Influence of hormonal functional status on survival in adrenocortical carcinoma: systematic review and meta-analysis

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Abstract

Objective: Adrenocortical carcinoma (ACC) is a malignancy with a poor prognosis. Many publications in ACC report on risk factors for a poor outcome; one risk factor studied is hormonal hypersecretion (cortisol, sex-hormones, steroid precursors or aldosterone). The aim of this systematic review was to study the association between hormonal secretion and recurrence or mortality in ACC.

Design: Systematic review and meta-analysis. We searched PubMed, EMBASE and The Cochrane library (January 2018) for cohort studies examining the association between hormonal secretion on overall or recurrence-free survival in ACC.

Methods: A random-effects model meta-analysis was performed to obtain a weighted relative risk comparing cortisol-secreting and/or androgen-secreting ACCs to non-secreting tumours regarding overall and recurrence-free survival. Risk of bias assessment was performed for all studies included.

Results: Nineteen publications were included representing a total of 3814 patients. Most studies were generally considered low/intermediate risk of bias. Meta-analysis showed higher mortality risk for cortisol-secreting ACCs, weighted relative risk 1.71 (95% CI: 1.18–2.47) combining studies that adjusted for tumour stage; also a higher recurrence risk was found for cortisol producing ACCs, relative risk 1.43 (95% CI: 1.18–1.73). Androgen secretion was not clearly associated with survival (RR: 0.82, 95% CI: 0.60–1.12).

Conclusion: This systematic review and meta-analysis show that cortisol-secreting ACCs are associated with a worse overall survival; future research is needed to establish whether this association points to negative effects of cortisol action, whether it signifies a more aggressive ACC subtype or whether cortisol is merely a prognostic marker.

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Introduction

Adrenocortical carcinoma (ACC) is a rare tumour with an incidence of less than 2 per million population. The prognosis remains poor with a 5-year overall survival of less than 50% and in metastatic disease less than

20% (1, 2, 3, 4, 5). Recurrences are frequent, even after apparent complete surgical resection. Symptoms of hormonal excess (Cushing syndrome, virilization) and abdominal tenderness are common ways of presentation but incidental discovery of an adrenal mass on CT or MRI is becoming increasingly common, currently in

more than 15% of ACC diagnoses (2, 6). The hallmark of ACC treatment remains complete surgical resection (5). Adjuvant mitotane treatment is currently considered to have a positive effect on survival rates, although data from randomized control trials are lacking (7).

In recent years, considerable efforts were made to determine tumour characteristics influencing survival, which was well established for tumour stage, age and completeness of resection (8, 9, 10). In recent years, larger studies have reported on overall and recurrence-free survival of hormone-secreting ACCs (cortisol, androgens or aldosterone) (2). Potentially, hormone excess such as in cortisol-secreting ACC could influence prognosis. Cushing's syndrome is known to decrease overall survival, mainly due to long-term cardiovascular complications even after complete remission (11, 12, 13). Also the effects of hypercortisolism on infection risks are well known (13). Cortisol excess is also associated with a transcriptome signature related to an aggressive ACC subtype (14).

The prognostic role of ACC hormonal functional status, overt cortisol secretion as well as overt androgen secretion in ACCs, was investigated in this systematic review and meta-analysis.

Methods

Study selection

We searched for publications assessing the prognostic role of tumour functional status in ACCs, overt cortisol secretion as well as overt androgen secretion. PubMed, EMBASE and The Cochrane Library were searched January 2018 (Supplementary data 1, see section on [supplementary data](#) given at the end of this article). RCTs or cohort studies published after 1990 on the prognostic role of adrenocortical hormones in ACC were eligible. Publications were considered eligible if the study reported a ratio measure (relative risk (RR), odds ratio, hazard ratio (HR)) for hormone secretion (specific hormone or hormonal functional status in general) on overall or recurrence-free survival. Publications that did not provide a ratio measure were eligible if they provided raw data in the article or supplementary data (number of events/total number of patients for functional vs non-functional tumours).

