: Multiple factors affect prognosis of ECS patients: type of NET, grading, distant metastases, severity of hypercortisolism, hypokalemia and diabetes mellitus. BCs have the highest curative surgical rate and better survival compared with occult tumors and pNETs. Hypercortisolism plays a primary role in affecting outcome and quality of life; therefore, prompt and vigorous treatment of hormonal excess by NET surgery and medical therapy should be a key therapeutic goal. In refractory cases, adrenalectomy should be considered as it affects outcome positively at least in the first 2 years.

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Introduction

Ectopic Cushing's syndrome (ECS) is a rare condition accounting for 10–20% of all cases of ACTH-dependent Cushing (1, 2). Neuroendocrine tumors (NETs), mainly bronchial carcinoids (BC) (3–54.8%), are the most frequent causes of ectopic ACTH secretion in more recent series (3, 4, 5, 6, 7, 8), whereas small-cell lung carcinoma (SCLC) represented the most common tumor associated with ECS in early series (3.3–50%) (9). Other less-frequent causes are thymic carcinoids (TC) (5–42%), pancreatic (p) NETs (7.5–25%), pheochromocytomas (2.5–25%) and medullary thyroid carcinomas (MTC) (2–8%) (3, 4, 5, 6, 7, 8). Unknown primary tumors account for 12–36.5% of all causes of ectopic ACTH production (3).

Available data on patients affected by ECS deriving from NETs are relatively scarce and outdated. The largest retrospective series is from the Mayo Clinic, including 106 patients followed between 1958 and 1986 (5). This study addressed the clinical characteristics, modalities of treatment and follow-up of the patients, without reporting on histopathological features and prognosis of the tumors. In the second most numerous retrospective study, data regarding performance of diagnostic tests, therapies, pathological examinations and survival of 90 patients from NIH between 1983 and 2004 were analyzed (6). It was found that 47% of the whole group, represented mainly by BC, underwent curative resection compared with 12% of the series from Mayo Clinic; patients affected by gastrinoma, MTC and SCLC displayed the poorest prognosis. In another series from the United Kingdom including 40 patients, those affected by BC had the highest surgical curative rate (83%), whereas the remainders needed adrenolytic therapy or adrenalectomy to control hypercortisolism (7). Histology and distant metastases were the main prognostic factors.

The aim of our study was to assess which factors affect survival on a large multicenter series of patients with NETs and ECS with complete clinical annotations.

Patients and methods

We did a retrospective analysis of data from patients with ECS from NETs collected in 17 Italian referral centers between 1986 and 2014, obtained by means of a specific questionnaire divided in different items. The study received the approval of the institutional ethical committees of each center.

Patients with diagnosis of ECS due to NETs were identified from the institutional database of patients of each center. Data were retrieved by medical personnel from medical records both in paper and electronic form. The centers were asked to report on all their series of patients with ECS due to NETs.

The diagnosis of ECS was based on a review of the patient's medical history, clinical features associated with cortisol excess and laboratory tests. These included increase in 24-h urinary free cortisol (UFC) levels in at least 2 samples, unsuppressed serum cortisol after 1 mg overnight dexamethasone suppression test (DST), loss of physiological cortisol diurnal rhythm with assessment of midnight plasma and/or salivary cortisol levels and increase in ACTH levels. To differentiate between pituitary and ectopic ACTH production, at least 2 of the following tests were performed: overnight 2, 8 mg DST, 100 µg CRH test and desmopressin test.

The first item of the questionnaire referred to the site of ACTH production, histological features of NET according to the 2010 WHO classification for gastroenteropancreatic (GEP) NETs (10) and to the 2004 WHO classification for lung carcinoids when applicable (11), proliferative activity by staining for the Ki-67 antigen or by mitotic count per 10 high-power fields, presence of local and distant metastases and association with inherited syndrome, such as multiple endocrine

Table 1 Clinicopathological characteristics of the patients.

