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Lymphadenectomy for Adrenocortical Carcinoma: Is There a Therapeutic Benefit?

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Abstract

Background—Lymph node metastasis is an established predictor of poor outcome for adrenocortical carcinoma (ACC); however, routine lymphadenectomy during surgical resection of ACC is not widely performed and its therapeutic role remains unclear.

Methods—Patients undergoing margin-negative resection for localized ACC were identified from a multi-institutional database. Patients were stratified into 2 groups based on the surgeon's

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effort or not to perform a lymphadenectomy as documented in the operative note. Clinical, pathologic, and outcome data were compared between the 2 groups.

Results—Of 120 patients who met inclusion criteria from 1993 to 2014, 32 (27 %) underwent lymphadenectomy. Factors associated with lymphadenectomy were tumor size (12 vs. 9.5 cm; $p = .007$), palpable mass at presentation (26 vs. 12 %; $p = .07$), suspicious lymph nodes on preoperative imaging (44 vs. 7 %; $p < .001$), and need for multivisceral resection (78 vs. 36 %; $p < .001$). Median number of lymph nodes harvested was higher in the lymphadenectomy group (5.5 vs. 0; $p < .001$). In-hospital mortality (0 vs. 1.3 %; $p = .72$) and grade 3/4 complication rates (0 vs. 12 %; $p = .061$) were not significantly different. Patients who underwent lymphadenectomy had improved overall survival (5-year 76 vs. 59 %; $p = .041$). The benefit of lymphadenectomy on overall survival persisted on multivariate analysis (HR = 0.17; $p = .006$) controlling for adverse preoperative and intraoperative factors associated with lymphadenectomy, such as tumor size, palpable mass, irregular tumor edges, suspicious nodes on imaging, and multivisceral resection.

Conclusions—In this multicenter study of adrenocortical carcinoma patients undergoing R0 resection, the surgeon's effort to dissect peritumoral lymph nodes was independently associated with improved overall survival.

Complete resection is critical in the management of adrenocortical carcinoma (ACC) as multidisciplinary approaches continue to evolve.[1,2] Autopsy studies have demonstrated that two-thirds to three-quarters of ACC patients have lymph node involvement at the time of death.[3,4] In addition, regional nodal involvement is a major predictor of poor long-term outcome after resection of ACC.[5,6] However, the impact of lymphadenectomy (LAD) on long-term outcome of ACC patients remains controversial, with some studies showing a significant association between LAD and survival, one showing a marginal association, and some showing no association at all.[7–11] Moreover, these studies differ significantly in their inclusion criteria with some excluding patients with metastatic disease and others including patients of all stages.[7–11] In addition, the definition of what constitutes a LAD for ACC has been variable among these different studies, with some defining LAD as the removal of at least 5 lymph nodes, one as the removal of at least 4 lymph nodes, and some without a formal definition.[7–11]

It remains unclear whether LAD confers a therapeutic benefit in ACC patients or is simply a staging and prognostication tool to guide the use of multimodal adjuvant therapy and/or the intensity of surveillance. The aim of this study was to determine if lymph node dissection offers a therapeutic benefit for patients with localized ACC who undergo otherwise complete, margin-negative resection.

METHODS

Study Design

Data were collected from 13 academic medical centers participating in the U.S. Adrenocortical Carcinoma Study Group: Emory University, Johns Hopkins University, Medical College of Wisconsin, New York University, The Ohio State University, Stanford University, University of California San Diego, University of California San Francisco, University of Texas Southwestern, University of Wisconsin, Vanderbilt University, and

Washington University. The institutional review board of each of the participating institutions approved the study. In order to examine the specific impact of LAD on outcome, only patients with localized (nonmetastatic, M0) ACC who underwent complete (R0) resection were included; patients with metastatic disease and positive resection margins were excluded, as these factors have been shown to be powerful independent predictors of poor outcome in ACC.[6,12–14] Given the clinicopathologic and prognostic differences between pediatric and adult ACC patients, only patients aged 18 and older were included.[15,16] We grouped patients based on the reported effort by the surgeon to perform LAD (either en bloc with the tumor or with additional sampling of resection bed lymph nodes) through retrospective review of the operative note. This attempt for LAD was analyzed in an “intention to treat” fashion and was correlated with the actual end result (the number of actual lymph nodes retrieved for histological analysis).

