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Differences in outcomes of bilateral adrenalectomy in patients with ectopic ACTH producing tumor of known and unknown origin

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ABSTRACT

Background: Endogenous Cushing syndrome (CS) can be caused by ectopic corticotropin-producing tumors of known (EK) and unknown origin (EU). Bilateral adrenalectomy (BA) can be used as definite treatment of hypercortisolism in such cases. This study compared patients undergoing BA for CS secondary to EK vs EU.

Methods: Retrospective review (1995–2017) of patients undergoing BA due to EK or EU. We analyzed demographic characteristics, laboratory values, intraoperative variables, surgical outcomes, and survival.

Results: 48 patients (26 EU, 22 EK) were identified. Serum cortisol and ACTH concentrations were similar. 92% of BA for EU were performed minimally invasively vs 77% for EK, $P = 0.22$. Complications occurred in 19% of EU and 4.5% EK, $P = 0.2$. Mean survival was 4.3 years for EU and 4.0 years for EK without difference in all-cause mortality $P = 0.63$.

Conclusion: BA cure rate was 100% for CS in EU and EK. Morbidity, long term and all-cause mortality differences were not statistically significant between EK and EU.

Introduction

Cushing syndrome (CS) is a state of hypercortisolism, which can be corticotropin (ACTH) dependent or independent. Its clinical presentation varies from asymptomatic patients to florid cases with severe metabolic derangements, proximal muscle weakness, body fat redistribution, hyperpigmentation, among other clinical manifestations.[1–5] Among endogenous causes, ectopic ACTH production accounts for 5–18% of cases, with multiple types of tumors being known for this presentation, such as lung carcinomas, thymic carcinomas and other neuroendocrine tumors.[1,3,5–10] However, 12–40% of cases of ectopic ACTH production arise from occult tumors, or of unknown primary origin (EU), posing a diagnostic and therapeutic challenge.[1,6,11–16]

Bilateral adrenalectomy (BA) is a well-established treatment for refractory CS secondary to ACTH-secreting pituitary adenomas that have failed other therapeutic options. BA is also performed for refractory CS due to ectopic ACTH secretion (EA) in the setting of unresectable or incurable primary tumor of known origin (EK), or in cases of EU.[1,2,5,16–21] EA is a very heterogenous population, with EK presenting a very complex group of patients that undergo numerous multi-modal treatments for their primary disease prior to BA. Multiple techniques have been described for BA, with minimally-invasive approaches gaining popularity due to lower morbidity and shorter hospital stay.[12,17,18]

Data on differences between BA in EA and EU is scarce, and so the aim of this study was to assess differences in surgical outcomes in BA performed for ectopic ACTH CS due to EK or EU in a tertiary referral center.

Patients and methods

This retrospective review was approved by the Mayo Foundation Institution Review Board. All patients of age 18 years or more at time of surgery, who underwent BA due to ectopic ACTH-producing tumors of known (EK) and unknown origin (EU), between January 1st, 1995 and December 31st, 2017, were included. Patients with

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Table 1
Basic Demographic and pre-operative laboratory values for patients with EU and EK.[a].

	EU (n = 26)	EK (n = 22)	Total (n = 48)	*P*
Sex				
Males	14 (53.8%)	12 (54.5%)	26 (54.2%)	0.96
Age, years (Median, IQR)	50 (32)	49.5 (37.25)	50 (30.5)	0.25
BMI, kg/m^2 (Median, IQR)	30.5 (7.8)	27.6 (8.43)	29.1 (8.93)	0.37
Highest pre-operative serum cortisol, mcg/dL (Median, IQR)	57 (36.2)	56.5 (29.9)	57 (32)	0.89
Highest pre-operative urinary cortisol, mcg/24 h (Median, IQR)	1208.5 (1938.63)	1260 (3652.25)	1223 (2150.63)	1
Highest pre-operative ACTH, pg/ml (Median, IQR)	137 (141)	188.5 (179.75)	148 (146)	0.48

[a] EU = Ectopic ACTH = producing tumor of unknown origin, EK = Ectopic ACTH = producing tumor of known origin.