	Source of ectopic ACTH *n* (%)	Age at diagnosis (years; mean ± S.D.)	Tumor diameter (mm; mean ± S.D.)	Symptom duration before diagnosis (months; mean ± S.D.)	Distant metastases, *n*/total *n* (%)	Lymph node metastases, *n*/total *n* (%)
BC	45 (40.9)	44.9 ± 16.6	23.4 ± 18	16.5 ± 24.5	9/36 (20)	20/45 (44.4)*
Occult tumors	25 (22.7)	55.4 ± 13.5*	–	18.5 ± 28.3	4/25 (16)	2/25 (8)
pNETs	17 (15.5)	48.3 ± 14.7	48.4 ± 34.7*	3.9 ± 5.6*	13/17 (76)*	8/17 (52.9)*
Pheochromocytomas	7 (6.4)	50.1 ± 17	26.5 ± 14	11 ± 8.5	0/7 (0)	0/7 (0)
TC	6 (5.5)	42 ± 14	57.4 ± 9.9*	11.6 ± 8.3	5/6 (83)*	3/6 (50)*
SCLC	4 (3.6)	69.7 ± 7.6*	33.3 ± 5.8	3.25 ± 2.1*	3/4 (75)*	2/4 (50)*
Intestinal NETs	3 (2.7)	66 ± 9	21.5 ± 13.4	13 ± 19.92	2/3 (66.7)	1/3 (33.3)
MTC	2 (1.8)	57.5 ± 3.5	30	6.5	1/2 (50)	2/2 (100)
SCCC	1 (0.9)	24	42	5	1/1 (100)	1/1 (100)

*$P < 0.05$.

BC, bronchial carcinoid; MTC, medullary thyroid carcinoma; NETs, neuroendocrine tumors; pNETs, pancreatic neuroendocrine tumors; SCCC, small cells cervical carcinoma; SCLC, small cells lung cancer; TC, thymic carcinoids.

neoplasia (MEN) type 1, MEN 2 and von Hippel–Lindau disease (VHL). Results from biopsy of the primary tumor or metastases were also reported when available.

Diagnosis of occult/unknown primary tumor was reserved for patients with clinical features of hypercortisolism and hormonal tests suggestive of an ectopic ACTH source including lack of central–peripheral ACTH gradient during inferior petrosal sinus sampling (IPSS), without primary tumor localization after prolonged and repeated imaging follow-up established by negative radiological and/or nuclear medicine procedures, and exclusion of other tumors known to cause ECS (12). In 2 cases of occult ECS of our series pituitary exploration had been performed in only 2 patients with occult tumors and ECS without the finding of any pituitary lesion.

Other items regarded clinical data, including type and duration of symptoms before ECS diagnosis, the biochemical and hormonal profile including serum potassium, 24-h UFC, serum cortisol at 08:00 h, at midnight and salivary if available, plasma ACTH, dynamic tests (overnight 1, 2, 8 mg DST, 100 µg CRH test, desmopressin test) and central–peripheral gradients of baseline and CRH-stimulated ACTH assessed during IPSS. Considering different assay techniques, hormonal levels were classified in 3 categories: up to 3-fold increase over the upper limit of normal (ULN) of the reference range of each center, between 3- to 5-fold increase and above 5-fold increase. Chromogranin A and neuron-specific enolase (NSE) levels were also collected when available. Other specific items were pituitary magnetic resonance imaging (MRI) and diagnostic imaging procedures performed to identify the NET, including radiological and nuclear medicine ones. Data regarding modalities of treatments for ECS (steroidogenesis inhibitors and adrenalectomy) and for tumor control (surgery of the NET, antiproliferative agents, transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE), radiofrequency ablation (RFA), selective internal radiation therapy (SIRT), peptide receptor radionuclide therapy (PRRT)) and results of treatment in terms of ECS control (complete or partial defined as UFC level above the ULN, but reduced by ≥50% from baseline) and survival were collected.

Statistical analysis

The results are expressed as means (±S.D.) or median. Two-sample Student's *t*-test was used to verify statistical differences between means, whereas χ^2 test to evaluate the association between categorical variables. Values of $P < 0.05$ were considered statistically significant. Survival probabilities were estimated employing the Kaplan–Meier method. Survival curves were compared employing the log-rank test. The joint prognostic role of considered variables was evaluated employing the Cox model. All the analyses were performed employing the software R (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing (Vienna, Austria)).

Table 2 Clinical features at diagnosis.

Clinical features at diagnosis	%
Hypertension	89.1
Diabetes mellitus	65.5
Proximal myopathy	70.9
Skin fragility	54.5
Osteoporosis	48.2
Psychiatric diseases	34.5
Hypercoagulability	30
Serum potassium <3.5 mEq/L	71.3

Table 3 Laboratory data.

