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Role of Additional Organ Resection in Adrenocortical Carcinoma: Analysis of 167 Patients from the U.S. Adrenocortical Carcinoma Database

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Abstract

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Background.—Adrenocortical carcinoma (ACC) is a rare and aggressive cancer. This report describes factors and outcomes associated with resection of extra-adrenal organs en bloc during index adrenalectomy.

Methods.—Patients who underwent ACC resection for nonmetastatic disease from 1993 to 2014 at 13 participating institutions of the US-ACC Group were included in the study. Factors associated with en bloc resection were assessed by uni- and multivariate analysis. The primary end point was overall survival.

Results.—In this study, 167 patients were included and categorized as adrenalectomy with en bloc resection (AdEBR) if they had extra-adrenal organs removed or adrenalectomy (Ad) if they did not. The demographics were similar between the AdEBR (n = 68, 40.7%) and Ad groups, including age, gender, race, American Society of Anesthesiology (ASA) class, and body mass index (BMI). The AdEBR group had larger tumors (13 vs. 10 cm), more open operations (97.1 vs. 63.6%), and more lymph node dissections (LNDs) (36.8 vs. 12.1%). The most common organs removed were kidney (55.9%), liver (27.9%), and spleen (23.5%). Multiple organs were removed in 38.2% (n = 26) of the patients. Margin-negative resections were similar between the two groups. In the multivariate Cox regression adjusted for T and N stages, LND, margin, size, and hormone hypersecretion, en bloc resection was not associated with improved survival (hazard ratio [HR], 1.42; p = 0.323).

Conclusion.—The study findings validated current practice by showing that en bloc resection should occur at index adrenalectomy for ACC when a T4 lesion is suspected pre- or intraoperatively, or when it is necessary to avoid tumor rupture. However, in this study, when a negative margin resection was otherwise achieved, removal of extra-adrenal organs en bloc was not associated with additional survival benefit.

Adrenocortical carcinoma (ACC) is a rare but aggressive malignancy with a poor prognosis.[1] Its incidence has remained stable during the past several decades at 0.7 per million in the United States.[2] Approximately 60% of ACC patients present with stage 1, 2, or 3 disease,[5] making them amenable to complete surgical resection. Even for those with fully resectable disease, the 5-year survival rate approaches only 50%.[1,3] Those with unresectable disease, on the other hand, have a median survival of < 1 year[3,6,7] and a 5-year survival rate of approximately 0%.[3,8]

Due to the rarity of the disease and sparse reporting systems, literature on the ideal medical and surgical management of these tumors is based on limited data, and survival improvement of patients with ACC lags behind that of patients with more common solid cancers.[9,10] Complete surgical resection remains the only curative treatment for ACC,[10] yet notwithstanding negative-margin resection, the incidence of locoregional and distant recurrence remains disappointingly high.[7,11–14] Retrospective data suggest that surgical resection[14] and early specialized follow-up[15–17] assessment are associated with improved recurrence-free and overall survival,[7,13,18,19] and there is consensus that negative margins and avoidance of intraoperative tumor rupture are critical to better outcomes.[11,20–22] Performance of lymph node dissection (LND) also may be associated with improved survival.[23–25]

Extra-adrenal organs often are removed en bloc during index adrenalectomy for ACC.[14,26] In the past, some have advocated compulsory ipsilateral nephrectomy due to the close association of the adrenal gland and the kidney and their lack of separation by a complete fascial layer, suggesting concurrent nephrectomy may improve outcomes.[17,27] However, no data exist to support this approach. The anatomic and intraoperative factors that lead to resection of the extra-adrenal organs, the most common organs removed, and the benefits and risks of these additional organ resections have yet to be described in detail. The current study attempted to examine the anatomic and intraoperative factors associated with en bloc resection and to determine whether such resections are associated with differences in outcome.

