Prevalence and Prognostic Value of Lymph Node Dissection in Treating Adrenocortical Carcinoma: A National Experience

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Abstarct. *Aim: We examined a national database to investigate the role of lymph node dissection (LND) in adrenocortical carcinoma (ACC) treated surgically. Patients and Methods: Patient data diagnosed with ACC between 1991 and 2011 were extracted from a national database. Predictors of LND, positive lymph nodes on LND, and the association between positive LND and cancer-specific death were examined. Results: Only 5.39% of patients underwent LND, and 31.03% had positive lymph nodes. Disease stage was the only significant predictor of LND (odds ratio=3.061; 95% confidence interval=1.158-8.091), and finding more than one positive lymph nodes on LND was the only significant predictor of cancer-specific death (hazard ratio=3.13; 95% confidence interval=1.233-7.95) in tumors larger than 3 cm in size. Conclusion: LND is not a common practice in treating ACC in the United States. The finding of more than one positive lymph nodes on LND for ACC is associated with poor prognosis.*

Adrenocortical carcinoma (ACC) is a rare disease with a high mortality rate (1, 2). Surgery for localized disease provides the best chance for cure (3-5), and while such treatment is established as the standard of care whenever possible, the role of lymph node dissection (LND) in the management of ACC remains controversial (6). There are few studies that have examined the role of LND in ACC, and the function of LND as a prognostic and therapeutic tool remains to be established.(7) Due to the rare nature of ACC, there is no single-center experience that is sufficient to examine this disease. Therefore, we used a national database to examine the role of LND in ACC, the predictors of LND, and the effect of positive findings of LND on the prognosis of the disease.

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Key Words: Adrenocortical carcinoma, lymph node dissection, prognosis, prevalence.

Patients and Methods

Data on patients diagnosed with ACC between 1991 and 2011 were extracted from the Surveillance, Epidemiology, and End Results database of the National Cancer Institute, which is a national database that records all cases of invasive cancer diagnosed in residents of 18 geographic areas of the United States, comprising 26% of the American population (8). We focused on patients diagnosed after 1990 to provide a more contemporary cohort of patients. We chose to identify LND using SEER variable "Regional nodes examined (1988+)" value of more than 5 lymph nodes found on pathological examination. This choice was made based on the fact that there is no current definition of LND in ACC, and in order to compare results to those of previous large series on the subject found in the literature (7). The number of positive lymph nodes (PLN) found on pathological examination of LND tissue was identified using SEER variable "Regional nodes positive (1988+)". Chi-square analysis was used to examine the association between the likelihood of LND/PLN and ACC size, stage, and cancer-specific death (CSD). Multivariate logistic regression analysis was then used to examine predictors of LND controlling for age, sex, race, disease stage, and tumor size. Finally, Cox proportional hazard model was used to examine the association between LND/PLN and CSD in our cohort controlling for the same confounders. Race was categorized as Black, White, other, and unknown. Age was categorized in 5-year age groups from 20 to 85 years and older. Data were analyzed using commercially available statistical software (SAS 9.3; Cary, NC, USA). The survival time variable was calculated by determining the number of months between the date of diagnosis and the most recent follow-up. Patients with unknown survival status or who had died but for whom cancer status was undetermined were categorized as having missing survival data. *p*-Value of less than 0.05 was considered significant.

Results

The population included 1,732 patients diagnosed with primary ACC in the SEER database between 1991 and 2011, out of whom 1,037 (60%) were treated with surgery with or

Table I. *Demographics of patients with adrenocortical carcinoma, those who underwent surgery, those who had lymph node dissection, and of those, the patients with lymph nodes positive for metastatic disease.*

Variable		Population	%	Surgical patients	%	LND patients	%	LND –positive patients	%
Total		1723		1037	00.60	58	00.06	18	00.31
Race	White	1472	85.43	905	87.27	50	86.21	16	88.89
	Black	136	07.89	61	05.88	6	10.34	2	11.11
	Other (American Indian/Alaska Native, Asian/Pacific Islander)	106	06.15	67	06.46	2	03.45		
	Unknown	9	00.52	4	00.39	0	00.00		
Gender	Female	970	56.30	611	58.92	35	60.00	12	67.00
	Male	753	43.70	426	41.08	23	40.00	6	33.00
Age (years)	<50	522	30.30	384	37.02	24	42.00	5	29.00
	50-69	735	42.66	479	46.20	28	49.00	10	56.00
	>69	466	27.05	174	16.79	6	11.00	3	17.00
Disease stage	Distant	310	17.99	113	10.90	6	07.00	3	17.00
	Localized	299	17.35	279	26.90	8	10.00	0	00.00
	Regional	145	08.42	125	10.05	10	12.00	4	22.00
	Unknown	118	06.85	520	50.14	59	71.00	11	61.00
Radiation	Yes	167	09.70	98	09.45	8	14.00	4	22.00
	No	1625	91.30	1037	90.55	50	86.00	14	78.00
Number of LN examined	0	1330	77.19	778	75.02				
	1-3	130	07.55	124	11.95				
	4-10	41	02.89	41	03.67	26	00.45	8	44.00
	>10	32	01.87	32	03.12	32	69.00	10	56.00
	Unknown	190	11.02	62	05.98				

