

CLINICAL STUDY

Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up

G Ntali, A Asimakopoulou¹, T Siamatras, J Komninou, D Vassiliadi¹, M Tzanela¹, S Tsagarakis¹, A B Grossman, J A H Wass and N Karavitaki

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK and ¹Department of Endocrinology, 'Evangelismos' General Hospital, Athens, Greece

(Correspondence should be addressed to N Karavitaki; Email: niki.karavitaki@ouh.nhs.uk)

Abstract

Objective: In this study, we aim to assess the long-term survival and causes of death in a retrospective cohort study on patients with all aetiologies of endogenous Cushing's syndrome (CS) (except adrenal cancer), presenting to two large tertiary endocrine referral centres, and to identify variables predicting mortality.

Subjects and methods: The records of all patients presenting with endogenous CS in the Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK and the Department of Endocrinology, 'Evangelismos' General Hospital, Athens, Greece between 1967–2009 (Oxford series) and 1962–2009 (Athens series) were reviewed. The standardised mortality ratio (SMR) was calculated for the Oxford series.

Results: In total, 418 subjects were identified (311 with Cushing's disease (CD), 74 with adrenal Cushing's (AC) and 33 with ectopic Cushing's (EC)). In CD, the probability of 10-year survival was 95.3% with 71.4% of the deaths attributed to cardiovascular causes or infection/sepsis. SMRs were significantly high overall (SMR 9.3; 95% CI, 6.2–13.4, $P < 0.001$), as well as in all subgroups of patients irrespective of their remission status. In AC, the probability of 10-year survival was 95.5% and the SMR was 5.3 (95% CI, 0.3–26.0) with $P = 0.2$. Patients with EC had the worst outcome with 77.6% probability of 5-year survival.

Conclusions: In this large series of patients with CS and long-term follow-up, we report that in CD the mortality is significantly affected, even after apparently successful treatment. The SMR of patients with AC was high, but this was not statistically significant. The implicated pathophysiological mechanisms for these findings need to be further elucidated aiming to improve the long-term outcome.

European Journal of Endocrinology 169 715–723

Introduction

Endogenous Cushing's syndrome (CS) is a rare condition resulting from a heterogeneous group of disorders leading to adrenocorticotrophin (ACTH)- or non-ACTH-dependent cortisol hypersecretion. The association of chronic hypercortisolaemia with a number of morbidities has been well established (e.g. central obesity, insulin resistance and abnormalities in glucose metabolism, hypertension, dyslipidaemia, hypercoagulability, osteoporosis and neuropsychiatric disorders) (1, 2, 3, 4, 5, 6, 7), and if left untreated it has a major negative impact on survival (8). Furthermore, even after successful treatment, a number of complications and risks may persist (1, 3, 4, 7, 9, 10, 11), raising concerns regarding the long-term mortality of these patients.

Most of the studies published looking at the survival of patients with endogenous hypercortisolaemia have focused on Cushing's disease (CD) with standardised mortality ratios (SMRs) between 0.98 and 4.8 and

with 95% CI ranging between 0.44 and 8.3 (2, 3, 11, 12, 13, 14, 15, 16, 17). The small number of patients (as a result of the rarity of CD) or limited follow-up, the inclusion of patients from large neurosurgical centres only and the variable criteria used for the definition of remission are the factors posing difficulties in the interpretation of the published data. Furthermore, it is essential to clearly discriminate between patients who are in remission, and those with persistently active disease: it is generally agreed that persistent disease activity is associated with diminished survival. However, there is no consensus as to whether the SMR is significantly higher than expected in patients in maintained remission, although a recent meta-analysis proposed that overall the mortality of patients with CD is double of that of the general population (17). Furthermore, a recently published large series of patients with CS showed that mortality is twice as high in the CS patients compared with controls, and that in particular the risk of myocardial infarction remained elevated

during long-term follow-up (7). On the other hand, series providing survival data on ectopic (EC) or adrenal Cushing's (AC) aetiologies are very limited, showing high mortality for EC (18, 19) with no agreement for AC (7, 14, 15, 18, 20).