METHODS

Patient Population and Study Design

The U.S. Adrenocortical Carcinoma Group (US-ACCG) consists of the following 13 academic medical centers: Vanderbilt University, Emory University, Stanford University, The Johns Hopkins University, Medical College of Wisconsin, New York University, The Ohio State University, Washington University in St. Louis, University of Wisconsin, University of California San Diego, University of Texas Southwestern, University of California San Francisco, and Wake Forest University. This collaboration retrospectively identified all patients who underwent resection for ACC between 1993 and 2014 at each institution. The institutional review boards at all the participating centers approved this study.

From this patient population (n = 265), only the patients with localized (M0) disease (n = 167) were included in our analysis. The patients were stratified into the two following groups based on the extent of their resection at the index operation: adrenalectomy with en bloc resection (AdEBR) if they had extra-adrenal organs removed or adrenalectomy (Ad) if they did not. Venous resections and tumor thrombectomy were not considered additional organ resection. Demographic, preoperative, intraoperative, pathologic, perioperative morbidity, and survival data were collected through review of the medical record at each institution. The preoperative variables included age, race, comorbidities, presence of hormonal excess, symptoms, and suspicion of vein involvement or tumor thrombus. The intraoperative variables included operative approach, extent of resection, LND, and performance of tumor thrombectomy or venous resection. Intraoperative factors were obtained from the surgeon's operative report (e.g., if a surgeon dictated that a LND was performed, this was recorded as such regardless of anatomic landmarks used as limits of dissection or number of lymph nodes removed).[23] The pathologic variables included tumor size, tumor weight, tumor-node-metastasis (TNM) stage, tumor grade, number of lymph nodes in the specimen, vein involvement, and margin status.

The American Joint Commission on Cancer Staging Manual, seventh edition, was used to determine TNM classification.[12] Postoperative morbidity was graded using the modified Clavien-Dindo classification of surgical complications.[28] Survival data were determined by chart review and confirmed with the Social Security Death Index database.

Statistical Analysis

Categorical variables were presented as frequency and percentages and compared using Chi square or Fisher's exact test, as appropriate. Continuous variables were reported as median values with interquartile range (unless otherwise specified) and compared using the Kruskal–Wallis test. Overall, disease-free and disease-specific survival were calculated using the Kaplan–Meier method and compared using the log-rank test. Clinical and pathologic data were analyzed using multivariate Cox regression methods. Significance was set at a p value lower than 0.05. All statistical analyses were performed using the STATA 15.0 statistical software package (STATA Corp., College Station, TX, USA).

RESULTS

Of the 265 patients who underwent surgical resection for ACC during the study period (1993–2014), 167 had localized (M0) disease and were included in our analysis. Of these 265 patients, 99 (59.3%) underwent adrenalectomy only and were categorized into the adrenalectomy(Ad) group, and 68 (40.7%) had additional organs resected and were categorized into the adrenalectomy with en bloc resection (AdEBR) group.

The rates of en bloc resection did not change significantly during the study period (35.9% for the patients between 1993 and 2003 and 42.2% for the patients between 2004 and 2014; $p = 0.76$). Comparison of the two groups by demographics is summarized in Table 1. The mean follow-up period was 37.5 months overall (40.3 months for the Ad group and 33.6 months for the AdEBR group; $p = 0.20$). The groups were similar in age, sex, race, and American Society of Anesthesiology (ASA) class.

The groups had similar frequencies of pre- and postoperative chemoradiation and mitotane therapy. The Ad group had a higher rate of minimally invasive resections ($n = 34$, 34.3%) than the AdEBR group ($n = 1$, 1.5%). In the AdEBR group, 26 patients (38.2%) had multiple extraadrenal organs resected. The most common extra-adrenal organs resected were kidney ($n = 38$, 55.9%), liver ($n = 19$, 27.9%), spleen ($n = 16$, 23.5%), and pancreas ($n = 11$, 16.2%) (Table 2).