Statistical Analysis

Categorical variables were reported as counts and percentages that excluded missing data. Comparisons were made using the χ^2 test or Fisher exact test. Continuous variables were displayed as medians and interquartile ranges. Comparisons were made with the Wilcoxon rank-sum test. Survival and recurrence were calculated using the Kaplan–Meier method and compared using the log-rank test. Additionally, multivariate Cox proportional hazards models were created to account for significant differences leading to LAD being performed in ACC patients with unfavorable characteristics. A p value of less than .05 was considered statistically significant. All analyses were performed on Stata 11 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

During the study period (1993–2014), 265 patients underwent surgical resection for ACC in the 13 institutions participating in this multi-institutional collaborative. Of the 265 patients overall, 120 patients (45 %) met inclusion criteria (Fig. 1). A total of 32 patients (27 %) were classified as having an intended LAD and 88 (73 %) as not.

Demographics shown in Table 1 indicate similar age, gender, and race distribution between the 2 groups. Clinical characteristics including BMI, ASA classification, hormonal hypersecretion, and leg edema were also similar. Patients who underwent LAD tended to more often have a palpable mass on presentation, but this did not reach statistical significance (26 vs. 12 %; $p = .070$). In terms of radiographic characteristics, preoperative radiographic diagnosis of ACC (vs indeterminate or other) was not different (50 vs. 51 %) between the 2 groups. Moreover, radiographic evidence of tumor calcifications, large venous involvement, or tumor thrombus were similar between the groups. Critical radiographic features that prompted surgeons to perform LAD were larger tumor size (12 vs. 9.5 cm; $p = .007$) and suspicious-appearing lymph nodes on imaging (44 vs. 7 %; $p < .001$). Irregular tumor edge on imaging also tended to be more frequent among LAD patients, but this difference was not statistically significant (84 vs. 63 %; $p = .080$).

Perioperative Outcomes

LAD was more typically performed using open versus minimally invasive techniques (26 vs. 0 %; $p = .002$) and was associated with multivisceral resection (78 vs. 36 %; $p < .001$) (Table 2). However, operative time, estimated blood loss (EBL), and intraoperative blood transfusion rates were similar between the 2 groups.

On final pathological assessment, patients who underwent LAD had a larger tumor size and tumor weight (13 vs. 11 cm; $p = .064$; 851 vs. 525 g; $p = .012$). The median number of lymph nodes harvested was higher in the LAD group (5.5 vs. 0; $p < .001$). Of LAD patients, 60 % had 5 or more nodes examined histologically and 9 % of them had no nodes evaluated pathologically. A distribution graph of the frequency of patients per number of nodes removed for the 32 patients who underwent LAD is provided in Supplemental Fig. 1. The anatomic location of harvested lymph nodes was the aortocaval space for 22 patients, renal hilum for 18, retroperitoneum for 5, peripancreatic area for 4, celiac axis for 1, and porta hepatis for 1. The prevalence of involved lymph nodes was 27 % in patients with harvested aortocaval nodes, 44 % with renal hilum, 40 % with retroperitoneal, 25 % with peripancreatic, 0 % with celiac, and 100 % with porta hepatis nodes.

Postoperative complications, readmission, and mortality were not different between the 2 groups, but there was a trend toward a longer hospitalization in LAD patients by 1 day. Utilization of adjuvant therapy and repeat surgery for recurrent disease was similar between the 2 groups.

Survival

Median follow-up times were 25.4 months and 26.0 months for the LAD and no LAD groups, respectively. In unadjusted analysis, LAD was associated with an overall survival benefit (5-year, 76 vs. 59 %; $p = .041$) (Fig. 2). Patients alive (at risk) at 5 years were 6 for the LAD group and 22 for the no LAD group. A multivariate Cox proportional hazards model was created to include preoperative and operative variables that were associated with LAD. When controlled for these factors, which are suggestive of more advanced disease, LAD was again shown to be independently associated with decreased risk of death (HR, 0.17; $p = .006$) (Table 3).

