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Risk factors associated with positive resection margins in patients with adrenocortical carcinoma

Nicholas J. Skertich [a, *], John F. Tierney [a], Sitaram V. Chivukula [a], Nasim T. Babazadeh [a], Martin Hertl [b], Jennifer Poirier [a], Xavier M. Keutgen [c]

[a] Department of Surgery, Rush University Medical Center, 1750 W. Harrison, Suite 785, Chicago, IL, 60612, USA
[b] Department of Surgery, Division of Transplant Surgery, Rush University Medical Center, 1750 W. Harrison, Suite 785, Chicago, IL, 60612, USA
[c] Department of Surgery, Division of General Surgery and Surgical Oncology, Endocrine Research Program, The University of Chicago Medicine and Biological Sciences Division, 5841 S. Maryland Ave, Chicago, IL, 60637, USA

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ABSTRACT

Background: Positive resection margins are associated with worse survival after surgery for adrenocortical carcinoma (ACC). We aimed to identify risk factors for positive margins post-resection.
Methods: The NCDB was queried for ACC patients from 2006 to 2015. Patients with positive versus negative resection margins post-surgery were compared using Chi-square tests. Survival based on adjuvant treatment was assessed using Kaplan-Meier curves.
Results: 1,973 patients with ACC were identified, 217 (11.0%) with positive margins. Multivariable analysis identified extra-adrenal extension (HR 4.92, $p < 0.001$), lymph node metastases (HR 2.64, $p = 0.001$), and distant metastases (HR 1.53, $p = 0.03$) as risk factors for positive margins. No significant difference in margin status existed between patients who had an open versus minimally invasive procedure ($p = 0.6$). Positive margin patients receiving adjuvant radiation ($p = 0.007$) or combined chemo-radiation ($p = 0.001$) had the longest survival.
Conclusion: No modifiable risk factors were identified, but patients with positive margins receiving adjuvant radiation or chemo-radiation had the longest survival.

Introduction

Adrenocortical carcinoma (ACC) is a rare cancer with a poor prognosis. It has a yearly incidence of 0.7–2 per million and a 5-year survival ranging from 15 to 40%.[1–4] It is responsible for only 0.2% of cancer deaths annually, but is the second most aggressive endocrine malignancy behind anaplastic thyroid cancer.[2,5] Surgical resection is the mainstay of treatment, but survival has not improved substantially over the past six decades.[2,6,7]

Multiple studies have demonstrated that incomplete surgical resection is associated with increased mortality.[2,4,6,8] Two previous studies used the National Cancer Database (NCDB) to examine factors associated with decreased survival after resection from 1985 to 2015, and both found that positive margins was the only potentially modifiable risk factor for death.[2,4] Complete resection nevertheless offers the only effective and potentially curative treatment for ACC.[2,8]

The strongest evidence for adjuvant therapy exists for mitotane, which was shown in a retrospective study by Terzolo et al. to be associated with improved recurrence-free survival, as well as improved overall survival when controlling for age, sex, and tumor stage.[1] The effectiveness of mitotane, however, is limited by the need to achieve therapeutic drug levels. Adjuvant radiation has recently been reported to be associated with improved overall survival, local recurrence free survival and disease free survival, although prior studies had shown no change in overall survival.[9,10] Due in part to these advances, the rate of patients who received adjuvant therapy after resection increased from 16% from 1985 to 2005 to 31% from 2006-2015.[2,4] In this study, we sought to identify risk factors for positive resection margins in ACC and to evaluate whether adjuvant therapy is associated with improved survival among patients with positive resection margins.

* Corresponding author. Rush University Medical Center, Department of Surgery, 1750 W. Harrison, Suite 785, Chicago, IL, 60612, USA.
E-mail addresses: Nicholas_J_Skertich@rush.edu (N.J. Skertich), xkeutgen@surgery.bsd.uchicago.edu (X.M. Keutgen).

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Table 1
Characteristics of patients with adrenocortical carcinoma by margin status.