Compared with the Ad group, the AdEBR group had significantly larger tumors (13 vs. 10 cm; $p < 0.001$) and T stage ($p < 0.001$) by final pathology, and more node-positive disease ($p < 0.001$). The AdEBR group also was more likely to undergo an LND (36.8 vs. 12.1%; $p < 0.001$), to have lymph nodes available for analysis on final pathology (47.1 vs. 16.2%; $p < 0.001$), and to have more lymph nodes removed (3.4 vs. 0.6; $p < 0.001$). The AdEBR group had higher-grade tumors than the Ad group (p = 0.023).

In the AdEBR group, 38.2% of the patients ($n = 26$) had preoperative imaging suggestive of renal vein (RV) or inferior vena cava (IVC) involvement compared with 18.2% ($n = 18$) of the Ad group. Similarly, 22.1% ($n = 15$) of the AdEBR group had concern for RV or IVC thrombus on preoperative imaging compared with 4% ($n = 4$) of the Ad group.

Among the AdEBR group, 76.5% of the patients ($n = 52$) did not have extra-adrenal organ involvement by tumor on final pathology (T1–T3 tumors). Of these 52 patients, 26.9% ($n =$

14) had concern for RV or IVC involvement and 11.5% ($n = 6$) had concern for RV or IVC thrombus on preoperative imaging, whereas 19.2% ($n = 10$) had RV or IVC involvement on final pathology.

The rates of R0 resections were similar between the Ad and AdEBR groups (67.6 vs. 66.7%), as were the rates of R1 (22.1 vs. 21.2%) and R2 (4.4 vs. 2.0%) resections ($p = 0.703$) as well as the rates of intraoperative tumor rupture (12.1 vs. 7.4%; $p = 0.400$) (Table 3).

The median rates for survival were 91.8% at 1 year, 53.4% at 5 years, and 37.0% at 10 years for the Ad group and respectively 83.3, 52.4, and 45.2% for the AdEBR group. The overall ($p = 0.470$), disease-free ($p = 0.299$), and disease-specific ($p = 0.442$) survival rates were similar between the groups according to the log-rank test (Fig. 1). Among the patients who experienced recurrence, the Ad and AdEBR groups showed similar rates of locoregional (40 vs. 22%), distant (45 vs. 51%), and locoregional + distant (15 vs. 26%) recurrence ($p = 0.093$).

In the multivariate Cox regression analysis adjusted for T stage, N stage, LND, margin status, tumor size, and hormone production, en bloc resection of extra-adrenal organs was not associated with a survival advantage (hazard ratio [HR], 1.42; $p = 0.323$) (Table 4). Furthermore, for the patients with T1–T3 tumors and negative surgical margins, removal of extra-adrenal organs was similarly not associated with a survival advantage according to multivariate Cox regression (HR, 1.70; p = 0.149).

DISCUSSION

This large multi-institutional analysis demonstrated that the operating surgeons believed en bloc resection of extraadrenal organs was necessary for more than 40% of ACC patients without evidence of metastatic disease at the time of index adrenalectomy. This is similar to previously reported series (37–54%).[18,26] The patients who underwent en bloc resection of extra-adrenal organs were more likely to have preoperative imaging concern for large vein invasion or thrombus than the patients who underwent adrenalectomy alone, and they also had larger and higher-grade tumors. The most commonly resected extra-adrenal organs in our analysis were kidney, liver, spleen, and pancreas. Despite their more advanced tumors, en bloc resection led to equivalent rates of margin-negative resections and similar disease-free and overall survival rates.

