Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study

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Summary

Background No agreement has been reached on the long-term survival prospects for patients with Cushing's disease. We studied life expectancy in patients who had received curative treatment and whose hypercortisolism remained in remission for more than 10 years, and identified factors determining their survival.

Methods We did a multicentre, multinational, retrospective cohort study using individual case records from specialist referral centres in the UK, Denmark, the Netherlands, and New Zealand. Inclusion criteria for participants, who had all been in studies reported previously in peer-reviewed publications, were diagnosis and treatment of Cushing's disease, being cured of hypercortisolism for a minimum of 10 years at study entry, and continuing to be cured with no relapses until the database was frozen or death. We identified the number and type of treatments used to achieve cure, and used mortality as our primary endpoint. We compared mortality rates between patients with Cushing's disease and the general population, and expressed them as standardised mortality ratios (SMRs). We analysed survival data with multivariate analysis (Cox regression) with no corrections for multiple testing.

Findings The census dates on which the data were frozen ranged from Dec 31, 2009, to Dec 1, 2014. We obtained data for 320 patients with 3790 person-years of follow-up from 10 years after cure (female:male ratio of 3:1). The median patient follow-up was 11·8 years (IQR 17–26) from study entry and did not differ between countries. There were no significant differences in demographic characteristics, duration of follow-up, comorbidities, treatment number, or type of treatment between women and men, so we pooled data from both sexes for survival analysis. 51 (16%) of the cohort died during follow-up from study entry (10 years after cure). Median survival from study entry was similar for women (31 years; IQR 19–38) and men (28 years; 24–42), and about 40 years (IQR 30–48) from remission. The overall SMR for all-cause mortality was 1·61 (95% CI 1·23–2·12; p=0·0001). The SMR for circulatory disease was increased at 2·72 (1·88–3·95; p<0·0001), but deaths from cancer were not higher than expected (0·79, 0·41–1·51). Presence of diabetes, but not hypertension, was an independent risk factor for mortality (hazard ratio 2·82, 95% CI 1·29–6·17; p=0·0095). We noted a step-wise reduction in survival with increasing number of treatments. Patients cured by pituitary surgery alone had long-term survival similar to that of the general population (SMR 0·95, 95% CI 0·58–1·55) compared with those who were not (2·53, 1·82–3·53; p<0·0001).

Interpretation Patients with Cushing's disease who have been in remission for more than 10 years are at increased risk of overall mortality compared with the general population, particularly from circulatory disease. However, median survival from cure is excellent at about 40 years of remission. Treatment complexity and an increased number of treatments, reflecting disease that is more difficult to control, appears to negatively affect survival. Pituitary surgery alone is the preferred treatment to secure an optimum outcome, and should be done in a centre of surgical excellence.

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See Comment page 551

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Introduction

The predominant cause of endogenous Cushing's syndrome is Cushing's disease, which is characterised by increased secretion of adrenocorticotropic (ACTH) hormone from the anterior pituitary gland.[1–4] If untreated, Cushing's disease leads to markedly increased mortality from circulatory diseases. Findings from population-based studies and patients with adrenal incidentalomas suggest that higher concentrations of cortisol within normal reference ranges might be linked to increased cardiovascular mortality (appendix).[5–9]

Several cohort studies[10–18] have examined whether mortality in Cushing's disease is affected by restoration of normal cortisol concentrations, or not, with variable results. Findings from meta-analyses have shown that patients with Cushing's disease who have initial remission of hypercortisolism have a reduced standardised mortality ratio (SMR) compared with that of patients with persistent disease, although overall SMR (2·5) was still increased. Considerable heterogeneity in SMR exists between studies, and with respect to definition of remission, timing of remission (which

See Online for appendix

Research in context

Evidence before this study

We searched the MEDLINE database for English-language articles with the search terms "meta-analysis", "mortality", and "Cushing's disease" and identified two articles. Findings from a published meta-analysis of mortality outcomes in individuals with treated Cushing's disease in initial remission after treatment (the definition of which varies between studies) shows an increased standardised mortality ratio (SMR) of 2·5 but with marked heterogeneity (SMR range 0·3–10·0).