The objectives of our study were to assess the long-term survival/outcome and causes of death in a large series of patients with all aetiologies of endogenous CS (except adrenal cancer), presenting in two large tertiary endocrine referral centres covering two distinct geographical populations (Oxford, UK and Athens, Greece) over a period of more than four decades, and to identify variables predicting mortality, and particularly the impact of remission on survival.

Subjects and methods

The records of all patients presenting with endogenous CS in two tertiary referral centres (Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism (Oxford, UK) and Department of Endocrinology, 'Evangelismos' General Hospital (Athens, Greece)), between 1967–2009 (Oxford series) and 1962–2009 (Athens series) were reviewed retrospectively. Patients with adrenocortical carcinoma were excluded. The study was approved by the local Ethics Committees.

The biochemical diagnosis of endogenous CS was based on the presence of relevant clinical features combined with at least one abnormal biochemical test (elevated 24-h urine cortisol or urinary corticosteroids, lack of suppression of serum cortisol on low-dose dexamethasone suppression testing or absence of serum cortisol diurnal variation). The confirmation of the diagnosis of CD was based on the demonstration of a corticotroph adenomas following pituitary surgery, or on the development of hypoadrenalism or improvement/resolution of clinical and biochemical abnormalities after pituitary surgery or pituitary radiotherapy, or on the development of Nelson's syndrome after bilateral adrenalectomy. The diagnosis of EC was based on confirmation of ACTH-dependent CS in combination with abnormal responses to tests as per local protocols (including lack of cortisol suppression on the high-dose dexamethasone suppression testing, lack of cortisol/ACTH response to the corticotrophin-releasing hormone (CRH) test, an absence of an ACTH gradient on bilateral inferior petrosal sinus sampling) and positive pathology in cases in which surgical removal or diagnostic biopsies were performed. Those with no identified neuroendocrine tumour at the most recent imaging were considered to have occult EC. The diagnosis of AC was based on a suppressed 0900 h plasma ACTH levels in the absence of exogenous corticosteroid use and pathology confirming an adenoma following adrenalectomy.

Remission of hypercortisolaemia was defined as an 'undetectable' 0900 h serum cortisol (according to local

assays) after pituitary surgery, adrenalectomy or removal of an ectopic ACTH-producing tumour (in such a case, the patient was put on a replacement dose of hydrocortisone with regular assessments for the recovery of the ACTH axis). Remission following pituitary radiotherapy was considered if the patient had achieved normal 24 h urine cortisol levels or a mean serum cortisol in the range 150–300 nmol/l on a 5-point cortisol day curve or had developed ACTH deficiency and during medical treatment, if the patient had achieved a mean serum cortisol 150–300 nmol/l on a 5-point day curve. The diagnosis of recurrence relied on clinical and biochemical (elevated 24-h urine cortisol and lack of suppression of serum cortisol on overnight or low dose dexamethasone suppression tests) evidence. During their follow-up, the patients were assessed clinically and biochemically (as per local protocols, including 0900 h serum cortisol after omitting evening and morning dose of hydrocortisone, overnight or low dose dexamethasone suppression tests, 24-h urine cortisol, mean serum cortisol on 5-point cortisol day curve, dynamic assessment of the adrenal reserve). Follow-up duration was defined from the time of biochemical diagnosis until last clinical and/or biochemical assessment or death. For patients not under the follow-up in the two centres, referring endocrinologists or general practitioners (GPs), were contacted to obtain information at last assessment. Demographic data, treatment modalities and morbidities at diagnosis and at last assessment, as documented in the medical records of the patients, were collected.