pituitary source of ACTH as well as carriers of metastatic disease of unknown primary were excluded from this study. Patients who had location of primary disease identified after BA were categorized as EU for the purpose of this study. Information regarding demographics, pre-operative presentation, previous treatments, as well as intra and post-operative variables was retrieved from electronic medical records. Data were recorded up to death or last follow-up. Descriptive statistics were used to report categorical data. Continuous data are reported as mean and standard deviation (SD), or median and interquantile ranges (IQR 25–75). Group differences are analyzed by chi-squared test for discrete variables and two sample t-tests as well as Wilcoxon-Mann-Whitney test for non-parametric continuous variables. Survival analysis was performed by Kaplan-Meier and compared with log-rank test. Complications were classified following the Clavien-Dindo classification.[22] The software JMP 14.1.0 (SAS, Cary, NC, 2018) was used for the statistical analysis. Study data were recorded and managed using the Research Electronic Data Capture system. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies.[23]

Results

A total of 53 patients were identified: 26 were categorized as having ectopic ACTH-dependent CS of EU and 23 as EK, with a mean follow-up of 2.96 years after BA. Five patients were excluded, four patients were diagnosed having metastatic adenocarcinoma of unknown primary through biopsies of lymph nodes and one patient did not undergo BA due to inability to tolerate surgery. Sex distribution of patients was similar in groups, 53.9%[14] of EU cohort and 54.5%[12] of EK cohort were of female sex, $P = 0.96$. Median age and IQR in years was 50 (32) for EU and 49.5 (37.25) for EK, $P = 0.84$ (Table 1). At the time data were gathered, 10 patients from the EU were deceased, vs 16 from the EK cohort. Four patients (15.4%) of the EU cohort had their primary tumors localized after performing BA, median 0.9 (25.99) months; all of them found to be either bronchial carcinoid or lung carcinomas. For the purpose of this study they were left in the EU cohort as BA was performed when the origin of their primary tumor was still unknown. Amongst the EK cohort, pancreatic neuroendocrine tumor was the most common etiology (32%, n = 7), followed by thymic carcinoid (22%, n = 5), medullary thyroid cancer (14%, n = 3) and bronchial carcinoid (14%, n = 3). Twenty-one (95.5%) of the EK cohort had metastatic disease at the time of BA, and one patient had unresectable primary disease. Twenty-three patients in our cohort were treated medically for hypercortisolim prior to BA, and all failed medical therapy. Surgical treatment of primary neoplasia was attempted in 17 patients (77.3%) in the EK cohort prior to BA. Pre-operative laboratory parameters were similar amongst cohorts: serum cortisol (mcg/dL) was 57 (36.2) for EU and 56.5 (29.9) for EK ($P = 0.89$); urinary cortisol (mcg/24 h) was 1208.5 (1938.63) for EU and 1260 1260 (3652.25) EK ($P = 1$) and highest serum ACTH (pg/ml) was 137 (141) for EU and 188.5 (179.75) for EK ($P = 0.48$) (Table 1).

Time from diagnosis of CS until BA was 1.5 (5.16) months for EU and 1.28[2] for EK, $P = 0.32$. Twenty-four (92.3%) of the EU cohort underwent BA through a minimally invasive approach, vs 17 (77.3%) from the EK group, $P = 0.22$. Most MIS cases were planned as an anterior approach, with only one patient in our cohort undergoing retroperitonescopic BA. Four patients from the EK cohort also underwent other surgical procedures at the same time as BA with the goal of controlling primary or metastatic disease.[1] Three patients from the EK cohort required conversion to open procedures vs none from the EU, $P = 0.03$. Operative time in minutes was 242 (95.75) for EU and 207 (86.5) for EK, $P = 0.25$. Estimated blood loss (EBL) and need for intra-operative transfusion were similar between groups ($P = 0.62$ and $P = 1$ respectively). When a transfusion was needed, EK required a higher number of units 2.5 (1.75) vs 1 (0.75) for EU, $P = 0.03$.