Added value of this study

We did a retrospective cohort study of 320 individuals who have been cured of Cushing's disease for more than 10 years using various treatments, and who remain in remission. These patients have an overall SMR of 1·6 and an SMR from circulatory disease of 2·7. We noted a stepwise reduction in survival with increasing number of treatments, but patients cured by pituitary surgery alone had no increase in SMR (0·95). There was no heterogeneity between countries, and median survival from time of cure was 40 years (IQR 30–48) from remission.

Implications of all the available evidence

For Cushing's disease, treatment complexity and increasing the number of treatments negatively affects patient survival. Pituitary surgery alone is the preferred treatment to secure an optimum outcome, and should be done in a centre of surgical excellence.

Panel: Criteria for definition of cure or remission in Cushing's disease by study centre

Birmingham UK (15)
- Initial: morning plasma cortisol less than 50 nmol/L between 4 days to 6 weeks after surgery
- Follow-up: normal UFC or suppression of plasma cortisol to less than 50nmol/L after o/n dexamethasone

Stoke on Trent UK (13)
- Initial: normal UFC plus plasma cortisol less than 100 nmol/L after o/n dexamethasone
- Follow-up: normal UFC × 2 or plasma cortisol less than 50 nmol/L after o/n dexamethasone

Oxford UK (17)
- Initial: undectable morning plasma cortisol within days after surgery
- Follow-up: one or more of the following—normal plasma cortisol after o/n dexamethasone, normal UFC, or normal mean plasma cortisol from five samples taken between 0800–1800 h

Auckland (14)
- Initial: information not provided
- Follow-up: normal UFC or normal plasma cortisol after o/n dexamethasone

Leiden (11)
- Initial: information not provided
- Follow-up: plasma cortisol less than 100 nmol/L after o/n dexamethasone and normal UFC (<220 nmoL per day)

Aalborg (10)
- Initial: subnormal plasma cortisol after synthetic ACTH 250 µg with or without UFC less than 50 nmoL per day
- Follow-up: UFC less than 250 nmoL/day

The presence of adrenal insufficiency requiring glucocorticoid treatment=cure. Follow-up occurred at various regular intervals according to local protocols. UFC=24 h urine free cortisol. o/n dexamethasone=plasma cortisol measured between 0800–1000 h after dexamethasone 1 mg or 2 mg given at 2300 h the previous evening. ACTH=adrenocorticotropic hormone. Normal refers to the local reference range for the centre, which varied by centre according to the assays used, and which themselves changed during the course of the follow-up.

differed between studies), and persistence of Cushing's disease (appendix).[13,19] A major limitation of these individual studies was that the division of the cohorts[13,19] was based on remission immediately after initial treatment, with no information provided on relapse or recurrence of hypercortisolism during follow-up that could clearly drive mortality. In an attempt to eliminate these issues, minimise participant heterogeneity, and measure the long-term survival for Cushing's disease in remission, we examined mortality in patients who had survived 10 years or more from the time of curative treatment and were in continued remission up until the census date or their death.

Methods

Study design and participants

We did a multicentre, multinational, restrospective cohort study using individual case records from specialist referral centres in the UK (Birmingham, Oxford, and Stoke on Trent), Denmark (Aalborg), the Netherlands (Leiden), and New Zealand (Auckland). The patients included were all part of previous studies reported in peer-reviewed publications,[10,11,13,14,15,17] and were managed at tertiary referral centres using extant best-practice management techniques to national and international standards of the time, so are likely to reflect national data. Unlike for acromegaly, there are no national registries or datasets for Cushing's disease. Inclusion criteria were diagnosis and treatment of Cushing's disease, cured of hypercortisolism for a minimum of 10 years at study entry, and continued cure with no relapses of hypercortisolism until database was frozen or death. Definitions of cure from each centre are in the panel.

The studies from Birmingham, Oxford, Stoke on Trent, New Zealand, and Denmark were approved and registered as audits by the respective institutions so did not require ethical approval. The study from the Netherlands had ethical approval.