For the Athens series, mortality data were retrieved from the hospital records, and for the Oxford series, through the National Health Service Central Register and from the hospital records. The survival curves were generated by the Kaplan–Meier method and differences in the survival of various subgroups were checked by the log-rank test. Cox regression analysis was used to assess the effect of various parameters on survival. The frequency of morbidities at diagnosis and last follow-up were compared by the McNemar's test. SMRs were calculated for the Oxford series as the ratio of observed over expected deaths (status was recorded as either dead or alive, as of 31 December 2009). The expected number of deaths was estimated by multiplying age, sex, calendar year-specific mortality rates for the general population of England and Wales by the corresponding person-years at risk amongst the CD, AC and EC patients (21). SMRs were not estimated for the Athens series as the population normative values are unavailable and not all deaths were recorded until the time the database was 'frozen' (31 December 2009). The level of significance was set at $P < 0.05$. Statistical advice was offered by experts from the Department of Statistics, Oxford University and from Harokopio University, Athens. Statistical analyses were performed by SPSS 19.0 for Windows (SPSS, Inc.).

Results

Characteristics of the patients

After excluding patients with CS attributed to adrenal cancer, 418 subjects were identified. Their characteristics are shown in Table 1.

CD series

The treatment modalities offered to the CD patients during their follow-up period are shown in Table 2. Amongst those who had transsphenoidal adenectomy (TSA) as an initial treatment, an undetectable (usually < 50 nmol/l) post-operative 0900 h serum cortisol was found in 56.5% (138/244) (Oxford series 62.3% (99/159), Athens series 45.8% (39/85)). In this group, relapse of CD was diagnosed in 13% (18/138) (Oxford series 9% (9/99) – median time of diagnosis after surgery 8.5 years (0.5–18), Athens series 23% (9/39) – median time of diagnosis after surgery 7 years (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)). At last

assessment, 235 patients were in remission (76.5% – four patients with no information on their cortisol status were excluded from the evaluation). Nelson's syndrome was diagnosed in 37 patients (45% (37/82) of those who had adrenalectomy (Oxford series 40%, Athens series 50%)).

At diagnosis, 151/311 (49%) of the patients had documented hypertension, 67/311 (22%) impaired glucose tolerance/diabetes mellitus type 2, 88/311 (28%) depression and 27/311 (9%) a history of cardiovascular disease. At last assessment, the frequency of hypertension, impaired glucose tolerance/diabetes mellitus type 2 and depression were significantly reduced (hypertension 117/311 (38%), $P=0.001$; impaired glucose tolerance/diabetes mellitus type 2 53/311 (17%), $P=0.02$; depression 43/311 (14%), $P<0.001$). At last follow-up, 167/311 (54%) of the patients had GH deficiency, 153/311 (49%) gonadotrophin deficiency, 133/311 (43%) were on thyroxine treatment and 68/311 (22%) had diabetes insipidus.

During the follow-up period, 28/311 (9%) of the patients with CD died; 19/28 (71%) had been in

Table 1 Characteristics of the patients with CS.

	CD	AC	EC
Number of patients (F/M)			
Total series	311 (241/70)	74 (67/7)	33 (13/20)
Microadenomas	272 (209/63)	–	–
Macroadenomas	39 (32/7)	–	–
Oxford	182 (137/45)	16 (15/1)	11 (5/6)
Microadenomas	159 (120/39)	–	–
Macroadenomas	23 (17/6)	–	–
Athens	129 (104/25)	58 (52/6)	22 (8/14)
Microadenomas	113 (89/24)	–	–
Macroadenomas	16 (15/1)	–	–
Median age at diagnosis (years) (range)			
Total series	40 (10–76)	46 (20–81)	49 (15–77)
Females	40 (10–72)	46 (20–81)	53 (39–68)
Males	39 (10–76)	36 (34–63)	39 (15–77)
Oxford	39.5 (10–76)	45.5 (23–81)	39 (15–67)
Females	38 (13–72)	45 (23–81)	42 (39–67)
Males	41 (10–76)	55	37 (15–64)
Athens	40.5 (10–69)	46 (20–79)	56 (19–77)
Females	42 (10–69)	46.5 (20–79)	64 (40–68)
Males	28 (12–64)	36 (34–63)	52 (19–77)
Median follow-up (years) (range)			
Total series	9 (0.1–46)	3 (0.1–21)	4 (0.1–18)
Oxford	12 (0.1–46)	5 (0.1–14.5)	4.5 (0.1–15)
Athens	5.5 (0.1–44)	2 (0.1–21)	4 (0.1–18)
Median time from diagnosis to remission (months) (range)			
Total series	7 (1–328)	5 (1–225)	
Oxford	7 (1–269)	8 (1–126)	
Athens	6 (1–328)	4 (1–225)	
Mean age at death (years) (\pm s.d.)			
Total series	65 \pm 12	80 \pm 2	58 \pm 18
Oxford	67 \pm 10	81	52 \pm 19
Athens	44 \pm 7	78	64 \pm 15
Median time from diagnosis to death (years) (range)			
Total series	14 (0.1–35)	2 (1–3)	1 (0.1–12)
Oxford	15 (0.1–35)	1	1 (0.1–12)
Athens	5 (0.1–9)	3	0.1 (0.1–6)