Characteristics	Total	Clear Margins	Positive Margins	Unknown Margins	p-value
Patients	1,973	1,322	217	434	N/A
Median age (IQR)	55 (44–66)	55 (44–65)	53 (41–65)	55 (44–67)	0.31
Sex					0.96
Women	1,191 (60.4%)	527 (67.4%)	85 (10.9%)	170 (21.7%)	
Men	782 (39.6%)	795 (66.8%)	132 (11.1%)	264 (22.2%)	
Race					0.65
White	1,710 (86.7%)	1,149 (67.2%)	187 (10.9%)	374 (21.9%)	
Asian/Pacific Islander	53 (2.7%)	31 (58.5%)	8 (15.1%)	14 (26.4%)	
Black	169 (8.6%)	116 (68.6%)	20 (11.8%)	33 (19.5%)	
Other/Unknown	41 (2.1%)	26 (63.4%)	2 (4.9%)	13 (31.7%)	
Ethnicity					0.06
Hispanic	117 (5.9%)	69 (59%)	10 (8.5%)	38 (32.5%)	
Non-Hispanic	1,752 (88.8%)	1,183 (67.5%)	198 (11.3%)	371 (21.2%)	
Unknown	104 (5.3%)	70 (67.3%)	9 (8.7%)	25 (24.0%)	
Median Income (2012)[a]					0.95
< $38,000	295 (15.2%)	193 (65.4%)	30 (10.2%)	71 (24.4%)	
$38,000 - $47,999	469 (24.1%)	316 (67.4%)	51 (10.9%)	102 (21.7%)	
$48,000 - $62,999	534 (27.5%)	359 (67.2%)	60 (11.2%)	115 (21.5%)	
$63,000 +	645 (33.2%)	437 (67.8%)	73 (11.3%)	135 (20.9%)	
Education (2012) (% w/o high school degrees)[b]					0.70
21% +	315 (16.2%)	203 (64.4%)	35 (11.1%)	77 (24.4%)	
13–20%	511 (26.3%)	346 (67.7%)	53 (10.4%)	112 (21.9%)	
7–12.9%	626 (32.2%)	428 (68.4%)	64 (10.2%)	134 (21.4%)	
< 7%	493 (25.3%)	328 (66.5%)	63 (12.8%)	102 (20.7%)	
Laterality[c]					0.12
Right	884 (44.8%)	577 (65.3%)	109 (12.3%)	198 (22.4%)	
Left	1,064 (53.9%)	735 (69.1%)	104 (9.8%)	225 (21.1%)	
Unilateral NOS	3 (0.2%)	2 (66.7%)	0 (0%)	1 (33.3%)	
Bilateral	2 (0.1%)	0 (0%)	0 (0%)	2 (100%)	
Unknown	20 (1.0%)	8 (40%)	4 (20%)	8 (40%)	
Median tumor size in mm (interquartile range)[d]	100 (70–141)	100 (70–144)	100 (72–138)	100 (70–140)	0.56
Extension[e]					<0.001
Confined to gland	1,077 (54.6%)	833 (77.3%)	57 (5.3%)	188 (17.4%)	
Extended beyond	860 (43.6%)	475 (55.2%)	159 (18.5%)	226 (26.3%)	
No extension info	36 (1.8%)	14 (40.0%)	1 (2.9%)	20 (57.1%)	
Distant Metastases[f]					<0.001
Absent	1,598 (83.1%)	1,129 (70.7%)	159 (9.9%)	310 (19.4%)	
Present	324 (16.9%)	168 (51.9%)	52 (16.0%)	104 (32.1%)	
Hospital Type					0.15
Academic/Research Program	877 (44.5%)	600 (68.4%)	93 (10.6%)	184 (21.0%)	
Comprehensive Community Cancer Program	73 (3.7%)	49 (67.1%)	9 (12.3%)	15 (20.5%)	
Integrated Network Cancer Program	500 (25.3%)	338 (67.6%)	41 (8.2%)	121 (24.2%)	
Community Cancer Program	169 (8.6%)	104 (61.5%)	24 (14.2%)	41 (24.3%)	
Unknown	354 (17.9%)	231 (65.3%)	50 (14.1%)	73 (20.6%)	
Surgical Approach[g]					<0.001
MI proc conducted	295 (24.0%)	215 (72.9%)	29 (9.8%)	51 (17.3%)	
Surgery elsewhere	167 (13.6%)	88 (52.7%)	23 (13.8%)	56 (33.5%)	
Open or unspecified	766 (62.4%)	535 (69.8%)	80 (10.4%)	151 (19.7%)	
Pre-op Biopsy[h]					0.13
Biopsy	309 (15.7%)	204 (66.0%)	26 (8.4%)	79 (25.6%)	
No biopsy	1,647 (83.5%)	1,108 (67.3%)	186 (11.3%)	353 (21.4%)	
Unknown	17 (0.9%)	10 (58.8%)	5 (29.4%)	2 (11.8%)	
Lymph Node Status					<0.001
Positive	121 (6.1%)	60 (49.6%)	29 (24.0%)	32 (26.4%)	
Missing	1,528 (77.4%)	1,020 (66.8%)	154 (10.1%)	354 (23.2%)	
Negative	324 (16.4%)	242 (74.7%)	34 (10.5%)	48 (14.8%)	