Procedures

Our primary endpoint was mortality. Follow-up for the present analyses started after 10 years of cure. We

identified the number and type of treatments used to achieve cure, with cure being defined after the last treatment. In the case of radiotherapy, if this was given prophylactically to reduce the risk of Nelson's syndrome after bilateral adrenalectomy, we used the date of the adrenalectomy as the cure date. The diagnostic criteria for Cushing's disease and definition of remission could not be standardised and relied on those used by the individual centres which have all been published in their respective publications[10,11,13,14,15,17] (appendix). Similarly, treatment methods varied between centres and with time. Initial diagnosis and treatment was from as early as 1958 (Stoke-on-Trent) through to 1997 (Leiden). In addition to data for demographic characteristics and primary endpoint status of alive or dead and cause of death (from National Registry Offices or patient records), we obtained information on initial treatment, subsequent treatments and dates thereof, radiotherapy usage, glucocorticoid and thyroxine replacement, and treatment for hypertension or diabetes mellitus.

Statistical analysis

We summarised continuous data as medians (IQR) and discrete data as proportions. We analysed survival data with multivariate analysis (Cox regression; factors associated with survival were examined individually, including age at baseline as a covariate) and displayed them in Kaplan-Meier plots. Significance was taken as p less than 0·05 (Wilcoxon rank sum test), and CIs, with no correction for multiple testing, are presented. We only included age at study entry in the models; other age variables were given for information. There was no significant departure from proportional hazards assumptions for any of the variables.

We obtained reference mortality rates from the Human Mortality Database for the relevant countries. We calculated the expected numbers of deaths (needed for the calculation of SMRs) with standard cohort techniques described in detail by Breslow and Day.[20] Briefly, we derived expected numbers by aggregating the person-years in each sex, age (1-year bands), and calendar year (1-year bands) strata, then multiplying the person-years by the corresponding mortality rate for the general population of the relevant country. We then added the expected numbers across the strata and calculated SMRs as the sum of observed number of deaths divided by the sum of expected number of deaths. All cause population mortality rates were available for: Denmark from 1901–2011, New Zealand 1948–2008, Netherlands 1901–2012, and UK 1922–2013. Tests for linear trends and heterogeneity of SMRs were based on likelihood ratio tests comparing the deviance between relevant Poisson regression models. We did all analyses with Stata version 13.1.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The final text was approved by all coauthors.

Results

Census dates (ie, the last date on which information was available for all patients from a specific centre) at which the data were frozen were: Dec 31, 2013 (Birmingham), Dec 31, 2009 (Oxford), Jan 12, 2014 (Stoke-on-Trent), Jan 1, 2014 (Leiden), Jan 1, 2012 (Aalborg), and Jan 1, 2012 (Auckland) or earlier. We obtained data for 320 patients with 3790 person-years of follow-up from 10 years after cure (female to male ratio of 3:1). No patients were lost to follow-up. There were no significant differences between women and men with respect to age at study entry, cure,

	Women (n=246)	Men (n=74)
Age at study entry (years)	46 (38–56)	43 (32–52)
Age at cure (years)	36 (28–46)	33 (22–42)
Age at census date (years)	58 (51–69)	53 (46–62)
Diabetes*	24 (10%)	7 (9%)
Hypertension*	125 (51%)	39 (53%)
Receiving glucocorticoid replacement therapy treatment†	158 (64%)	52 (70%)
Receiving thyroxine treatment‡	95 (39%)	28 (38%)

Data are median (IQR) or n (%). *Defined as receiving treatment at census date or death. †Information missing for seven women and two men. ‡Information missing for 28 women and ten men.

Table 1: **Baseline characteristics of the cohort**

	Women (246)	Men (74)
Pituitary surgery only	144 (59%)	45 (61%)
Pituitary surgery plus bilateral adrenalectomy	40 (16%)	12 (16%)
Pituitary surgery plus radiotherapy*	20 (8%)	5 (7%)
Bilateral adrenalectomy only	7 (3%)	2 (3%)
Bilateral adrenalectomy plus radiotherapy	15 (6%)	5 (7%)
Radiotherapy only*	16 (7%)	5 (6·8%)
Radiotherapy plus bilateral adrenalectomy plus pituitary surgery	4 (2%)	0 (<1%)
Pituitary surgery as first treatment	204 (83%)	62 (84%)
Bilateral adrenalectomy as first treatment	22 (9%)	7 (9%)
Radiotherapy as first treatment	20 (8%)	5 (7%)
Number of treatment methods		
One	160 (65%)	47 (64%)
Two	54 (22%)	17 (23%)
Three or more	32 (13%)	10 (14%)

Data are n (%). *These patients were given treatment with metyrapone, with or without aminoglutethamide, for different periods while awaiting the effects of radiotherapy.