Table 2 Treatment modalities in patients with CD and remission rates.

Treatment modalities	Total series Oxford Athens (number (%))	Remission at last assessment	Total series Oxford Athens (number (%))
TSA	178 (57%) 116 62		130 (75%) ^a 98 (88%) ^a 32 (62%)
TSA and RDT	41 (13%) 21 20		22 (54%) 12 (57%) 10 (50%)
TSA and BA	27 (9%) 22 5		26 (96%) 21 (95%) 5 (100%)
TSA and BA and RDT	9 (3%) 7 2		9 (100%) 7 (100%) 2 (100%)
BA	46 (15%) 13 33		43 (93%) 13 (100%) 30 (91%)
RDT	7 (2%) 2 5		5 (71%) 1 (50%) 4 (80%)
Medical treatment	3 (1%) 1 2		0 (0%) 0 (0%) 0 (0%)
Total	311 182 129		235 (77%) ^a 152 (85%) ^a 83 (64%)

TSA, transsphenoidal adenectomy; RDT, radiotherapy; BA, bilateral adrenalectomy.

^aFour patients with no information on their cortisol status were excluded from the evaluations.

remission. The cumulative probabilities of survival for the CD patients are shown in Table 3. The deaths were attributed to cardiovascular causes in 14/28 (50%), infection/sepsis in 6/28 (21.4%), malignancy in 7/28 (25%), multiple organ failure in 1/28 (3.6%) and unknown reason in 1/28 (3.6%). Also, one of the 28 (3.6%) patients died peri-operatively. Amongst factors including age at diagnosis, sex, radiotherapy, development of Nelson's syndrome, size of adenoma (micro- or macro-), remission status and relapse, only age was found to be an independent predictor of survival (hazard ratio 1.12; 95% CI, 1.08–1.17, $P < 0.001$). The SMRs for the Oxford series are shown in Table 4.

AD series

Fifty-seven of 74 (77%) of the patients had a unilateral adrenal adenoma and 17/74 (23%) bilateral hyperplasia. Amongst those with an adrenal adenoma, 55/57 (96%) underwent unilateral adrenalectomy resulting in remission in 54/55 (98%), while 2/57 (4%) had no surgical procedure at the time of the last assessment; 14/17 (82%) of the patients with bilateral hyperplasia underwent bilateral adrenalectomy which resulted in remission, 1/17 (6%) had a unilateral adrenalectomy which resulted in improvement but not remission of the

hypercortisolaemia and 2/17 (12%) had no surgical intervention until their last assessment. At last assessment, 68/74 (92%) of the AC patients were in remission.

During the follow-up, 2/74 (3%) of the patients with AC died, neither of whom was in remission. The cumulative probabilities of survival are shown in Table 3. The cause of death was attributed to cardiovascular events in both patients (100%). Age at diagnosis and sex were not the predictors of survival. The SMRs for the Oxford series are shown in Table 4.