[a] 30 (1.5%) patients were missing data on income.
[b] 28 (1.4%) patients were missing data on education.
[c] Chi-square test was based on cases with Right or Left only.
[d] 116 (5.9%) patients were missing data on tumor size.
[e] Chi-square test was based on cases with information only.
[f] 51 (2.6%) patients were missing data on distant metastases.
[g] Surgical Approach was only recorded for patients with a diagnosis of 2010 or later.
[h] Chi-square test was based on patients with biopsy or no biopsy only.

Methods

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB and the hospitals participation in the NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The NCDB contains 70% of all patients diagnosed with cancer in the United States and is an excellent database for evaluating cancer treatment patterns.[11,12] This study received approval from Rush University Medical Center and was deemed exempt from IRB review since the

NCDB database contains no patient identifiers.

Patients 18 years or older, diagnosed with ACC from 2006 to 2015, who had either a primary site of the adrenal gland not otherwise specified (NOS) (C74.9) or the adrenal cortex (C74.0), with histology of adrenal cortical carcinoma (8370) who had primary site surgery were included. Patient demographic characteristics (age, sex, race, ethnicity, income, education), tumor characteristics (laterality, size, extension into adjacent organs, distant metastases), adjuvant therapies (no adjuvant therapy, chemotherapy only, radiation only, and chemotherapy and radiation combined), hospital type, open vs. laparoscopic surgery, pre-op biopsy status and lymph node status (positive, negative, or missing/unexamined) were examined. Tumor sizes above 50 cm were assumed to be in error and were not included. Surgical treatments were combined into four categories: resection, resection with contiguous organ, debulking, and surgery NOS. Margin data was combined into three categories: involved resection margins (positive margins), did not involve resection margins (negative margins), and unknown.

Chi-square tests were used to measure relationships between predictive variables and margin status except where expected cell sizes were too small, in which case Fisher exact tests were used. To examine the potential influence of multiple variables at the same time, multinomial analyses were conducted. Nested multivariable models were created and compared to look at the relationship between variables that were significant on univariable analysis and margin status. Among patients with positive margins, the sample was limited to those who had been diagnosed between 2006 and 2010, and Kaplan-Meier curves were created and compared to look at whether there was a difference in survival between patients who received different types of adjuvant therapy or no adjuvant therapy. Within the same group (patients with positive margins), nested linear models were used to determine whether adjuvant therapy grouping was related to tumor size, and chi-square tests were used to determine whether adjuvant therapy grouping was related to either extension beyond the adrenal gland or distant metastases. To examine multivariable survival, Cox proportional hazard models were created and compared. All analyses were conducted in R 3.3.2.[13]

Results

A total of 1,973 patients diagnosed with ACC, who had had primary site surgery were identified in the NCDB. The majority of patients (60.4%) were female, and median age was 55 years. Among all patients who underwent resection, median survival was 40.9 months. Additional patient characteristics and tumor characteristics are found in Table 1.