Laboratory data	24-h UFC, *n*/total *n* (%)	08:00 h s-cortisol, *n*/total *n* (%)	08:00 h ACTH, *n*/total *n* (%)
Normal	2/93 (2.2)	18/105 (17.1)	5/102 (4.9)
<3 times ULN	19/93 (20.4)	68/105 (64.8)	48/102 (47.6)
3–5 times ULN	7/93 (7.5)	10/105 (9.5)	24/102 (23.5)
>5 times ULN	65/93 (69.9)	9/105 (8.6)	25/102 (24.5)

ACTH, adrenocorticotropic hormone; UFC, urinary free cortisol; ULN, upper limit of normal.

Results

Clinicopathological characteristics of the patients

The study included 110 patients (58.2% female) diagnosed with ECS from NET, with mean (±S.D.) age at diagnosis of 49.5±15.9 years. The clinicopathological characteristics of the patients are summarized in Table 1. The sources of ectopic ACTH were 45 (40.9%) BC (30 typical, 12 atypical and 3 not otherwise specified), 25 (22.7%) occult/unknown primary tumors, 17 (15.5%) pNETs, 7 (6.4%) pheochromocytomas, 6 (5.5%) TC, 4 (3.6%) SCLC, 3 (2.7%) intestinal (1 ileal, 1 caecal, 1 rectal) NETs, 2 (1.8%) MTC and 1 (0.9%) small-cell carcinoma of the cervix (SCCC).

Ki 67% or mitotic count was available in 54 NETs, allowing stratification in 3 groups: (1) G1 NETs characterized by Ki 67%/mitotic count of 0–2, including 17 typical BC, 3 pNETs, 1 pheochromocytoma (38.9% of patients); (2) G2 NETs characterized by Ki 67%/mitotic count of 3–20, including 9 atypical BC, 6 pNET, 3 TC, 1 pheochromocytoma, 1 caecal, 1 metastatic occult tumor; (38.9% of patients); (3) G3 NETs characterized by Ki 67%/mitotic count of >20 including 4 pNETs, 2 atypical BC, 2 metastatic occult tumors, 1 SCLC, 1 TC, 1 rectal NET and 1 SCCC (22.2% of patients). Immunostaining for ACTH was reported positive in 42/52 (84.6%).

Distant metastases were significantly ($\chi^2=40.9$; $P<0.001$) more prevalent in p-NETs (13/17, 76.5%), SCLC (3/4, 75%), TC (5/6, 83%) and atypical BC (6/12, 50%) than those in typical BC (4/30, 13.3%) and metastases from occult tumors (4/25, 16%). No pheocromocytoma was malignant. One out of 2 MTC had distant metastases. Lymph node metastases were present in 11/30 (36.7%) typical BC, 8/12 (66.7%) atypical BC, 8/17 (47%) pNETs, 3/6 (50%) TC, 2/25 (8%) occult tumors, 2/4 (50%) SCLC and 2/2 MTC (100%). These percentages were significantly different ($\chi^2=22.7$; $P=0.004$).

Clinical features at diagnosis are summarized in Table 2. No significant difference neither in the prevalence of symptoms nor in the number of symptoms was found among the type of NET subgroups.

The mean duration of symptoms before NET diagnosis was 13.1±21.2 months.

Two (1.8%) patients (1 with pNET and 1 with typical BC) were affected by MEN1 and 1 (0.9%) with pNET by Von Hippel–Lindau disease.

Laboratory data

Hypokalemia (serum potassium <3.5 mEq/L) was present in 72 (71.3%) patients. 24-h UFC was increased in 91/93 (97.8%) patients, s-cortisol at 08:00 h in 87/105 (82.9%) and ACTH in 97/102 (95.1%). In the 2 patients with normal 24-h UFC the diagnosis of ECS was made on the basis of at least other 2 altered tests. Serum cortisol at midnight was collected in 52/110 (47.3%) patients and was increased in all. No significant difference was observed in hormonal levels among the subgroups of NETs. A significant correlation was found between hormonal levels (s-cortisol, 24-h UFC and ACTH) and hypokalemia ($P<0.05$), but not between hormonal levels and clinical features. The laboratory data and the sensitivity of dynamic tests are summarized in Tables 3 and 4.

Diagnostic procedures

In all cases (45) in which pituitary MRI was carried out, no pituitary mass was found.