Eight (30.8%) of EU patients required intensive care unit (ICU) management post-operatively, vs three (13.6%) from the EK, $P = 0.11$. Length of ICU stay was similar between groups, 4.5 (11.5) days for EU and 3[6] days for EK, $P = 0.64$. LOS differences were also not statistically different among groups, 7.5 (10.25) for EU and 5.5 (7.5) for EK, $P = 0.28$. Resected adrenal glands showed no difference in weight or longest diameter, 10.8 (5.21) gr and 6.7 (1.3) cm for EU and 9.1 (6.26) gr and 6.5 (1.55) cm for EK, $P = 0.62$ and 0.25 respectively (Table 2). Five (19.2%) of the EU cohort presented a complication during the first 30 post-operative days, vs one (4.5%) of EK, $P = 0.2$. The most common complications were of embolic origin[2] (50%), followed by respiratory failure (33%) and bleeding (17%). All complications were IIIa-IVa according to the Clavien-Dindo Classification (22). There was 30 day mortality detected in any of the groups. One of the patients presented with an acute hypercortisolism crisis, and during the time of the operation was found to have a large gastric ulcer with extensive intra-abdominal contamination, so BA was postponed until clinical stabilization of the patient, unfortunately the patient died shortly after, without having BA performed. All patients who underwent BA had biochemical cure of CS, with no difference in post-operative cortisol levels, $P = 0.83$. Mean survival in years was 4.3 for EU and 4.0 for EK, $P = 0.79$, Fig. 1. Out of the 26 deaths, 13 (50%) are attributed to progression of primary disease, one (3.8%) to cardiovascular disease, and 12 (46.2%) have no attributed cause. No deaths are attributed to Addisonian crisis.

Discussion

EA is a rare and heterogeneous group of neoplasms.

[1] Procedures performed for primary or metastatic disease control at same intervention as BA: liver wedge resections, small bowel resection, distal pancreatectomy.

[2] DVT, ischemic CVA.

Table 2
Intra and Post-Operative variables.

	EU (n = 26)	EK (n = 22)	Total (n = 48)	*p*
Time from diagnosis of CS until BA, months (Median, IQR)	1.5 (5.16)	1.28[2]	1.46[2]	0.32
Specimen characteristics (Median, IQR)				
Adrenal weight, gr	10.8 (5.21)	9.1 (6.26)	10.5 (5.66)	0.32
Adrenal diameter, cm	6.7 (1.3)	6.5 (1.55)	6.7 (1.4)	0.29
Operative time, min (Median, IQR	242 (95.75)	207 (86.5)	218 (83.5)	0.25
Minimally Invasive Approach	24 (92.3%)	17 (77.3%)	41 (85.4%)	0.22
Conversion to open procedure	0 (0%)	3 (13.6%)	3 (5.3%)	0.03
EBL, ml (Median, IQR)	100 (150)	75 (149.5)	100 (162)	0.62
Need for Intra-operative Transfusion	4	4	8	1
Amount of units needed, (Median, IQR)	1 (0.75)	2.5 (1.75)	2 (3.25)	0.03
Post-Op ICU stay	8 (30.8%)	3 (13.6%)	11 (22.9%)	0.12
Length of ICU stay, days (Median, IQR)	4.5 (11.5)	3 (6)	3 (6)	0.64
Length of hospital stay, days (Median, IQR)	7.5 (10.25)	5.5 (7.5)	6 (8.75)	0.28
30 day Complication rate	5 (19.2%)	1 (4.5%)	6 (12.5%)	0.2
Post-operative cortisol level (mg/dL) (Median, IQR)	1.5 (4.8)	1.6 (10.8)	1.6 (5.2)	0.83

Hypercortisolism can play a defining role in morbidity associated to it. BA can be performed safely in EK and EU, with no statistically significant differences in early morbidity and long-term and all-cause mortality.

Our cohort had a male sex predominance (54%) and median age was 49 years with no statistical difference between EU and EK cohorts. Age at presentation was consistent with some series in current literature.[8,10,12] There are a few series, however, that show a younger population, with age being described around 30–40 years.[1,7,24] From a sex distribution perspective, many studies show a slight predominance of female sex.[7,10,12] We attribute these differences to the fact that these are rare conditions, with small and heterogeneous case series.