On univariate analysis, extra-adrenal extension, positive lymph nodes, and distant metastases were each associated with increased risk of positive margins (Table 1). On multivariable analysis, ($n = 1,894$ patients, as patients with missing data were eliminated) extra-adrenal extension (relative risk (RR) of 4.92, $p < 0.001$), distant metastasis (RR 1.53, $p = 0.03$) and positive lymph nodes (RR 2.64, $p = 0.001$) were predictive of positive resection margins, when controlling for other significant variables. Moreover, presence of extra-adrenal extension ($p = 0.02$), positive lymph nodes ($p = 0.009$) or distant metastasis ($p = 0.001$) were also predictive of shortened survival times. On multivariable analysis, there was no significant difference in margin status between patients who had an intended open procedure and an intended minimally invasive procedure ($p = 0.93$) or between patients who had an actual open procedure and those who had an actual minimally invasive procedure ($p = 0.6$).

Patients with negative margins were less likely to receive adjuvant therapy compared to patients with positive margins who had higher rates of chemotherapy alone, radiation alone, or both chemotherapy and radiation ($p < 0.001$, Table 2). Amongst patients with positive margins, survival differed according to the adjuvant therapy received ($p < 0.001$; Table 3, Fig. 1). Patients who received radiation with ($p = 0.001$) or without ($p = 0.007$) chemotherapy lived significantly longer than those who had no adjuvant therapy. There was no significant difference in survival between those who had no adjuvant therapy and those who had chemotherapy only ($p = 0.99$). Patients with positive resection margins were less likely to receive adjuvant radiation therapy if they had distant metastases ($p < 0.001$, Table 4).

Discussion

Despite ongoing research into the treatment of ACC, nearly all publications have emphasized the completeness of resection as the most important prognostic factor for survival.[2,4,14–16] Therefore, we sought to identify modifiable risk factors associated with positive resection margins, so that clinical interventions could be implemented to potentially improve survival. Extra-adrenal extension, lymph node metastases and distant metastases were each associated with positive margins after ACC resection. Although none of these risk factors are modifiable, surgeons should be particularly cognizant of achieving negative margins in cases when these factors are present.

Interestingly, surgical approach did not affect post-operative margin status. Although the literature has had divergent results on this topic, multiple studies show no difference in recurrence rate (RR), disease free survival (DFS) or overall survival (OS) in laparoscopic versus open resections for ACC.[17–22] Laparoscopic adrenalectomy does have the benefit of reduced blood loss, less perioperative complications, less postoperative pain, shorter recovery, shorter length of hospital stay and improved cosmetic outcome.[16,23] However, initial studies found that the laparoscopic approach had higher recurrence rates.[16,21] Moreover, many of these corroborating studies were small, or only included patients with localized disease, and tumor size was generally smaller in the laparoscopic group.[18–20,22] Current guidelines recommend an open approach for confirmed or highly suspected ACC unless the tumor size is small and is without local invasion.[24] Therefore,

Table 2
Adjuvant therapy received by margin status.

Adjuvant Therapy	Total Group	Clear Margins	Positive Margins	Unknown Margins
None	1,042 (52.8%)	757 (57.3%)	80 (36.9%)	205 (47.2%)
Chemo only	534 (27.1%)	336 (25.4%)	65 (30.0%)	133 (30.6%)
Radiation only	127 (6.4%)	63 (4.8%)	26 (12.0%)	38 (8.8%)
Both chemo and radiation	198 (10.0%)	120 (9.1%)	37 (17.1%)	41 (9.4%)
Missing	72 (3.6%)	46 (3.5%)	9 (4.1%)	17 (3.9%)

Table 3
Survival statistics by adjuvant therapy status.