With regard to occult tumors, 21/25 patients had undergone computed tomography (CT), 8/25 patients MRI, 17/25, somatostatin receptor scintigraphy (SRS), 6/25 ^{18}F-FDG-PET/CT, 4/25 ^{68}Ga-DOTA-peptide PET/CT, 17/25 radiological imaging (CT/MRI) plus a functional

Table 4 Sensitivity of dynamic tests.

Dynamic tests	*n*/total *n* (%)
Overnight 1 mg DST (not suppressed)	63/63 (100)
2 mg DST (not suppressed)	13/13 (100)
HDDST (not suppressed)	60/70 (85.7)
CRH test (no response)	55/58 (94.8)
Desmopressin test (no response)	20/26 (76.9)
IPSS (no gradient at baseline and after CRH)	25/28 (89.3)

CRH, corticotropin-releasing hormone; DST, dexamethasone; HDDST, high dose dexamethasone suppression test; IPPS, inferior petrosal sinus sampling.

imaging (SRS/PET) and 1 colonoscopy. In 4 cases (3 typical BC and 1 TC), the NET was found after a mean time of 4 years (range 3–5 years) from the ECS diagnosis by CT scan in all, ^{68}Ga-DOTA-peptide PET/CT in 2 and SRS in 1. Two of them had been submitted to adrenalectomy as first therapeutic choice.

The prevalence of occult tumors among patients recruited in the period between 2006 and 2014 decreased (17.2%), compared with those recruited in the previous periods (25% between 1986 and 1994 and 32.4% between 1995 and 2005).

Medical treatment of ECS

The majority of patients (78/110, 70.9%) were treated with steroidogenesis inhibitors, even in combination (ketoconazole in 69/78 (88.5%), mitotane in 13/78 (16.7%) and metyrapone in 5/78 (6.4%)). Other drugs were the glucocorticoid receptor antagonist mifepristone in 1 (0.9%), cabergoline in 8 (7.3%) and somatostatin analogues (SA: lanreotide or octreotide LAR) in 60 (54.5%). In 59/110 (53.6%) patients, each drug was given alone, whereas in 51/110 (46.4%) in combination, the most used being ketoconazole plus SA (41 patients) or mitotane plus SA (11 patients). Steroidogenesis inhibitors were used before surgery in 33/60 patients (55%) and after surgery in 4/60 (6.6%). Complete hormonal control was achieved in 15/51 (29.4%) and partial control in 36/51 (70.6%) patients who received only medical treatment.

Surgical treatment of the NET and adrenalectomy

Sixty out of 110 (54.5%) patients underwent etiologic surgery: 37/45 (82.2%) BC (8 atypical, 26 typical, 3 unspecified), 9/17 (52.9%) pNET, 5/6 (83.3%) TC, 5/7 (71.4%) pheocromocytomas, 1 SCCC, 1 ileal NET, 1 MTC and 1 patient who resulted as a false positive. Curative surgery was obtained in 34/60 (56.7%): 26/37 (70.2%) BC (21 typical, 4 atypical, 1 not otherwise specified), 1/9 (11.1%) pNETs, 5/5 pheocromocytomas (100%), 1 TC, 1 ileal NET. In 8 ECS relapsed (4 typical BC, 1 atypical BC, 2 BC not otherwise specified, 1 pNET), after a mean time of 5.2 years from surgery. Palliative surgery, i.e. resection of the primary in the presence of distant metastases was performed in 16/60 patients (26.6%), of whom 1 typical BC, 3 atypical BC, 4 TC, 7 pNETs and 1 SCCC.

Thirty-one (28.2%) patients underwent adrenalectomy: 18 as primary treatment (5 BC, 1 TC, 4 pNETs, 8 occult tumors) and 13 following other treatments (4 BC, 3 pNETs, 2 TC and 4 occult tumors). Five out of 31 patients (2 pNETs, 1 BC, 1 TC and 1 occult tumor) underwent monolateral adrenalectomy due to poor clinical conditions with the intent of 2-step adrenalectomy. The prevalence of patients who underwent adrenalectomy was significantly higher in occult tumors and p-NETs compared with BC (48% and 41.2% vs 20%, $P=0.038$).