Table 2: **Treatments categorised by sex**

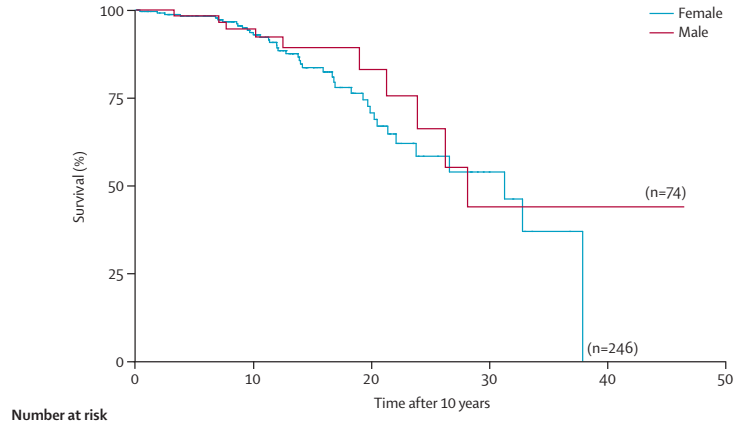

Figure 1: **Kaplan–Meier survival curves stratified by sex**

	Women (246)	Men (74)
Number of deaths	41 (17%)	10 (14%)
Age at cure years (deceased)	42 (34–56)	43 (23–52)
Age at entry years (deceased)	52 (44–66)	53 (33–62)
Age at death years	69 (60–78)	66 (59–77)
Follow-up to death* (years)	14 (9–20)	16 (8–25)
Duration of follow-up for live participants* (years)	11 (6–16)	11 (6–15)
Causes of death		
Cardiovascular†	18 (44%)	8 (80%)
Cancer‡	9 (22%)	0
Pulmonary embolism	2 (5%)	2 (20%)
Disseminated sepsis	2 (5%)	0
Other or unknown§	10 (24%)	0

Data are n (%) or median (IQR). *From study entry; ie, 10 years after remission of hypercortisolism, add 10 years to each for total follow-up from time of remission. †Included cerebrovascular-related deaths (n=6) and ruptured aortic aneurysm (n=3). ‡Cancer types were lung (n=2), nasopharyngeal (n=1), bladder (n=1), metastatic uterine (n=1), malignant small bowel (n=1), pancreatic (n=1), meningioma (n=1), and metastatic primary unknown (n=1). §Included acute asthma (n=1), fibrosing alveolitis (n=1), chronic obstructive pulmonary disease or bronchopneumonia (n=2), acute bronchitis (n=1), old age (n=1), and unknown (n=2)

Table 3: **Summary statistics for deaths categorised by sex**

or census date (table 1), so data from the sexes were pooled for survival analysis and predictors. The proportions with diabetes, hypertension, or receiving glucocorticoid replacement therapy were also similar between the sexes. We noted no differences in treatment methods between women and men (table 2). More than 80% (266/320) of the cohort were initially given transsphenoidal pituitary surgery with 60% (189/320) requiring only this treatment to achieve a long-term cure. However, 40% (128/320) required additional treatment. Less than 10% (29/320) had bilateral adrenalectomy or radiotherapy (10%; 25/320) as first treatment and these participants were diagnosed and treated in the early years of the study (mostly before 1975). Only 13% (43/320) of the cohort required three or more treatments to achieve cure. The median patient follow-up was 11·8 years (IQR 17–26) from study entry and did not differ between countries.