Publications that included adenomas and publications with a sample size <50 were not considered. Only publications in English were eligible. We further assessed potentially eligible publications for overlap. In case of

>25% overlap, the publication with the smallest sample size was excluded. When two publications used the same patient group but reported on different outcomes we included both publications and used the largest study to extract patient characteristics.

Data extraction

Data extraction was performed by two authors independently (TV and OMD). We tried to retrieve missing data by emailing the corresponding author. Extracted data included first author, hospital location, year of publication, starting and final year of patient recruitment, study design, number of included patients, age, sex, stage, recurrence and overall survival in years, tumour grade, tumour size, number of functional tumours, cortisol-secreting tumours, androgen-secreting tumours, aldosterone-secreting tumours, multiple hormones-secreting tumours, number lost to follow-up.

Definition of hypersecretion and assessment method

The European Society of Endocrinology/European Network of the Study of Adrenal Tumours (ENSAT) guideline suggests hormonal evaluation of clinically non-functional adrenocortical tumours using a 1 mg dexamethasone suppression test (assessing glucocorticoid excess) and screening for increased aldosterone and suppressed renin levels and hypersecretion of androgens (15). Given most publications included patients from multiple centres, and often details on biochemical work-up were not provided, we relied on the author's definitions in use for the definition of hormone-secreting ACCs. We aimed to extract data for cortisol- and androgen-secreting ACCs separately; however, in some studies ACC were classified as functional in general.

Risk of bias assessment

We used a component approach for risk of bias analysis, judging all publications individually. The following elements were assessed:

- histological confirmed in almost all ACC (>95%) was considered low risk of bias; histological confirmation in 90–95% was considered intermediate risk; otherwise as high risk of bias;
- inclusion of consecutive ACCs (inclusion of all ACCs according to the predetermined eligibility criteria of the study) was considered low risk of bias;

- loss to follow-up: 5–10% was considered intermediate risk of bias; more than 10% or loss to follow-up was not mentioned articles was considered high risk of bias;
- biochemical confirmation of ACC functional status: publications that used only clinical parameters were considered high risk; publications that included biochemical ACC or clinical confirmed functional ACC were considered intermediate risk of bias; publications using biochemical assessment in all ACC were considered low risk of bias;
- missing data on secretion of ACCs: if more than 5% of values were missing or no report was made on this issue articles, were considered high bias risk;
- statistical adjustment for age and tumour stage was considered low risk of bias, adjusting for age or tumour stage was considered intermediate risk of bias and adjusting for none was considered high risk;
- non-standardized follow-up procedures were considered high risk of bias.

Statistical analysis

Heterogeneity was first assessed by visual inspection of the forest plot. Study-specific estimates and their CIs or standard errors were used for meta-analyses. RRs were pooled in a random effects model. Small study effects were assessed in a funnel plot; funnel plots were provided only if more than five studies were available. I^2 was used to quantify statistical heterogeneity between publications (16). We conducted a meta-regression to quantify the difference between risk measures unadjusted and adjusted for tumour stage.

Results

Study inclusion and study characteristics

Of 1523 eligible publications, nineteen (eighteen cohort studies, one RCT (1, 4, 7, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32)) were included, representing a total of 3814 patients (Fig. 1 for flow-chart of study inclusion). All publications except one (17) were published after the year 2000; eleven publications (57%) were published between 2012 and 2017. Publications included 76 to 524 patients. Four publications included less than 100 patients and five publications more than 300 patients. Eight publications excluded children; one study (18) included children only. The average follow-up time across publications was 42.5 months. The average age at diagnosis across publications ranged from 42 to 52 years,

Figure 1

Search strategy.

with the exception of the study in children (18). Thirteen publications included all stages of ACC; two publications investigated stage IV disease only. In total, 102 patients had stage I, 961 stage II, 1063 stage III and 1138 had stage IV ACC. Overall, average tumour size was 11.5 cm (Supplementary data 2 for details of included studies).