Antineoplastic treatment

As additional therapy, 8 (7.3%) patients (1 BC, 1 TC, 5 pNETs and 1 occult tumor) received Everolimus and 1 (0.9%) patient (pNET) Sunitinib. Chemotherapy was performed in 27 (24.5%) patients including strepto/doxo/5FU in 3 patients (1 atypical BC, 1 TC and 1 pNET), etoposide/cisplatin in 14 patients (2 atypical BC, 2 SCLC, 3 TC, 4 pNETs, 1 SCCC, 2 occult tumors) and temozolomide/capecitabine 10 patients (1 typical BC, 1 atypical BC, 1 TC, 5 pNETs, 1 occult tumor and 1 caecal NET). Chemotherapy was administered alone in 12 (44.4%) patients, in combination with surgery of the NET in 12 patients and after tumor relapse in 3 (11.1%) patients.

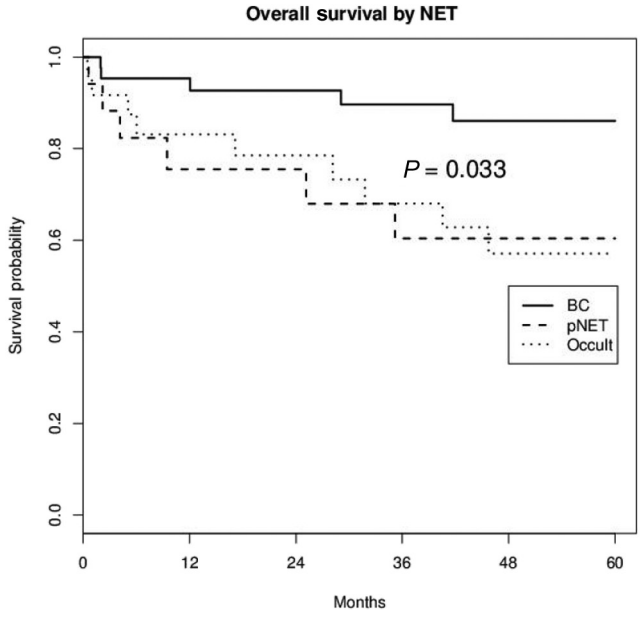

Figure 1

Overall survival by neuroendocrine tumor (NET). BC, bronchial carcinoid; pNET, pancreatic NET, occult tumor. Number of patients at risk at 12, 24, 36, 48 and 60 months are 36, 32, 27, 24, 21 (BC), 11, 10, 8, 6, 4 (pNET), 18, 16, 13, 10 and 10 (occult tumor). Survival probabilities were estimated employing the Kaplan–Meier method. Survival curves were compared employing the log-rank test.

TACE/TAE of liver metastases were performed in 5 (4.5%, all pNETs) patients, RFA in 3 (2.7%) of whom 2 pNET, 1 BC and SIRT in 1 (0.9%) BC. PRRT was carried out in 13 (11.8%) (6 BC, 2 TC and 5 pNETs) of whom 10 (76.9%) obtained a partial or complete ECS control.

Follow-up and survival rate

Considering the whole population of 110 patients, the median follow-up (from diagnosis to last evaluation) was 60 months. During the follow-up period, 30 patients died: 18 patients (2 typical BC, 2 atypical BC, 2 TC, 5 pNETs, 1 caecal, 1 SCCC, 1 MTC and 4 occult tumors) due to tumor progression, 11 patients (2 typical BC, 2 SCLC, 2 pNETs, 1 rectal and 4 occult tumors) due to the consequences of cortisol excess (4 respiratory failure secondary to thromboembolism or pneumonia, 1 acute myocardial infarction, 5 septic shock and 1 severe hypokalemia) and 1 patient with occult tumor died for breast adenocarcinoma.

The overall survival (OS) was: 84% at 1 year of follow-up, 81% at 2 years, 74% at 3 years and 70% at 4 and 5 years.

Patients aged ≥60 years at diagnosis had a worse prognosis than younger patients (5-year OS 52% vs 81% <40 year and vs 77% between 40 and 59 years old at diagnosis, $P=0.016$).

There was no statistically significant difference in OS according to gender and period of diagnosis.

The 5-year OS rate for BC was significantly higher than that for pNETs and occult tumors (86% vs 60% for latter groups, $P=0.033$) (Fig. 1). With regard to the histologic grade, there was a significant trend toward worsening of 5-year OS for G1, G2 and G3-NETs (87.7, 72.4 and 37% respectively; $P=0.007$).