DISCUSSION

This multi-institutional collaborative study including 13 academic institutions in the United States demonstrates that the surgeon's effort to perform a lymph node dissection for ACC appears to be associated with improved long-term outcome. This demonstrated benefit persisted even when we adjusted for adverse factors that prompted surgeons to select patients for lymphadenectomy, such as large tumor size, presence of suspicious lymph nodes, tumor edge irregularity, and adjacent organ invasion. Our findings support the notion that ACC belongs to the group of abdominal malignancies, including esophageal, gastric, and colon cancer, where a regional lymph node dissection may be associated with a therapeutic benefit in addition to providing more accurate staging.[17–19]

Our study reproduced the exact findings of a previous study from the German ACC registry, that similarly examined patients with nonmetastatic ACC who underwent complete, margin-negative resection.[8] Of 283 patients included in this multicenter study, 17 % underwent lymphadenectomy and had a similarly improved disease-specific survival (80 vs. 67 % at 5 years; $p = .049$). This study arbitrarily defined lymphadenectomy as the presence of at least 5 lymph nodes at pathologic examination. Although this is certainly a reasonable way to measure the end result of a lymph node dissection, this endpoint is highly dependent on the completeness of pathologic examination. Furthermore, surgeons experienced in resections for ACC, who resect the tumor en bloc with all surrounding retroperitoneal fat, know how few lymph nodes, sometimes none, are found in the specimen, even when they are attempting to obtain lymph nodes for staging purposes.[20] Furthermore, involved lymph nodes can sometimes be "matted" together and therefore counted as single positive node. Also, lymph nodes can be found in the surgical specimen even though the surgeon did not demonstrate the effort to harvest those. Therefore, when designing our study, we sought to utilize an "intention to treat' methodology, where the surgeon's documented intent to dissect regional lymph nodes (and not the actual number of nodes examined by the pathologist) was used to classify patients as having undergone an "intended" LAD or not. We acknowledge that our method is highly susceptible to misclassification bias, especially because of the retrospective nature of our study. However, it is interesting to note that patients in both the German study and ours had an almost identical median number of nodes examined histologically for the LAD and no LAD groups, respectively: 6 and 0 for the German ACC registry study, 5.5 and 0 for our study.

Another multi-institutional study of 253 ACC patients from France, 35 % of whom underwent LAD, similarly showed a trend ($p = .06$) toward improved survival for patients having undergone a LAD.[9] It should be noted, however, that the definition of lymphadenectomy was not explicitly provided in this study, which additionally included patients of all stages and patients undergoing incomplete, palliative resections. Three previous studies have utilized the Surveillance, Epidemiology, and End Results (SEER) database to examine the impact of LAD on survival after ACC resection and have provided contradictory results mainly due to their differing inclusion criteria and LAD definition.[7,10,11] No difference in survival was noted when LAD was defined as 4+ nodes removed and all stages were included, or when stage 4 patients were excluded and LAD was defined as 5+ nodes examined.[10,11] However, on a subset analysis of T4M0 tumors, a survival benefit was noted if any lymphadenectomy was performed.[7] Based on the variable inclusion criteria and LAD definition of the aforementioned studies, a firm conclusion on the effect of LAD on outcome after ACC resection cannot be reached.

Another finding in our study that deserves attention was that the effort to perform a LAD was not associated with increased morbidity or mortality, despite the fact that LAD patients had larger tumors, often requiring multivisceral resections. This observation is in agreement with the findings of the German study, which showed similar length of stay and mortality irrespective of the performance of LAD.[8]

There are several aspects of this analysis that require careful interpretation. First, there are inherent selection biases submerged in any retrospective analysis that are difficult to control for. For example, patients who underwent LAD may have improved survival simply because they were “healthier” and likely to get more aggressive treatment, including more extensive nodal dissection. Second, the number of nodes removed does not only reflect the number of nodes dissected intraoperatively, but also the number of nodes identified during pathologic evaluation of the specimen. Third, although we did not identify a statistically significant difference in perioperative morbidity and mortality between the 2 groups, our study was perhaps not sufficiently powered to detect such a difference. Although collaboration between multiple institutions limits the ability to easily standardize surgical and pathologic practices, the multicenter nature of our study is also a strength as it contributes to the generalizability of our findings. Furthermore, the fact that all participating institutions were academic medical centers in the United States contributes to the homogeneity and granularity of our dataset.