In this study, when a margin-negative resection could otherwise be achieved, removal of extra-adrenal organs en bloc during index adrenalectomy for ACC was not associated with additional survival advantage. The current findings suggest that in the absence of extra-adrenal organ invasion by tumor and when margin-negative resection can otherwise be achieved without risk of tumor rupture, it may be best to avoid extra-adrenal organ resection due to lack of oncologic benefit, increased recovery time (longer hospital stay), and potential for increased morbidity both in the immediate postoperative period and in the future (e.g., susceptibility to post-splenectomy infections or increased risk of chronic kidney disease in the setting of surgical absence of a unilateral kidney). On the other hand, the equivalent

outcome between the two groups, despite the presence of more advanced tumors in the AdEBR group, suggests that whenever resection of additional organs is required to avoid violating the tumor capsule or to obtain clear margins, it should be performed.

Importantly, previous investigators have shown that a complete, margin-negative resection is associated with improved recurrence-free and overall survival for ACC patients.[1,20,29] Yet, pre- and intraoperative decision making regarding the ability to obtain negative margins in ACC is complex. Prior studies have indicated that opening/violating potentially invaded planes between the tumor and adjacent organs is a crucial factor in determining oncologic outcomes.[18,30] Adrenocortical carcinoma can be a large soft/friable tumor and may display adhesiveness to adjacent organs. Additionally, in patients with suspected large vessel invasion or tumor thrombus, it may be impossible to access the vessel or to mobilize the large ACC without removing other adjacent organs, even if those organs are not directly invaded. Finally, whether an organ is invaded by tumor cannot always be determined, and the decision to perform an en bloc resection may be made to avoid the potential for tumor spill as the surgeon tries to free the ACC from adjacent organ or organs.

Historically, some clinicians have advocated ipsilateral nephrectomy to improve locoregional control of disease recurrence through avoidance of tumor disruption and to facilitate a more extensive lymphadenectomy.[27,31]However, few data exist to support this practice. In fact, in small observational series, the addition of ipsilateral nephrectomy failed to demonstrate improved overall or disease-free survival.[32] Although direct invasion of the ipsilateral kidney is relatively rare, tumor invasion or thrombus of the ipsilateral large vein is more common.[33] Our series demonstrated that 26.3% ($n = 44$) of non-metastatic patients presented with large-vein invasion, consistent with previously published series.[34–36] Certainly, large-vein involvement or thrombus introduces unique challenges to surgical resection and, depending on the anatomy and tumor extent, may mandate ipsilateral nephrectomy even in the absence of direct renal involvement.

Several aspects of this analysis require careful consideration. First, inherent biases exist in any retrospective study, and our analysis was no different. For example, our en bloc resection group had larger tumors, higher T stage, and higher tumor grade than our control group, which is not unexpected given that larger and more aggressive tumors often require a more extensive resection. Despite this, the two groups had similar rates of margin-negative resections. This suggests that the removal of additional organs at the time of adrenalectomy was necessary to achieve a marginnegative resection even if those organs were not themselves involved by tumor. For example, resection of additional organs to avoid fracture of the tumor is justified in some circumstances even if no microscopic invasion is identified on final pathology because the process of dissecting large adrenal tumors (which often are soft, necrotic, and friable) from adjacent organs carries a bona fide risk of tumor rupture. Tumor rupture would render the operation non-curative, so extreme care must be taken to avoid such an event.

Second, to this effect, our study used a database, formulated by the collaborative effort of representatives at 13 institutions across the country, that had insufficient granularity to provide the *reason* for en bloc resection or to determine for patients with T4 lesions or

positive margins which extra-adrenal organs or surgical margins were involved by tumor. This information would provide more insight into the surgical decision-making that contributes to extra-adrenal organ resection.

Third, although we controlled for tumor size, T stage, and N stage in our multivariate analysis, the larger tumors and higher T stage in the AdEBR group were associated with worse prognoses,[7,37] suggesting that our study could have been underpowered to detect the benefit of extra-adrenal organ resection in patients with these large tumors.