51 (16%) participants died during follow-up from study entry (10 years after cure), and the proportions were similar for women and men. The median age at death for both sexes combined was 68 years (IQR 60–78). Median (50%) survival for women was 31 years (IQR 19–38) from study entry and 28 years for men (IQR 24–42; non-significant difference) (figure 1). The median age at death was 69 years (IQR 60–78) for women and 66 years (59–77) for men (table 3), and the median time to death from 10 years after cure was 14 years (IQR 9–20) for women, 16 (8–25) for men. Among patients who died, we noted no sex-related differences in age at cure, age at study entry, age at death, or duration of follow-up (table 3). However, when data for the sexes were combined and the deceased group compared with the alive group, we noted differences: the median age at cure for patients who were alive was 34 years (IQR 27–43) years versus 42 years (32–55) for those who were dead, p<0·0001. The median age at study entry for live patients was 44 years (IQR 33–54) years versus 52 years (42–66) for those who were dead, p<0·0001. The median duration of follow-up from study entry for live patients was 11 years (IQR 6–15) versus 14 (9–20) for those who were dead, p=0·008.

The causes of death were predominantly circulatory (n=30), including cardiovascular and cerebrovascular disease, ruptured aortic aneurysm, and pulmonary embolism, in both women and men but all nine cancer deaths occurred in women. Only two deaths from sepsis were recorded (table 3), despite 68% (210/311) of the cohort being on glucocorticoid replacement.

The standardised mortality ratio (SMR) for all cause mortality was 1·61 (95% CI 1·23–2·12) indicating a 61% increase in mortality risk (table 4). In absolute terms this translates to five excess deaths per 1000 individuals per year beyond those which would be expected on the basis of general population mortality rates. There was evidence for heterogeneity ($p_{heterogeneity}$=0·02) between countries, with the Netherlands showing a low absolute observed risk and New Zealand a high one (table 4). This heterogeneity disappeared after adjustment for pituitary surgery only (appendix) with fewer patients from New Zealand having pituitary surgery. Although men did not have an increased SMR and women did, this sex-related difference was not significant. The SMR for circulatory disease was 2·72 (95% CI 1·88–3·95; p<0·0001) with no heterogeneity between countries (p=0·22). There was no significant variation in circulatory SMR by time since study entry (ie, duration of follow-up). SMR for cancer (0·79, 95% CI 0·41–1·51; p=0·41) was not increased.

There was a tendency for increased SMR with longer follow-up (>20 years) although this did not reach significance. We calculated SMR by decade of treatment but no significant trend was observed (p_{trend}=0·17). We examined SMR by year of diagnosis before and after 1985, this year being chosen as about midway from the earliest patient entry (1957) and the close of databases (average 2012); results were not significantly different (table 4, appendix).

Half the patients in the cohort survived for 25 years or more from study entry (ie, 35 years from cure; figure 1). Presence of diabetes had a mortality hazard ratio (HR) of 2·82 (95% CI 1·29–6·17; p<0·0096); for hypertension HR was 1·59 (0·77–3·31, p=0·08). Patients not taking glucocorticoid treatment had an SMR no different from that of the general population, compared with patients taking glucocorticoids who had a significantly different SMR (table 4). 57% (108/190) of patients having pituitary surgery as the only treatment were receiving glucocorticoid replacement therapy, whereas the proportion who received other or additional treatments was 79% (102/130), a highly significant difference (p<0·0001). When we applied multivariate analysis, the effect of being on glucocorticoids was no longer significant, either alone (HR 1·57, 95% CI 0·78–16·0; p=0·21) or with pituitary surgery in the model (HR 1·31, 0·63–2·69; p=0·47). Hypothyroidism was not a risk for mortality. Being on sex hormones was not a risk factor (HR 1·46, 95% CI 0·54–3·97; p=0·46), but data were only available for 51% (162/320) of the cohort. There was an association between mortality and number of treatments, with higher risk noted with a higher number of treatments (figure 2). HRs were 1·77 (95% CI 0·93–3·38) for two versus one treatments (p=0·08), and 2·6 (1·15–5·87) for three versus one treatments (p=0·02). Median survival time from study entry for one treatment was 33 years (95% CI 26–38), for two was 27 years (19–28), and for three was 21 years (17–21). When considered by centre, Stoke-on-Trent, Oxford, and Auckland had the lowest proportions of patients receiving one treatment and the highest receiving three treatments (appendix). There was a significant difference (p<0·001 Anova) in the number of treatments between centres. Patients given pituitary surgery as a first and only treatment had an SMR that did not differ from that of the general population (0·94, 95% CI 0·57–1·53) versus those who did not (2·58, 1·85–3·59) the difference being highly significant (p<0·0005). There was no heterogeneity between countries in terms of the number of patients having pituitary surgery (appendix). Moreover, patients cured by pituitary surgery only had a longer median survival of 31 years (95% CI 26–38) versus 24 years (21–28) if radiotherapy had been required at any time (p=0·03). Median survival for patients requiring bilateral adrenalectomy at any time was not reached, although for 75% survival it was 17 years (95% CI 12–21) versus 26 years (20–28) for pituitary surgery only (p=0·1).