In conclusion, this multi-institutional US study of ACC patients undergoing complete R0 resection showed that an effort to dissect peritumoral lymph nodes was documented in 27 % of the cases, typically in the presence of larger tumors, macroscopically involving lymph nodes and invading adjacent organs. Despite these adverse features, the performance of a lymphadenectomy in these cases was independently associated with improved survival. Our findings reinforce the notion that lymphadenectomy during resection of localized ACC might have a therapeutic in addition to a prognostication benefit. Until further randomized data become available, we favor a systematic, extended lymphadenectomy during ACC resection planned preoperatively and not based on node gross appearance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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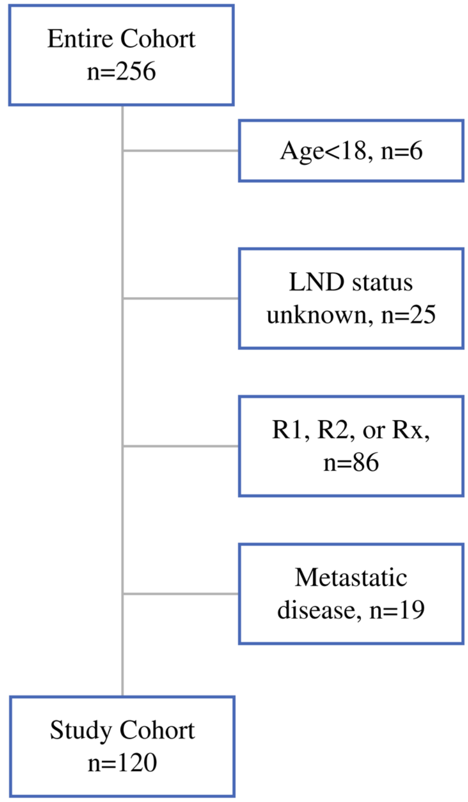

FIG. 1.
Flow diagram of study inclusion criteria

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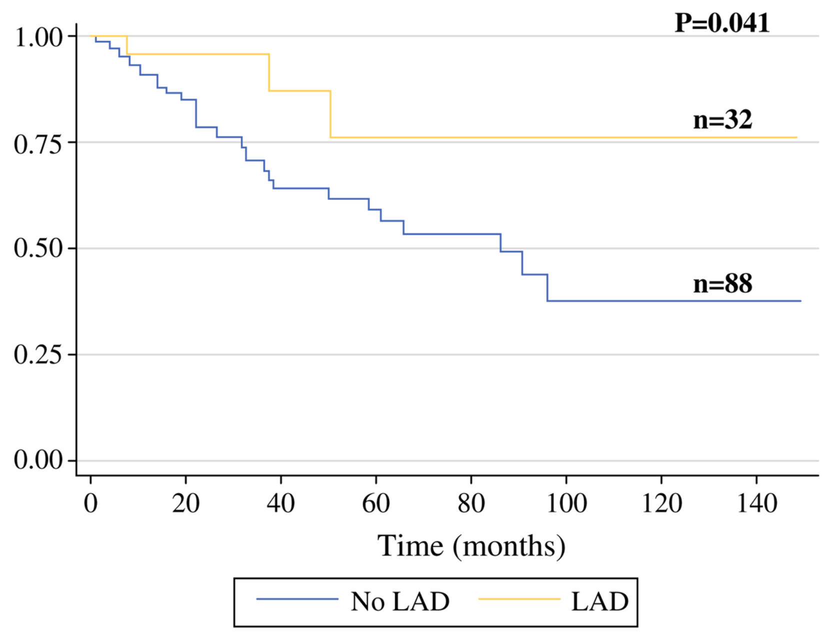

FIG. 2.

Overall survival curves following ACC resection stratified by the performance of lymphadenectomy (LAD)

TABLE 1

Demographic, clinical, and radiographic characteristics stratified by the performance of lymphadenectomy (LAD) for ACC