Ectopic ACTH-dependent CS of EU made up 54% of our cohort, more than described in other series, where occult tumors account for 5–19%.[7,8,10,20] We believe this difference is due to patient selection. Our study accounted only for EA patients undergoing BA, which excludes most of the population of EK that undergoes curative treatment for their primary disease, increasing the percentage of EU in our cohort. Most series report that the majority of their EK is intra-thoracic, 29–80%, similar to what our study showed.[1,6,8,10,12,25] Of the fifty-three patients initially found, four were excluded (7.7%), as they were found to have metastatic adenocarcinoma of unknown primary. The EU cohort presented no signs of metastatic disease, and so, it was decided to exclude these four patients, as they did not fit the categories of either known incurable or unresectable disease or presumed localized disease of unknown origin. This is similar to what Isidori et al. found in their study.[10] Four of our patients were classified as EU at the time of BA, and were subsequently diagnosed with pulmonary malignancies. Morris et al. describe that 2 out of the 9 patients in their EU cohort also had primary tumors localized later.[20] This helps to further demonstrate the diagnostic and therapeutic challenges associated with this heterogeneous group of neoplasms. Most EK patients undergoing BA present with metastatic disease, continuing the trend previously documented by Porterfield et al. in an earlier Mayo Clinic series.[6]

Serum cortisol, urinary cortisol and serum ACTH were found to be similar among EU and EK, similar to what Ilias et al. have found.[7] Other modern cohorts do not compare laboratory values between EU and EK, but have shown showed similar ranges for ACTH, serum and urinary cortisol.[1,7,8,10]

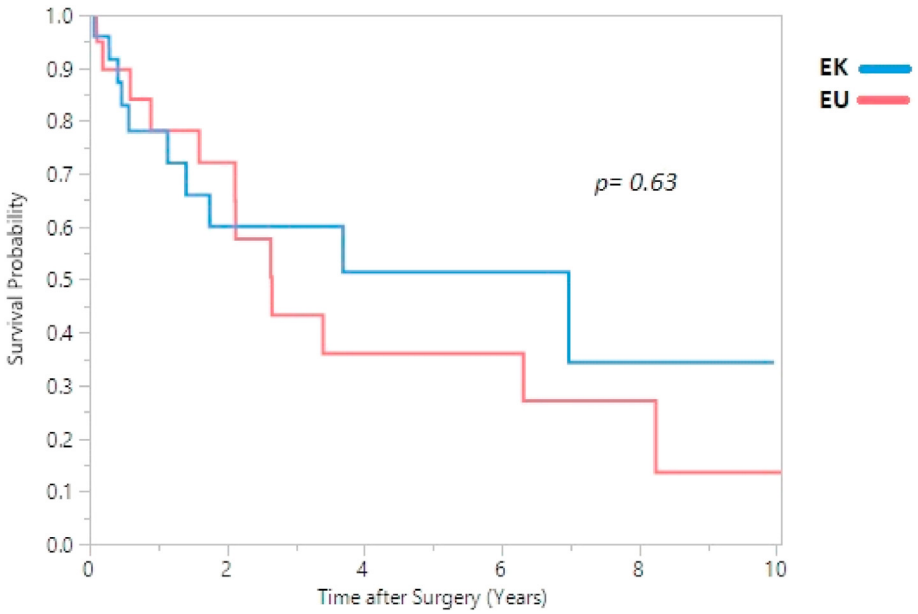

Fig. 1. Kaplan-Meier for 10 year survival for Patients with EK vs EU.[31].