EC series

Seventeen of the 33 (52%) patients had bronchial carcinoids, 2/33 (6%) small cell lung cancer, 3/33 (9%) medullary thyroid cancer and 1/33 (3%) islet cell tumours. The source of EC was not found in 10/33 patients (30%) despite extensive work-up. Management was individualised and 3/33 patients (two with occult and one with an islet cell tumour) underwent bilateral adrenalectomy resulting in remission in all (100%), 15/33 had resection of their primary tumour (12 with bronchial carcinoids and three with medullary thyroid cancers) leading to remission in 5/15 (29%), 1/33 had resection of primary tumour and radiotherapy (bronchial carcinoid) with no remission of the hypercortisolaemia, 3/33 had a combination of resection of the primary tumour and bilateral adrenalectomy (three with bronchial carcinoids, two of which also had radiotherapy) resulting in remission in all (100%), 3/33 had chemotherapy (two with small cell lung cancers and one with metastatic bronchial carcinoid), 2/33 had surgery for a possible source of the EC (all occult) resulting in no remission and 6/33 had no surgical procedure and were on medical treatment for

Table 3 Cumulative probabilities of survival in patients with CS.

Cumulative probability of survival	CD (number of subjects)	AC (number of subjects)	EC (number of subjects)
Total series (years)			
5	97.8% (304)	95.5% (71)	77.6% (26) ^a
10	95.3% (304)	95.5% (71)	
15	90.5% (278)		
20	87.0% (271)		
Oxford (years)			
5	97.0% (177)	93.3% (15)	
10	94.5% (172)	93.3% (15)	
15	88.1% (160)		
20	83.8% (153)		
Athens (years)			
5	99.2% (128)	95.7% (56)	
10	97.1% (125)	95.7% (56)	
15	97.1% (125)		
20	97.1% (125)		

^aData are not given separately for each centre due to the small number of cases.

Table 4 SMRs for the Oxford series. In remission: 136/155 (87.7%) with microadenomas and 16/23 (69.6%) macroadenomas.

	Observed deaths	Expected deaths	SMR (95% CI)	P value
CD overall	26	2.8	9.3 (6.2–13.4) ^a	<0.001
CD not in remission at last follow-up	5	0.5	9.9 (3.6–21.9)	<0.001
CD in remission immediately after TSA	13	1.3	10 (5.3–17.1)	<0.001
CD in remission immediately after TSA and no relapse	13	1.2	10.8 (6–18)	<0.001
CD macro – overall	5	0.3	15.6 (5.7–34.6)	<0.001
CD macro – not in remission	2	0.04	45.5 (7.6–150.2)	<0.001
CD micro – overall	19	2.5	7.6 (4.7–11.7)	<0.001
CD micro – not in remission	3	0.5	6.5 (1.7–17.8)	0.013
AC	1	0.2	5.3 (0.3–26.0)	0.2
EC overall	5	0.07	68.5 (21.5–151.8)	<0.001
EC in remission	1	0.01	83.3 (4.2–411)	<0.001
EC not in remission	4	0.06	66.7 (21.2–160.8)	<0.001
EC not in remission after excluding small cell lung cancers	3	0.059	50.8 (12.9–138.4)	<0.001

^aSMRs (95% CIs) for 1st and 2nd part of observation period (1967–1987 and 1988–2009): 10.5 (5.3–16.1) and 7.9 (3.2–12.5).

the hypercortisolaemia (all occult). At last assessment, 10/33 (30%) of the EC patients remained in remission of the hypercortisolaemia.

During the follow-up period, 10/33 (30%) of the patients with EC died; 2/10 (20%) post-operatively (one with medullary thyroid cancer and one with islet cell tumour), 4/10 (40%) from metastatic carcinomatosis (one with occult, one with small cell lung cancer and two with bronchial carcinoids), 3/10 (30%) from sepsis (two with occult and one with bronchial carcinoid) and 1/10 (10%) from unknown reason (one with occult). Amongst them, 2/10 (20%) were in remission (one with a bronchial carcinoid and one with an islet cell tumour). The cumulative probabilities of survival are shown in Table 3. The SMRs for the Oxford series are shown in Table 4. When analysing the bronchial carcinoids separately, the 5-year survival rate was 93.8%: amongst factors including age at diagnosis, sex, remission status and presence of lymph node metastases in the pathology of the excised tumour, none was identified as an independent predictor of survival.