	No LAD (*n* = 88)	LAD (*n* = 32)	*p* value
Demographics			
Median age (*n* = 120)	52 (44.5–61)	51.5 (40.4–58.3)	.36
Male (*n* = 120)	32 (36 %)	10 (31 %)	.60
Race (*n* = 115)			.37
White	67 (81 %)	28 (88 %)	
Black	6 (7 %)	0 (0 %)	
Other	10 (12 %)	4 (13 %)	
Clinical characteristics			
Median BMI (*n* = 99)	27 (24–31)	27 (22–37)	.97
ASA (*n* = 92)			.42
1	10 (14 %)	4 (19 %)	
2	20 (29 %)	9 (43 %)	
3	35 (50 %)	8 (38 %)	
4	5 (7 %)	0 (0 %)	
Palpable mass (*n* = 114)	10 (12 %)	8 (26 %)	.070
Leg edema (*n* = 110)	9 (11 %)	5 (17 %)	.29
Hormone secreting (*n* = 113)	28 (35 %)	10 (31 %)	.74
Preoperative chemotherapy (*n* = 117)	1 (1.1 %)	0 (0 %)	.74
Radiographic characteristics			
Radiographic diagnosis (*n* = 99)			.78
ACC	37 (51 %)	13 (50 %)	
Indeterminate	24 (33 %)	7 (27 %)	
Adenoma	6 (8 %)	2 (8 %)	
Sarcoma	1 (1.4 %)	1 (4 %)	
Other	5 (7 %)	3 (12 %)	
Median tumor size (cm) (*n* = 113)	9.5 (6–12.8)	12 (9.9–14.8)	.007
Irregular tumor edge (*n* = 65)	29 (63 %)	16 (84 %)	.080
Tumor calcifications (*n* = 81)	17 (29 %)	7 (30 %)	.56
Vein involvement (*n* = 87)	30 (46 %)	6 (27 %)	.10
Tumor thrombus (*n* = 95)	10 (15 %)	4 (15 %)	.61
Suspicious lymph nodes (*n* = 93)	5 (7 %)	11 (44 %)	<.001

TABLE 2

Operative, pathologic, and postoperative characteristics stratified by the performance of lymphadenectomy (LAD) for ACC

	No LAD (*n* = 88)	LAD (*n* = 32)	*p* value
Operative characteristics			
MIS approach (*n* = 119)	23 (26 %)	0 (0 %)	.002
Right side (*n* = 118)	41 (47 %)	13 (43 %)	.76
Tumor rupture (*n* = 106)	7 (9 %)	0 (0 %)	.14
Blood transfusion (*n* = 93)	21 (30 %)	4 (18 %)	.22
Multivisceral resection (*n* = 120)	32 (36 %)	25 (78 %)	<.001
Median OR time (minutes) (*n* = 78)	182 (150–284)	241 (200–300)	.13
Median EBL (mL) (*n* = 91)	500 (150–1500)	525 (250–1000)	.64
Pathologic characteristics			
Median tumor size (cm) (*n* = 184)	11 (7.5–15)	13 (10.5–16.5)	.064
Median tumor weight (g) (*n* = 148)	525 (127–880)	851 (392–1775)	.012
T3/T4 (*n* = 118)	35 (41 %)	19 (59 %)	.070
Median total LN harvested (*n* = 114)	0 (0–0)	5.5 (1–13)	<.001
N stage			<.001
N0	10 (11 %)	21 (66 %)	
N1	2 (2 %)	8 (25 %)	
Nx	76 (86 %)	3 (9 %)	
5+ lymph nodes harvested (*n* = 114)	3 (4 %)	18 (60 %)	<.001
Atypical ACC (*n* = 86)[a]	10 (16 %)	2 (8 %)	.26
Postoperative characteristics			
Median LOS (days) (*n* = 102)	5 (4–7.5)	6 (5–8)	.055
In-hospital mortality (*n* = 108)	1 (1.3 %)	0 (0 %)	.72
Reoperation (*n* = 110)	3 (4 %)	0 (0 %)	.41
Postoperative transfusion (*n* = 97)	8 (11 %)	1 (5 %)	.35
90-day readmission (*n* = 120)	9 (11 %)	3 (9 %)	.60
Grade 3/4 complications (*n* = 95)	8 (12 %)	0 (0 %)	.061
Postoperative chemotherapy (*n* = 114)	6 (7 %)	4 (14 %)	.23
Postoperative radiation (*n* = 101)	5 (6 %)	2 (9 %)	.50
Repeat resection for recurrence (*n* = 66)	17 (35 %)	8 (47 %)	.27

[a]Tumors meeting less than 3 Weiss criteria

TABLE 3

Multivariate analysis of overall survival

	HR (95 % CI)	*p* value
Palpable mass	0.71 (0.23–2.17)	.54
Tumor size 10 cm or more	3.30 (1.39–7.84)	.007
Irregular tumor edge	1.36 (0.66–2.81)	.41
Suspicious lymph nodes	1.76 (0.54–5.70)	.35
Multivisceral resection	0.97 (0.39–2.41)	.95
Lymphadenectomy	0.17 (0.05–0.61)	.006