Fourth, the multi-institutional nature of our collaborative data set may have been affected by inconsistencies in the operative practice and pathologic reporting practice among the institutions. The multi-institutional nature of this study was a benefit, however, because it allowed us to include in our analysis one of the largest groups of surgically resected ACC patients ever recorded. The fact that all our data came from large, academic referral centers, on the other hand, may have led to selection bias and may limit the generalizability of our conclusions.

The decision to resect extra-adrenal organs en bloc during adrenalectomy for ACC remains complex and may be influenced by preoperative imaging, size of the tumor, and venous involvement. Unfortunately, a randomized clinical trial examining the benefit of en bloc resection in ACC is not possible for a variety of reasons, and surgeons must make difficult management decisions based on a combination of retrospective and observational data and personal experience. We emphasize the critical importance of obtaining margin-negative resections without tumor spill during index resections for ACC, but suggest limiting extra-adrenal organ resection if a margin-negative resection free of tumor spill can otherwise be achieved.

In summary, this large, multi-institutional study of patients in the United States undergoing primary surgical resection for non-metastatic ACC demonstrated that en bloc resection of extra-adrenal organs was believed necessary by the operating surgeon for more than 40% of patients. Our findings validate current practice in that en bloc resection of extra-adrenal organs should occur when a T4 lesion is suspected on preoperative imaging or intraoperatively, or when additional organs must be removed to obtain negative margins and avoid tumor rupture. Additionally, when a margin-negative resection can otherwise be achieved, removal of extra-adrenal organs en bloc does not appear to provide additional survival benefit. However, it is important to note that we identified a large gap between preoperative concern for extra-adrenal organ involvement and true involvement on final pathology. Further investigation into methods that can more accurately determine histologic involvement of extra-adrenal organs pre- or intraoperatively could help to more reliably identify patients who will benefit from these extended resections.

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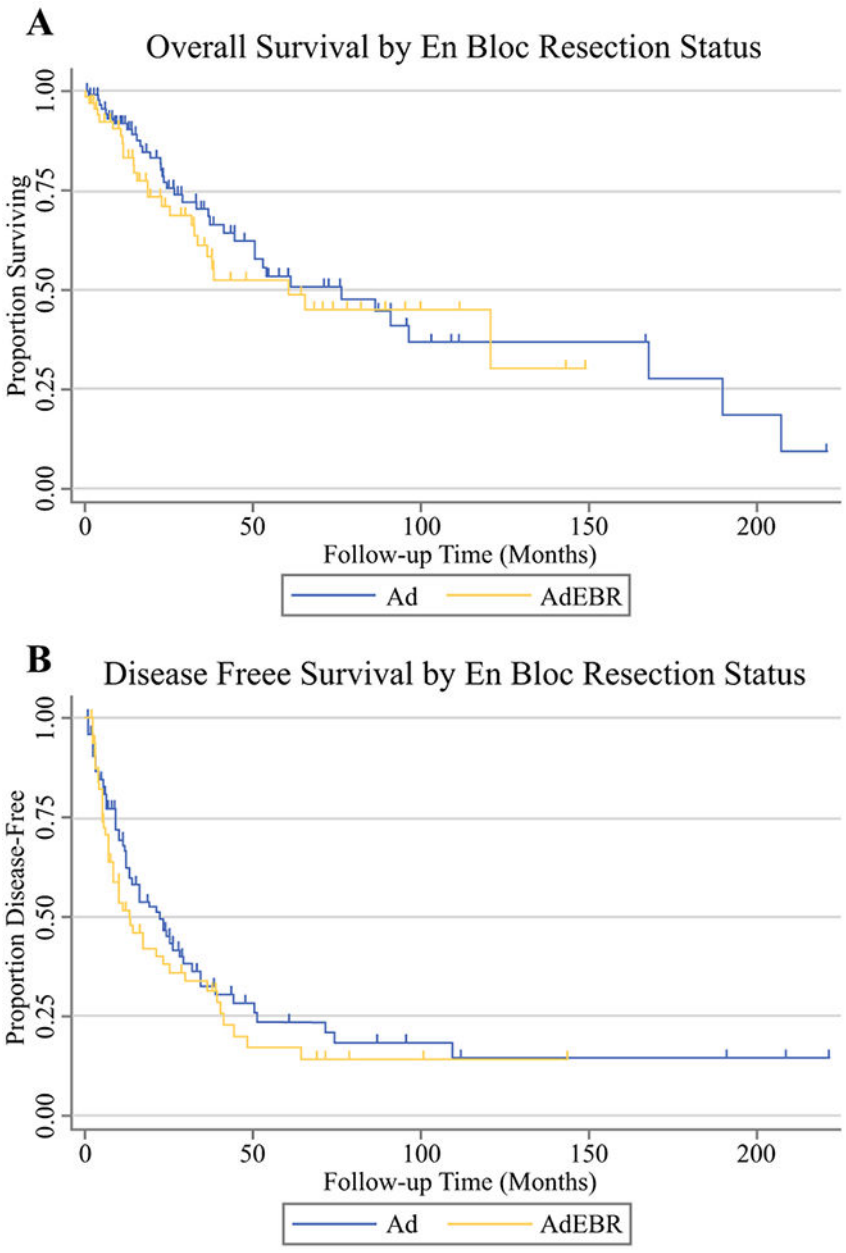