Patients with metastases had a poorer prognosis than those without (5-year OS: 79% vs 61%, $P=0.019$). This was true in particular for patients with distant metastases (5-year OS: 82% vs 47%, $P<0.001$) (Fig. 2).

Considering the s-cortisol levels, a worse survival rate was found in the group with >3-fold increase compared with the groups with up to 3-fold increase ($P<0.001$). Similarly for 24-h UFC and ACTH, patients with >5-fold increase had a worse survival rate compared with patients with up to 5-fold increase ($P=0.005$ and $P=0.01$ respectively) (Fig. 3).

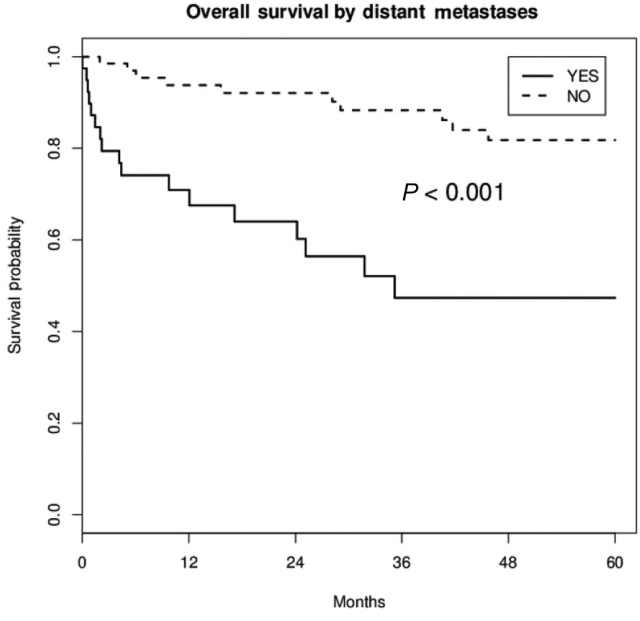

Figure 2

Overall survival by distant metastases. Number of patients at risk at 12, 24, 36, 48 and 60 months are 21, 17, 10, 9, 7 (Yes), 57, 52, 45, 37 and 31 (No). Survival probabilities were estimated employing the Kaplan–Meier method. Survival curves were compared employing the log-rank test.

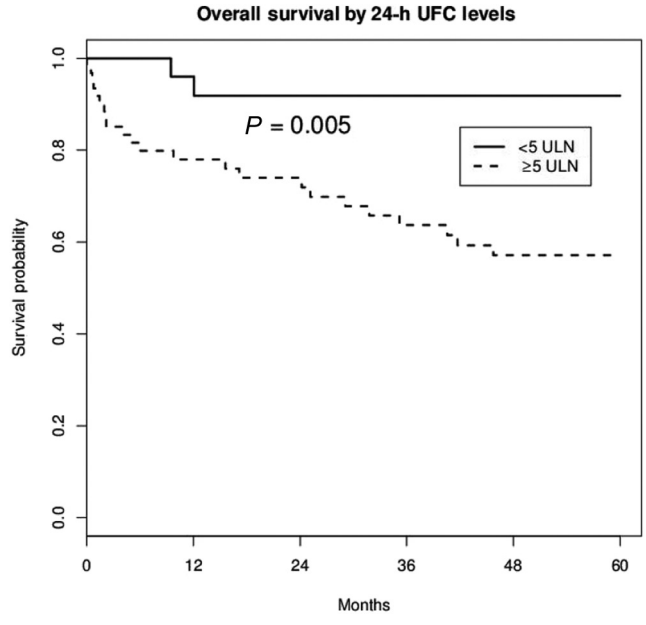

Figure 3

Overall survival by 24-h UFC levels. UFC, urinary free cortisol; ULN, upper limit of normal. Number of patients at risk at 12, 24, 36, 48 and 60 months is 23, 20, 16, 14, 11 (up to 5 ULN), 40, 36, 32, 26 and 21 (>5 ULN). Survival probabilities were estimated employing the Kaplan–Meier method. Survival curves were compared employing the log-rank test.

The presence of hypokalemia (<3.5 mEq/L) ($P=0.001$) and diabetes mellitus ($P=0.0146$) were negative prognostic factors.