Discussion

This is one of the largest series assessing the survival/mortality of patients with all aetiologies of CS (except adrenal cancer) from two large tertiary endocrine referral centres. Based on the Oxford series for which SMRs were estimated, we found that mortality is significantly elevated in patients with CD, irrespective of their remission status, with the majority of deaths related to cardiovascular causes or infections. In patients with AC, the SMR was also greater than expected, although this was not statistically significant; in those with hypercortisolism attributed to ectopic ACTH secretion from various sources of different

malignant potential, the overall mortality is dramatically affected.

In our group of 311 subjects with CD followed up for a median period of 9 years (range 0.1–46), 76.5% were in remission at last assessment (median interval from diagnosis 7 months). Amongst them, 28 (9%) died, 71% of which were in remission. The 10-year probability of survival was 95.3% (94.5 and 97.1% for Oxford and Athens, respectively) and the mean age at death was only 65 ± 12 years. Swearingen *et al.* (12) in a series of 159 patients treated by TSA as an initial approach (90% with microadenomas and a cure rate of 85%) described a 10-year survival probability of 93% (age of death between 62 and 81 years). In agreement with previously published data (2, 3, 13, 17), the mortality in our series was mainly attributed to cardiovascular causes and infection/sepsis (50 and 21.4% of our cases, respectively). Notably, in our series, at last evaluation, hypertension and impaired glucose tolerance/diabetes mellitus type 2 were found in 38 and 17% of the patients, respectively. It is well recognised that chronic hypercortisolaemia is associated with a number of cardiovascular risk factors (visceral obesity with insulin resistance, impaired glucose tolerance, atherosclerosis, arterial hypertension, dyslipidaemia and hypercoagulability (22)) and it has also been shown that these factors, as well as cardiac abnormalities, may persist even in patients who have achieved biochemical control of the disease activity (1, 9, 11, 23). These data support the view that the impact of the hypercortisolaemia on the cardiovascular system is long-lasting, remaining even after normalisation of the hypercortisolaemia, although the effect of hypopituitarism, and particularly GH deficiency, needs also to be taken into account (24). Amongst factors including age, sex, radiotherapy, development of Nelson's syndrome, size of adenoma (micro- or macro-), remission status and relapse, we

found that only age was an independent predictor of survival ($P < 0.001$) (younger patients living longer). The impact of age on survival has also been confirmed in previous studies (3, 12, 18) and it is possibly explained by the greater effect of hypercortisolism-related co-morbidities on older patients (17). In other series, diabetes mellitus at last follow-up or persistence of hypertension (3, 18) has been proposed to affect mortality, whereas the results on the influence of biochemical cure have not been consistent (12, 17, 18). SMRs were calculated only for the Oxford series, as for this group we had information on all the patients' status (dead or alive) at the time the database was 'frozen' ($n = 182$). In this large Oxford group and during one of the longest reported median follow-up periods (12 years, range 0.1–46), 14% of the patients (26/182) died. Overall, the mortality was significantly elevated (SMR 9.3; 95% CI, 6.2–13.4, $P < 0.001$), despite the fact that at last assessment, 84% were in remission (median time from diagnosis to remission 7 months) and that cure immediately after transsphenoidal surgery was achieved in a significant percentage of cases (62.3%). Notably, mortality was significantly increased in patients showing remission immediately after surgery (SMR 10; 95% CI, 5.3–17.1, $P < 0.001$), as well as in the non-remission group (SMR 9.9; 95% CI, 3.6–21.9, $P < 0.001$) and in both types of adenomas