FIG. 1.

Kaplan–Meier survival graphs for overall and disease-free survival by en bloc resection status. **a** Overall survival. Log-rank test for equality of survivor ($p = 0.4703$). **b** Disease-free survival. Log-rank test for equality of survivor ($p = 0.2991$)

TABLE 1

Summary of demographic and operative parameters

Variable	AdEBR (*n* = 68) *n* (%)	Ad (*n* = 99) *n* (%)
Gender		
Male	21 (30.9)	39 (39.4)
Female	47 (69.1)	60 (60.6)
Race		
White	59 (86.8)	74 (74.7)
Black	4 (5.9)	6 (6.1)
Other	4 (5.9)	16 (16.2)
Median age: years (IQR)	52.5 (46–61)	52 (42–61)
ASA class		
1	8 (11.8)	14 (14.1)
2	11 (16.2)	23 (23.2)
3	27 (39.7)	33 (33.3)
4	6 (8.8)	4 (4.0)
BMI		
< 20	1 (1.5)	1 (1.0)
20–25	20 (29.4)	19 (19.2)
25–30	13 (19.1)	26 (26.3)
30–35	10 (14.7)	11 (11.1)
> 35	4 (5.9)	6 (6.1)
Suspected IVC or RV involvement preoperatively		
Yes	26 (38.2)	18 (18.2)
Abutment (< 180°)	23 (33.8)	17 (17.2)
Encasement (> 180°)	3 (4.4)	1 (1.0)
No	22 (32.4)	48 (48.5)
Suspected IVC or RV thrombus preoperatively		
No	42 (61.8)	63 (63.6)
Yes	15 (22.1)	4 (4.0)
Surgical approach		
Open	66 (97.1)	63 (63.6)
Minimally invasive	1 (1.5)	34 (34.3)
Preoperative chemo		
No	66 (97.1)	93 (93.9)
Yes	1 (1.5)	1 (1.0)
Postoperative chemo		
No	58 (85.3)	81 (81.8)
Yes	9 (13.2)	13 (13.1)
Postoperative mitotane		
No	31 (45.6)	59 (59.6)
Yes	23 (33.8)	29 (29.3)

Variable	AdEBR (*n* = 68) *n* (%)	Ad (*n* = 99) *n* (%)
Postoperative XRT		
No	56 (82.4)	70 (70.7)
Yes	5 (7.4)	8 (8.1)
Postoperative complication		
No complication	30 (44.1)	46 (46.5)
Clavien-Dindo class 1	2 (2.9)	6 (6.1)
Clavien-Dindo class 2	13 (19.1)	13 (13.1)
Clavien-Dindo class 3	7 (10.3)	5 (5.1)
Clavien-Dindo class 4	3 (4.4)	0 (0.0)
Median hospital stay: days (IQR)	7 (6–10)	5 (3–6)
90-Day readmission		
No	47 (69.1)	68 (68.7)
Yes	13 (19.1)	7 (7.1)