Patients who underwent etiologic surgery had a better survival rate than those who did not (5-year OS 85% vs 51%, $P<0.001$) (Fig. 4). Patients who underwent adrenalectomy had a better survival rate in the first 2 years compared with those who did not. During the first 2 years of follow-up, there were no deaths in the former group vs 18 deaths in the latter, with a 2-year overall survival of 74%, although the 5-year OS was not significantly different (76% vs 68%, $P=0.168$).

The Cox model was employed to evaluate the joint effect of the following variables: age at diagnosis, distant metastases, NET surgery, adrenalectomy, Ki-67 and 24-h UFC. A significance prognostic role ($P<0.001$) was found for distant metastases and NET surgery. For the first variable the hazard ratio (yes vs no) was 5.4 (95% CI: 2.2–13.3), whereas for the second (no vs yes) was 6.1 (95% CI: 2.4–15.7). Also the ≥5-fold increase over ULN of 24-h UFC was significantly associated with worse prognosis ($P=0.012$); the estimate of the hazard ratio was 6.5 (95% CI: 1.5–28.2).

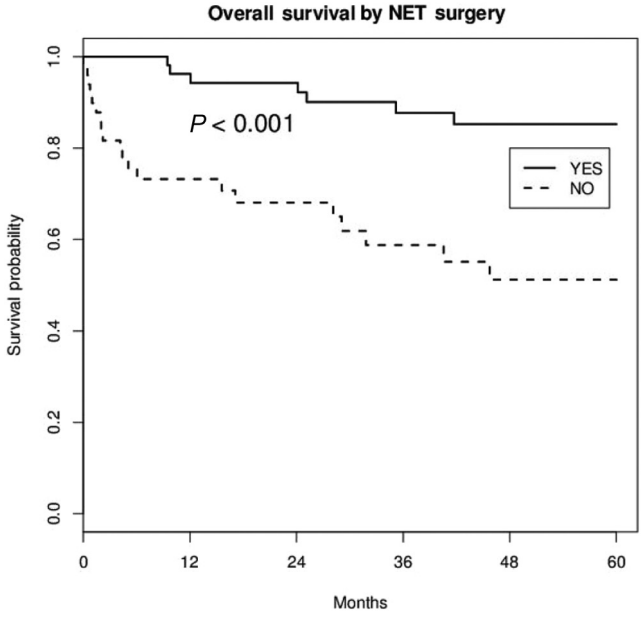

Figure 4

Overall survival by neuroendocrine tumor (NET) surgery. Number of patients at risk at 12, 24, 36, 48 and 60 months is 49, 46, 37, 33, 26 (Yes), 29, 23, 18, 13 and 12 (No). Survival probabilities were estimated employing the Kaplan–Meier method. Survival curves were compared employing the log-rank test.

Discussion

The aim of our study was to assess the factors affecting survival in patients with ECS due to NETs. The strengths of our study are the sample size, the largest up to now reported and the complete clinical annotation of our patients allowing assessment of factors never previously examined on a large scale. We acknowledge the limitation of the retrospective and multicenter nature of the study.

The major finding of our study is that the severity of cortisol excess impacts on survival. Hypercortisolism causes severe comorbidities due to its effects on glucose and lipid metabolism, the cardiovascular system, skeletal turnover and the immune system (13, 14, 15, 16). It is known that the consequences of hypercortisolism can lead to the death of the patient, sometimes more rapidly than tumor progression (17, 18). However, until now, the correlation between cortisol excess and survival had not yet been demonstrated on a large scale. We have herein shown that the severity of cortisol excess significantly affects overall survival and that the increase in 24-h UFC is an independent negative prognostic factor. This is a key clinical message for an appropriate management of ECS, prompting that a vigorous control of the hormonal syndrome should be one of the main therapeutic goals. Our results show that the outcome of patients with ECS did not improve over the 30 years of the study. As hypercortisolism is among the major causes of a poor prognosis in these patients, it seems advisable to actively counteract it with a more rapid and effective medical therapy or, in case of failure, an early bilateral adrenalectomy.

Our study also demonstrates how tumor grading and staging affect the prognosis of these patients. This is the first study to demonstrate that survival is progressively and significantly improved for moderate and well-differentiated NETs compared with that for poorly differentiated NETs. Overall survival was significantly worse for patients with distant metastases, as already shown in other studies (7, 8).