	Participants (%)	Observed/expected	SMR (95% CI)	p value	AER*
Cause of death					
Overall	320 (100%)	51·0/31·7	1·61 (1·23–2·12)	0·0001	5
Cancer	320 (100%)	9·0/11·4	0·79 (0·41–1·51)	0·41	0
Circulatory	320 (100%)	28·0/10·3	2·72 (1·88–3·95)	<0·0001	5
Country					
England	135 (42%)	15·0/9·3	1·62 (0·98–2·69)	0·06	4
New Zealand	75 (23%)	20·0/7·3	2·73 (1·76–4·23)	<0·0001	14
Netherlands	36 (11%)	4·0/6·0	0·66 (0·25–1·77)	0·41	0
Denmark	74 (23%)	12·0/9·1	1·33 (0·75–2·33)	0·33	4
$P_{heterogeneity}$	..	..	..	0·02	..
Sex					
Male	74 (23%)	10·0/9·0	1·11 (0·60–2·06)	0·75	1
Female	246 (77%)	41·0/22·6	1·81 (1·33–2·46)	<0·0001	6
$P_{heterogeneity}$	..	..	..	0·14	..
Year of cure					
<1985	89 (28%)	28·0/15·9	1·76 (1·17–2·54)	0·003	7
≥1985	23·1 (72%)	23·0/14·7	1·57 (1·04–2·35)	0·032	4
$P_{heterogeneity}$	..	..	..	0·68	..
Follow-up (years)					
10–14	56 (18%)	8·0/7·8	1·03 (0·51–2·06)	0·94	0
15–19	85 (27%)	13·0/8·4	1·55 (0·90–2·67)	0·12	4
20–24	86 (27%)	15·0/7·1	2·12 (1·28–3·51)	0·003	12
25+	93 (29%)	15·0/8·4	1·79 (1·08–2·96)	0·03	12
P_{trend}	..	..	..	0·17	..
Pituitary surgery					
No	143 (45%)	35·0/13·6	2·58 (1·85–3·59)	<0·0001	11
Yes	177 (55%)	16·0/17·1	0·94 (0·57–1·53)	0·80	0
$P_{heterogeneity}$	..	..	..	0·0005	..
Glucocorticoid replacement therapy					
No	101 (32%)	10·0/9·9	1·01 (0·54–1·89)	0·96	0
Yes	210 (66%)	39·0/19·6	1·99 (1·45–2·72)	<0·0001	8
Missing	9 (3%)				
$P_{heterogeneity}$	..	..	..	0·04	..

Table 4: **Standardised mortality ratios (SMRs) with date of entry as date of 'cure' plus 10 years**

Discussion

For patients who have been cured of Cushing's disease for 10 years or more, treatment complexity and an increased number of treatments, reflecting disease that is more difficult to control, appears to negatively affect survival. Pituitary surgery alone achieves a mortality outcome that is not different from the normal population, and should be performed in a centre of excellence.

The long-term outcome of successfully treated Cushing's disease has been uncertain. Short-term studies[10–18] and meta-analyses have produced conflicting results,[13,19] not least because these studies were heterogeneous with respect to timing after initial treatment, how cure or remission was defined, and methods of treatment, and they were of short duration. Findings from our first meta-analysis[13] suggested that SMR was not significantly increased compared with that of the general population, provided that patients achieved initial remission. But we were cautious in our conclusion

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