Data presented in the table reflect all available data from the authors' collaborative database. Percentages may not add up to 100% because data are missing for some variables

AdEBR adrenalectomy with en bloc resection, *Ad* adrenalectomy with no en bloc resection, *IQR* interquartile range, *ASA* American Society of Anesthesiology, *BMI* body mass index, *IVC* inferior vena cava, *RV* renal vein, *XRT* radiation therapy, *Open* open abdominal, thoracoabdominal, laparoscopic converted to open and open posterior, *Minimally invasive* laparoscopic, hand-assisted, robotic, and retroperitoneoscopic

TABLE 2

Organs/structures resected en bloc with the adrenal cancer

Organ	**(*n* = 68)**	**%**
Kidney	40	58.8
Liver	19	27.9
Spleen	16	23.5
Pancreas	11	16.2
Diaphragm	10	14.7
Colon	4	5.9
Rib	4	5.9
Omentum	2	2.9
Duodenum	1	1.5
Multiple (> 1 organ)	26	38.2

TABLE 3

Summary of pathologic parameters

Variable	AdEBR (*n* = 68) *n* (%)	Ad (*n* = 99) *n* (%)
Median tumor size: cm (IQR)	13(11–17.3)	10 (6.5–13)
T stage		
T1	1 (1.5%)	10 (10.1%)
T2	22 (32.4%)	49 (49.5%)
T3	29 (42.6%)	32 (32.3%)
T4	14 (20.6%)	3 (3.0%)
LN dissection		
No	40 (58.8%)	81 (81.8%)
Yes	25 (36.8%)	12 (12.1%)
N stage		
N0	21 (30.9%)	11 (11.1%)
N1	11 (16.2%)	5 (5.1%)
Nx	36 (52.9%)	81 (81.8%)
Mean number of LNs removed (95% CI)	3.4 (2.03–4.83)	0.63 (0.13–1.12)
Grade		
G1	0 (0.0%)	2 (2.0%)
G2	1 (1.5%)	2 (2.0%)
G3	6 (8.8%)	9 (9.1%)
G4	10 (14.7%)	4 (4.0%)
Venous invasion on final pathology		
No	15 (22.1%)	15 (15.2%)
Yes	15 (22.1%)	11 (11.1%)
Margin status		
R0	46 (67.6%)	66 (66.7%)
R1	15 (22.1%)	21 (21.2%)
R2	3 (4.4%)	2 (2.0%)

Data presented in the table reflect all available data from our collaborative database. Percentages may not add up to 100.0% because data were missing for some variables

AdEBR adrenalectomy with en bloc resection, *Ad* adrenalectomy with no en bloc resection, *IQR* interquartile range, *LN* lymph node, *CI* confidence interval

TABLE 4

Multivariate Cox regression

Variable	HR	95% CI	*p* value
EBR	1.42	0.71–2.85	0.323
T stage			
T2	1.83	0.22–14.89	0.572
T3	2.04	0.24–17.27	0.512
T4	2.56	0.26–25.09	0.419
N stage			
N1	1.73	0.54–5.56	0.358
Nx	0.85	0.30–2.47	0.771
LND	0.29	0.11–0.78	0.014
Margin status			
R1	2.92	1.44–5.94	0.003
R2	4.20	1.36–12.96	0.013
Tumor size	1.01	0.94–1.08	0.754
Hormone production	1.67	0.90–3.10	0.105

HR hazard's ratio, *CI* confidence interval, *EBR* en bloc resection of extra-adrenal organs, *LND* lymph node dissection