Considering the site of the primary tumor, BCs were confirmed to be the most prevalent source of ectopic ACTH, as reported in the most recent series (5, 6, 7, 8). Typical BCs were more frequent than atypical BC (66% vs 26.6%) and showed a more favorable behavior with less lymph node and distant spread (36.7% vs 66.7% and 13% vs 50% respectively). Surgery was curative in a high proportion of patients with BC (70.2%) even in the presence of positive lymph nodes without the need of post-operative mediastinal radiotherapy.

Moreover, BC showed a significantly better survival rate compared with that of pNETs and occult tumors. The favorable survival rate of BC compared with other ACTH-secreting tumors had already been observed in other studies (6, 7, 19). Conversely, survival rate of occult tumors in our series was poorer than that of BC and similar to that of pNET, in contrast to the results reported by Ilias *et al*. (6). Pancreatic NETs were the most frequent source of ECS among GEP-NETs; they were usually of great size with distant metastases. The majority of pNETs (9/13) were well differentiated (G2 and G1) as found in a recent report (20). These tumors did not have distinctive histological features compared with pNETs without ECS; however, they displayed signs of aggressiveness including vascular and perineural invasion. In our study, the outcome of pNETs was worse compared with that of BC, with a lower curative surgical rate (11% vs 70.2%) and a lower 5-year OS (60% vs 86%).

A significant percentage of tumors in our series (22.7%) remained occult after diagnostic work-up.

There is a current debate on the possibility of the presence of Cushing's disease in the patient with negative IPSS without evidence of ectopic tumor (21). In only 2 cases of our series, pituitary exploration had been performed without the finding of any pituitary lesion. The majority of our centers did not routinely perform surgical exploration of the pituitary in the presence of concordant dynamic tests for ECS and negative IPSS.

Only 4/25 patients had undergone ^{68}Ga-DOTA-peptide PET/CT, which is known to be highly sensitive in detecting NETs due to the limited and only recent availability among the centers. Some BC may be too small to be identified by CT scan or show heterogeneity of SSTR expression preventing them from being visualized by SRS (22). It is worth noting that in some cases, the negative somatostatin receptor scintigraphy or ^{68}Ga-DOTA-peptide PET/CT can be due to downregulated SSTR expression after long-term exposure to hypercortisolism (23, 24).

The survival rate of patients with occult tumors and ECS was similar to that of patients with pNETs but worse than that of patients with BC due to the metastatic spread or the consequences of hypercortisolism. Only one third of the patients (8/25) with occult tumors underwent adrenalectomy as first treatment. In our series, 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. Furthermore, patients who underwent adrenalectomy had a better survival rate at least in the first 2 years, highlighting the importance of prompt control of hypercortisolism. Nowadays, laparoscopic adrenalectomy is a safe and minimally invasive surgical treatment (25); thus, it should be considered more frequently as an option in the management of ECS, in particular in early stages, when the hormonal syndrome is not controlled by medical treatment and/or persists after surgical removal of the primary tumor.

Concerning the outcome of medical therapy, the variability of treatments employed did not allow us to draw a definitive conclusion.

In our experience, PRRT was an effective therapeutic option when SRS or ^{68}Ga-DOTA-peptide-PET/CT is positive, attaining partial or complete hormonal control in 76.9% of patients.

Conclusions

Several factors have an impact on prognosis of patients with ECS, namely, NET type, grading, presence of distant metastases, severity of hypercortisolism, hypokalemia and diabetes mellitus. BCs have the highest curative surgical rate and better survival than occult tumors, which still account for 23% of cases, and pNETs. Cortisol excess plays a major role in affecting duration and quality of life; therefore, a prompt treatment directed toward the primary tumor and inhibiting adrenal function is a key therapeutic goal. In refractory cases, adrenalectomy should be considered as it affected positively patients' outcome at least in the first 2 years.

Declaration of interest

M V D, E C, S P, N A, G M, A P, E A, F G, L C, M M, A G A, F P G, C M, A L, M A, D F, M C Z, D C, C S, L D M, S C, R M and G F have nothing to disclose. G R received research grants from Novartis and Shire; G A received research grants from Novartis and Shire; speaker fees from Novartis, consulting fees from Novartis and Pfizer, Inc. as a board member; A F received speaker fees from Novartis and Ipsen; N F is a member of Novartis and Ipsen Advisory Board; A C received research grants from Novartis, received speaker fees from Novartis and Ipsen, is a member of Novartis and Ipsen Advisory Board; M T is a member of HRA Pharma Advisory Board and received HRA Pharma research grant.

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