Definition of functional ACC differed across publications. Eight publications defined hypersecretion biochemically. Three publications added clinical symptoms of hormonal secretion as a criterion. Four studies defined clinical symptoms of hormonal secretion as the only criterion, one publication defined hormonal secretion as the presence of either clinical symptoms or biochemical secretion. In the remaining three publications, a definition was missing.

Risk of bias assessment

Of nineteen included publications, seven had a low, six had an intermediate and six had a high risk of bias (supplementary data 3 for risk of bias assessment of all included studies). ACC diagnosis of tumour functional status was often not (completely) based on biochemical evidence (5/19 publications) or it was not reported how tumour functional status was defined (3/19). Only two publications reported standardised follow-up procedures. Eleven publications had more than 5% missing secretion values and only 3/19 publications adjusted for both age and tumour stage.

Figure 2

Weighted relative risks of hormone-secreting ACCs for overall survival.

Meta-analysis of functional ACCs

Of all ACCs, 50.4% was considered functional. Nine publications reported on the relationship of all-sort functional status and overall survival, with reported relative mortality risk measures ranging from 0.70 to 2.30. All but one study suggested a decreased survival in hormonal functioning ACC. We pooled data from unadjusted and adjusted models (for tumour stage) separately (Fig. 2). The weighted RR for overall survival was 1.26 (95% CI: 1.03–1.54) for unadjusted estimates (8 publications, 1453 patients) and 1.54 (95% CI: 1.28–1.85) in data from models adjusting for tumour stage (4 publications, 1199 patients). Heterogeneity was $I^2=51\%$ in unadjusted and $I^2=0\%$ in data from models adjusting for tumour stage (Fig. 2 and Supplementary data 6).

Seven publications reported on the relationship of functional status and recurrence-free survival, with a reported RR ranging 1.00 to 1.80. In a meta-analysis, the weighted RR for recurrence in the unadjusted estimates (five publications, 1030 patients) was 1.24 (95% CI: 1.00–1.54) and 1.41 (95% CI: 1.09–1.81) in data from three publications (538 patients) adjusting for tumour stage (Fig. 2 and Supplementary data 7).

Meta-analysis cortisol-secreting ACCs

Cortisol secretion was reported in 36.5% of ACCs. Nine publications (2252 patients) reported on overall survival, of which four (1351 patients) provided data from a model adjusting for tumour stage. Reported mortality risk measures ranged 1.05 to 3.94, all pointing towards an increased mortality in cortisol-secreting ACCs.

The weighted relative risk for mortality was increased in cortisol-secreting ACCs compared to non-cortisol-secreting ACCs in the analysis with unadjusted estimates, RR: 1.52 (95% CI: 1.25–1.85) and adjusted estimates, RR: 1.71 (95% CI: 1.18–2.47), with I^2 of 80% and 74% respectively (Fig. 3).

All four publications (1453 patients) reporting on recurrence-free survival reported a worse recurrence-free survival in cortisol-secreting ACCs, risk measures ranging from 1.04 to 2.59. The weighted RR for recurrence for publications with unadjusted estimates was 1.26 (95% CI: 1.05–1.51); $I^2=88\%$. After pooling three publications (1149 patients) that provided data from tumour stage adjusting models was the pooled RR was 1.43 (95% CI: 1.18–1.73); $I^2=14\%$ (Figs 2 and 4). Exclusion of the study in children did not change our results (data not shown).

Meta-analysis of androgen-secreting ACCs

Of all ACCs, 18.5% produced androgens (with or without other hormones). Only four publications (1032 patients) provided a separate risk measure for androgen secretion: only one of which corrected for tumour stage (19). RR measures ranged from 0.40 to 1.09. The weighted RR was 0.82 (95% CI: 0.60–1.12) with $I^2=71\%$ (Fig. 2 and Supplementary data 8). Only one study assessed the effect of aldosterone overproduction (19).