Adjuvant Therapy	n	5-year survival rates	Median Survival	Hazard Ratio (95% CI)	p-value
None	72	28.4%	9.9	–	
Chemo only	60	13.9%	17.3	1.00 (0.67–1.48)	0.99
Radiation only	23	58.4%	73.7	0.40 (0.20–0.78)	0.007
Both chemo and radiation	32	47.1%	40.9	0.39 (0.22–0.70)	0.001

Reference group is No adjuvant therapy; Hazard ratios and p-values in Table 3 refer to differences between therapy group for that row and no adjuvant therapy.

Table 4
Tumor size, extension, presence of distant metastases by adjuvant therapy status.

	No adjuvant therapy	Chemo Only	Radiation Only	Chemo and Radiation	p-value
Median tumor size in mm (interquartile range)	101.5 (79.5–135)	105 (80–148)	84.5 (57.5–145)	105 (70–136)	0.78
Extension					0.04[a]
Confined to gland	26 (48.1%)	9 (16.7%)	6 (11.1%)	13 (24.1%)	
Extended beyond	54 (35.3%)	56 (36.6%)	19 (12.4%)	24 (15.7%)	
No extension info	0 (0%)	0 (0%)	1 (100%)	0 (0%)	
Distant Metastases					<0.001
Absent	57 (37.3%)	37 (24.2%)	25 (16.3%)	34 (22.2%)	
Present	18 (36.7%)	28 (57.1%)	0 (0%)	3 (6.1%)	

[a] Chi-square was based on only the “Confined to gland” and “Extended beyond gland” levels of Extension.