(SMR for microadenomas 7.6; 95% CI, 4.7–11.7, $P < 0.001$ and SMR for macroadenomas 15.6; 95% CI, 5.7–34.6, $P < 0.001$). The comparative results of previous studies are shown in Table 5. Swearingen *et al.* (12) suggested that the survival of patients with CD was similar to that of an age- and sex-matched sample from the USA population. It has been proposed, however, that in this series the mortality outcomes possibly represent a highly selected group of cases that would be expected to have the best surgical results (17). Dekkers *et al.* (13) reviewed the outcome of 74 patients during a mean observation period of 12.8 years and found that the SMR of those in remission after initial surgery was not significantly elevated in contrast to the SMR of those with persistent disease. The latter group, though, also included subjects achieving remission after additional treatment modalities. Clayton *et al.* (17) in a meta-analysis confirmed a significantly higher overall SMR (2.22; 95% CI, 1.45–3.41, $P = 0.005$), but the interpretation of the pooled data from the remission and the persistent disease groups may be difficult given the variability of the criteria used to define remission, the differences in the estimation of the time between diagnosis and remission and the multimodality of treatments offered. The SMRs in our study are amongst the highest reported in the literature and this may be explained by the fact that our series combines both a

Table 5 Studies reporting SMRs in patients with CD.

Reference	No. of patients	Period covered	Remission (%)	Follow-up (months) (range)	SMR (95% CI)
(12)	161	1978–1996 (18 years)	85	Mean 96 (12–240)	0.98 (0.44–2.2) NS
(15)	45 cured after initial surgery	1985–1995 (10 years)		Median 109	0.31 (0.01–1.72) NS
(13)	25 non-cured 74	1977–2005 (28 years)	80	Median 120 mean 120	5.06 (1.86–11.0) 2.39 (1.22–3.9) Remission after initial surgery: 1.8 (0.71–3.37) NS Persistent disease after initial surgery: 4.38 (1.38–9.07)
(18)	30 macro-adenomas 158 micro-adenomas	1960–2005 (45 years)	93 91	Median 83 (0–360) Median 90 (0–552)	3.5 (1.3–7.8) 3.2 (2.0–4.8) Microadenomas cured after first surgery: 3.1 (1.8–4.9)
(17)	60	1960–2009 (49 years)	90	Median 180 (6–492)	4.8 (2.8–8.3) Remission: 3.3 (1.7–6.7) Persistent disease: 16.0 (6.7–38.4)
(2)	80	1988–2009 (21 years)	83	Mean 132	3.17 (1.7–5.43) Cure at last follow-up: 2.47 (0.80–5.77) Persistent/recurrent disease: 4.1 (1.12–10.54) NS
This study	182	1967–2009 (42 years)	85	Median 144 (1–552)	9.3 (6.2–13.4) Remission at last follow-up: 8.3 (5.1–12.7) Persistent disease at last follow-up: 9.9 (3.6–21.9) Remission immediately after surgery and no relapse: 10.8 (6–18)

NS, not significant.

large number of patients (182) and long duration of follow-up (median 144 months). In fact, given the relatively young age of our patients at diagnosis, it is anticipated that with the extension of the observation period, the number of deaths would further increase. Interestingly, the study by Clayton *et al.* (17) which has the longest reported observation period (180 months) with 60 patients also showed a significantly increased SMR overall (4.8; 95% CI, 2.8–8.3, $P < 0.001$), as well as in the remission (3.3; 95% CI, 1.7–6.7, $P = 0.0006$) and in the persisting disease groups (16.0; 95% CI, 6.7–38.4, $P < 0.001$), with the number of cardiovascular deaths overall being higher than would be expected for the general population.