Meta-regression

We evaluated the difference between unadjusted and adjusted models (for tumour stage) formally using meta-regression. All coefficients showed a small increase in effect in data from models adjusting for tumour stage, meaning an underestimation of the effect in studies unadjusted for stage. Meta-regression results are shown in Supplementary data 9.

Discussion

Main result

This systematic review and meta-analysis shows that cortisol-secreting ACCs are associated with a worse

Figure 3
Weighted relative risk of cortisol-secreting ACCs for overall survival.

overall survival. This finding was robust as all individual publications report a higher mortality risk in cortisol-secreting ACCs. Recurrence risk was also higher in producing than in non-producing ACCs. Androgen secretion was not clearly associated with a worse prognosis; however, data on androgen-secreting ACCs are limited and its prognostic relevance thus uncertain.

Limitations

An important limitation of this systematic review is that articles providing a nonsignificant relationship for hormone secretion often did not report estimates adjusted for tumour stage. In some cases, adjustment for tumour stage seemed to be performed but was not reported due to lack of statistical significance. Importantly, the cortisol-

Figure 4
Weighted relative risk of cortisol-secreting ACCs for recurrence-free survival.

mortality association was not largely affected by statistical adjustment, and if anything, the associations were more pronounced. Despite these considerations we cannot exclude the possibility that (unmeasured) confounding is partly explains the results, which is in line with the general agreement that a meta-analysis of observational studies is not establishing causality formally. A second limitation was the difference in definition of hormonal excess. If a clear definition was provided, it was based on clinical and/or biochemical parameters, depending on the publication. A third limitation is the problem of overlapping cohorts. Since ACC is a rare disease (part of), the same patients are analysed in different publications. We restricted inclusion to publications with an overlap <25% but we acknowledge that a considerable percentage of overlap sometimes remains. A final limitation is the way data were presented. Most, but not all, publications provided us with (the possibility to calculate) a HR, but in some cases, we had to settle for the RR in which time-to-event is not accounted for.

Interpretation

Included publications robustly report a worse overall survival and higher recurrence risk in cortisol-secreting ACC. The interpretation of this finding is not straightforward, and a meta-analysis does not formally establish causality. A higher mortality risk could be explained by the negative effect of cortisol action on the immune and the cardiovascular system. This explanation is in line with the increased mortality risk in patients with Cushing's disease from benign causes; and this increased mortality risk was not only shown compared to the general population (13), but was also apparent when comparing Cushing's disease to other pituitary adenomas (33). However, the finding of a higher recurrence risk cannot convincingly be explained by cortisol action. One explanation is that cortisol signifies ACCs with a more aggressive behaviour. Recent research shows that cortisol excess is associated with a transcriptome signature related to aggressive subtype of ACC (14). However, we acknowledge that publication bias, only positive associations reported, may be another explanation.

Quite a substantial number of the ACCs included in this systematic review produced multiple hormones (30%). It is plausible that the negative effect of tumour functional status on survival is mainly related cortisol secretion. It is less likely that this effect is caused by another hormone since androgen and aldosterone (cortisol secretion is often accompanied by androgen secretion) were not associated

with overall survival, but data on these hormones are scarce and more research is required to make more firm conclusions about aldosterone- and androgen-secreting ACCs (20).

Clinical relevance

When considering ACC prognosis, clinicians can take functional status of the tumour into account as an additional prognostic marker.

Conclusion

This systematic review and meta-analysis shows that cortisol-secreting ACCs have a worse overall survival; future research is needed to establish whether this association points to negative effects of cortisol action, whether it signifies a more aggressive ACC subtype or whether cortisol is merely a prognostic marker.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0450>.

Declaration of interest

Authors Fassnacht M and Dekkers OM are editors of the European Journal of Endocrinology. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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