The majority of BA cases were performed with a minimally-invasive approach, with only three conversions to open, all of which occurred in the EK cohort. Alberda et al. report one conversion in their series of 21 patients, and median time of the operations being 246 min.[12] The EK group not only had a higher conversion rate to open procedure, but also a higher rate of planned open procedures, 22.7% vs 7.7% in the EU group. We attribute this difference to the fact that many of the patients in the EK group have undergone previous abdominal interventions, resulting in more technically challenging procedures as well as having planned combined procedures for controlling primary disease at the time of BA. Other series report mean time varying from 221 to 260 min plus standard deviations, similar to our operative times (Table 2).[2,21] EBL and intra-operative transfusion requirements were similar between groups. In cases where transfusion was needed, the number of units transfused was found to be higher for EK, which may be associated with the higher conversion rate in this cohort as well as the likelihood of these patients undergoing other procedures at the same time. Complication rates are described in the literature in 2–26% of patients.[1,12,17,21,26] A complication in the 30 day post-operative period developed in 12.5% of our patients, with a higher incidence in the EU cohort. In addition, more patients from the EU cohort required ICU care and for longer periods of time post-operatively, a difference not statistically significant. The most common complication was of thromboembolic nature (50%), followed by pulmonary complications requiring prolonged respiratory support, also contributing to the prolonged hospital stay in our cohort. Hypercortisolism is known to be associated with thromboembolic events, some series quoting up to 14% of patients suffering one type of embolic event.[8]

Mean survival after BA was 4.3 years for EK and 4.0 years for EU, $P = 0.63$ (Fig. 1). Survival rates are varied in literature due to variety of inclusion criteria in cohorts, varying from 38 to 51% at 5 years; 5 year survival rates were 52% for EU and 35% for EK in our study.[6,12,27]

Davi et al. reported that up 31% of EA patients underwent BA in their cohort.[15] However, we have only reviewed the cases of patients who did undergo BA. Hypercortisolism is described as developing at a fast pace in EA patients, with important clinical deterioration within a few months.[6] Even though overall complication rates in this patient population is very high due to the advanced stages of primary disease as well as the negative impact in their overall clinical status from CS, BA offers the possibility of patients achieving a better clinical status for other treatment forms for their primary neoplasm.[12,15,20] It is known that different types of EA have different prognosis, depending on histologic types and differentiation.[15,20] This was not accounted for in this study and makes the evaluation of survival in such a heterogeneous group difficult. Studies have suggested that EU may have better prognosis than EK.[7,10] In our study survival was similar. Four patients had been excluded from the study as they had been diagnosed with metastatic disease of unknown primary, which is different than our EU cohort (assumed to be metastasis free). This is an intrinsic bias to the populations being compared in this study. It is also important to note that 4 of our EU patients had their primary tumors localized after BA, depicting the difficult cross-over dilemma when studying the survival of this cohort.

This was a large retrospective cohort that contains patients treated over a period of more than 20 years, and so has some intrinsic limitations. Over the last 20 years imaging and laboratory as well as treatment modalities have evolved and may have impacted comparisons. Multiple charting systems have been employed, making retrieval and analysis of information subject to misinterpretation. Our study only looked at patients who were undergoing BA, so there is a bias of choosing patients who were likely not candidates for curative treatment of their primary neoplasm. Even though this is a long time frame, and one of the largest cohorts reported, it still represents a small and very heterogeneous group of patients, making interpretation of data difficult, and extrapolation of data should be done with caution. Our study shows few differences between groups but and this is likely due to the study being underpowered due to cohort size and so, more prospective studies are needed to better delineate the clinical characteristics and treatment outcomes for this patient population.

[3] EU = Ectopic ACTH = producing tumor of unknown origin, EK = Ectopic ACTH = producing tumor of known origin.

Conclusion

EA presents in a wide clinical spectrum, with EK and EU posing difficult diagnostic and therapeutic dilemmas. Hypercortisolism is a very important component of their rapid clinical deterioration and BA can be safely performed in order to halt progression of its deleterious effects. BA in patients with EU and EK can cure hypercortisolism and can be safely performed in both groups with limited morbidity and mortality. It can be an important tool in improving clinical status to allow patients to undergo further treatment options for their underlying neoplasm, but more robust prospective data is needed.

Data statement

Due to the sensitive nature of the questions asked in this study, patients were assured raw data would remain confidential and would not be shared.

Declaration of competing interest

Authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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