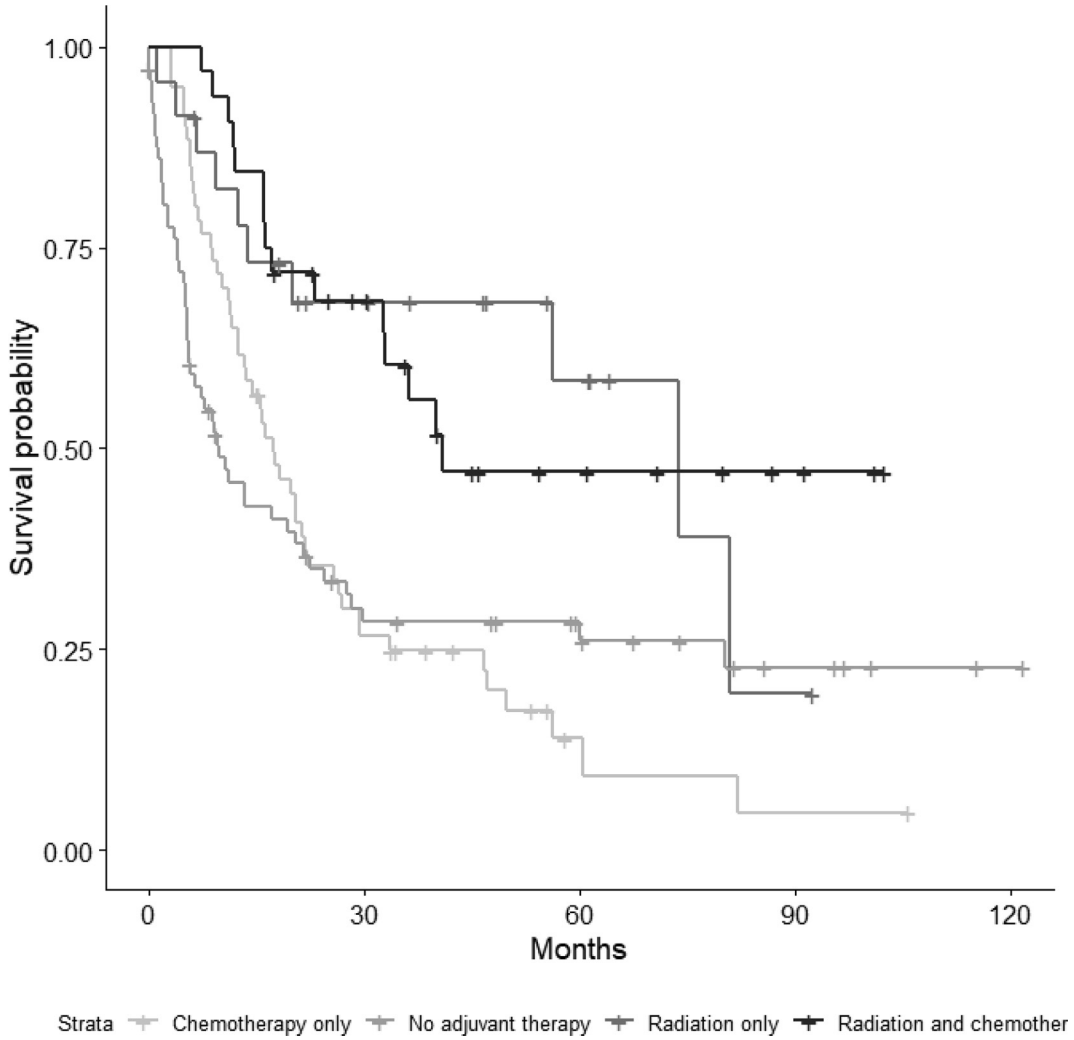

Fig. 1. Survival curves by adjuvant therapy status.

based on these results, and since we did not assess the effect of surgical approach on RR, DFS, or OS, the data presented here should not change current practice.

Our secondary objective was to identify whether adjuvant therapy is associated with improved survival among patients with positive resection margins. While the use of adjuvant therapy post-resection has been historically low in ACC compared to other cancer types, it has been used more frequently since Terzolo et al. showed that adjuvant mitotane is associated with increased survival.[1,2,4] In this study, we found that adjuvant therapy that included radiation was associated with prolonged survival in patients with positive resection margins.

Among patients with positive margins, those who received adjuvant radiation alone or both adjuvant radiation and chemotherapy survived significantly longer than those who received chemotherapy alone or no adjuvant treatment. Nelson et al. reported similar benefits to adjuvant radiation in patients with positive margins but not for any other high risk features or non-metastatic patients.[25] Whereas, adjuvant radiation was demonstrated to be associated with prolonged survival for all patients with ACC in a case-control study by Gharzai et al. but that study only included five patients with positive margins who received radiation.[9] In the current study, we demonstrate in a larger cohort of 55 patients with positive margins that adjuvant therapy that includes radiation is associated with prolonged survival of up to 73.7 months. The retrospective nature of the NCDB limits the conclusions that we can draw from these findings; it is, however, promising that radiation therapy is associated with prolonged survival among select patients who had incomplete resection of their primary tumors. Further studies should attempt to better elucidate proper selection criteria for radiation therapy among patients with ACC, with a particular focus on patients with positive resection margins.

This study had multiple limitations. First, we used the NCDB database, which is a large clinical oncology database derived from hospital registry data and is inherently subject to data entry errors and missing data. Second, since it is a retrospective database, the study is subject to observational and selection bias. Third, the granularity of the data is limited. For example, the NCDB only documents treatments within the first six months following diagnosis, and does not provide information related to recurrence. Moreover, information on the type of chemotherapy used, whether the course of chemotherapy was completed, and whether therapeutic levels of mitotane were achieved was not provided. Fourth, tumor grade and information regarding hormones secreted by the tumor are not included, and these can affect survival.[8,14]

Conclusion

Patients with ACC and extra-adrenal extension, lymph node metastases and distant metastases were most likely to have positive margins in this study, suggesting that clinicians should pay particular attention to achieve a complete resection in these patients. Minimally invasive versus open surgery did not impact resection margins. Adjuvant chemo- and radiation therapy is more frequently used in patients with positive margins, and radiation used in an adjuvant setting may confer a survival benefit in patients with positive resection margins.

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Declaration of competing interest

None.

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