The mortality of those with AC (as estimated by SMR from the Oxford series) was not found to be significantly greater than expected (5.3; $P = 0.2$) with broad 95% CIs (0.3–26.0). The 10-year probability of survival was 95.5% and the mean age of death was 80 years (vs 65 in CD). Our wide CIs are related to the small number of events, and the clinical value of the elevated SMR should not be overlooked with larger studies required to adequately assess this question. Porterfield *et al.* (25), in a series of 44 cases who underwent adrenalectomy for single cortisol-secreting adenomas, reported a 5-year survival 90%. Interestingly, Bolland *et al.* (18) in a group of 37 patients with adrenal adenoma followed up for a median period of 3.1 years found a significantly elevated SMR (7.5; 95% CI, 1.9–20). It should be noted, however, that all deaths occurred within 3 months of presentation (in the immediate post-operative period or prior to surgery) and that no deaths were observed during the post-operative follow-up. The same authors reported an increased SMR of nine with bilateral nodular hyperplasia (14; 95% CI, 3.7–40), but only 56% of them had biochemical cure during a median follow-up of 5.7 years. Dekkers *et al.* (7) reported an increased mortality risk in patients with AC compared with a control population (HR 2.4, 95% CI, 1.6–3.5). In this study, which also included patients with CD, the authors reported that detailed information on biochemical results and cure rate after surgery were lacking and that the risk of including patients with CD in the AC group could not be excluded. Lindholm *et al.* (15) found no significantly increased mortality in adrenal adenoma subjects who had unilateral adrenalectomy during a median follow-up of 8.3 years, and in a recent meta-analysis by Graversen *et al.* (20), benign AC has not been associated with increased mortality (SMR 1.90; 95% CI, 0.93–3.91). Possible explanations for the better outcome of AC cases compared with the CD ones are the high cure rate, the extremely low risk of relapse and the lack of permanent pituitary dysfunction. Furthermore, given that more complicated treatments are required for CD, iatrogenic effects may also play a role. Finally, the contribution of other adrenocortical steroids secreted in CD needs to be considered.

As expected, the survival of patients with EC was severely compromised. In our series including patients with heterogenous aetiologies, we found that the 5-year probability of survival being 77.6%. During a median follow-up of 4 years (range 0–18), 10/33 patients died at a mean age of 58 years (four with occult, three with bronchial carcinoid and three with other aetiologies). The SMR in the Oxford series was 68.5 with wide 95% CIs related to the rarity of the condition and the subsequent small number of deaths. The main causes of death were progression of the primary malignancy and infections, in accord with the previous limited literature (19, 26, 27, 28). In a series of 18 patients with EC who underwent bilateral adrenalectomy, O'Riordain *et al.* (26) found 5-year survival probability of 39%, with 73% of deaths related directly to metastatic malignant disease. Porterfield *et al.* (25), in a group of 35 subjects who also had bilateral adrenalectomy, reported 5-year survival probability of 51.3%. In a series of 90 patients with EC followed up for a median period of 26 months, Ilias *et al.* (27) 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. Due to the small number of patients, we did not proceed to the similar statistical analyses, but when analysing the bronchial carcinoids separately we found 5-year probability of survival of 93.8%.

The strength of our study is that it relies on one of the largest sample sizes of unselected CS patients reported in the literature, with a long follow-up in two centres adopting similar diagnostic and management protocols. We also looked at the outcome of all aetiologies (except adrenal cancer) of CS, thereby covering the wide spectrum of this rare condition. A potential limitation is that the data on morbidities relied on the documented information in the patients' notes and therefore, underestimation of their true prevalence cannot be excluded. Furthermore, the wide 95% CIs related to the small number of deaths needs to be taken into account when looking at the results of this and of previously published series. This is particularly relevant with our AC and EC groups, in which the number of subjects is small, and therefore, the SMRs need to be interpreted cautiously. Studies with a larger sample size are needed for providing more accurate data.

In conclusion, although it is widely accepted that persisting CD affects survival significantly, we report that elimination of hypercortisolaemia in these patients does not lead to a mortality rate similar to that of the general population and that, unfortunately, apparently well-treated CD still remains a condition associated with increased mortality. The pathophysiological mechanisms involved need to be further elucidated in order to improve the long-term outcome. The prognosis of patients with benign adrenal CS seems to be more optimal and the advances in surgical techniques may

have contributed to this. Not surprisingly, EC has the worse outcome, but large adequate powered studies are required for providing robust data on this heterogeneous group of conditions. Although early diagnosis and rapid successful management of the hypercortisolaemia are undoubtedly of major importance, the statement that 'CD is bad for you physically, emotionally, and for your survival' (17) still appears to reflect the landscape in this area.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

We are grateful to all physicians who contributed to the care of the patients of this series and to the physicians who provided information on the follow-up.

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Received 30 March 2013

Revised version received 24 August 2013

Accepted 30 August 2013