without LND. Table I lists descriptive characteristics of the whole population, patients treated with surgery, patients who underwent LND, and patients found to have PLN. At the time of analysis, 51% of all patients with ACC in the database had died because of ACC, including 44% of those treated with surgery. The median survival for the overall population of patients with ACC who died was 13 months (range=0-259 months, mean=35 months). The median survival was 26 months for patients who died after undergoing surgery (range=0-259 months, mean=49 months), and 3 months in patients who died with no surgery (range=0-222 months, mean=12 months).

In Tables II and III, we list the results of the Chi-square analyses describing the correlation of LND and PLN with tumor size, stage, and CSD. In this univariate analysis, LND did not significantly correlate with disease stage but had a significant correlation with tumor size and CSD. In patients with ACC tumor size larger than 3 cm (no LND was carried-out in those with tumors of 3 cm or less) found to have PLN, PLN significantly correlated with CSD.

Table IV shows the significant results of logistic regression analysis and Cox proportional hazard analysis for predictors of LND, and the association of LND/PLN with CSD. A more advanced disease stage was the only significant predictor of performing LND in the study population. Performing LND, more advanced disease stage, and treatment with radiation therapy were all significant predictors of CSD. We attempted to stratify patients by lymph node density and number of positive lymph nodes, but the numbers were too small to yield valid results. However, more than one PLN was the most significant predictor of CSD, and all other variables became insignificant once this variable was included in the model. Figure 1 shows survival curves (the proportion of patients surviving with time) for PLN. It is apparent that patients with PLN had worse survival than those who did not.

Discussion

The results of this large, population-based study shows LND to be a rare event in surgical treatment of ACC in the United States. Therefore, it is hard to make conclusions on the survival benefit of LND in ACC from this analysis. Patients who received LND in this analysis were found to have higher CSD, but considering the small sample size, and the advanced disease stage in patients with LND, a higher CSD in this group is probably related to more advanced disease in patients receiving LND, and not a true effect of the treatment. However, we corroborated and extended previously reported findings regarding the prognostic value

of PLN. Overall, finding PLN on LND was the only significant predictor of CSD when controlling for the most common confounding factors. Tumor size and disease stage were the most important predictors of a surgeon's decision to perform LND, and no patient with a tumor less than 3 cm in size underwent LND. Individually, each of our findings has unique implications.

LND was performed in 5.4% of the surgically-treated patients in this analysis. Only a few series have reported on the rate of LND in patients with ACC and have typically revealed a low LND rate of generally below 30%; this is in spite of the fact that LND is advocated in the treatment of many other malignancies, and the lymph node status is an inherent component of the staging system for ACC (3, 7, 9-11). Our definition of LND (more than five lymph nodes examined) may have led to the low level of LND in this series compared to previous literature, however, this definition was utilized by other large ACC registries as a clinically relevant definition (7). Regardless, the low rate of LND in SEER, representative of the practice patterns in the United States, is of concern. This is because LND has been suggested in previous series to be predictive of survival (7). Our findings should serve as a call to duty for surgeons involved in treating ACC to consider performing more thorough LND. A higher rate of thorough LND in the surgical community will allow us to produce better evidence for the presence, or absence, of survival benefit from LND in ACC. It may also help us select groups of patients for more aggressive therapy for this disease whose outcomes did not improve in the past few decades (12).

Only tumor size and disease stage were significantly associated with LND. No LND was performed in patients with tumors 3 cm or less in this study. This is understandable since the incidence of ACC of less than 3 cm in size is rare (13), and many such adrenal masses may have been removed not suspecting ACC. In fact, there were only 26 tumors of less than 3 cm in size in our analysis (3% of all carcinomas), a very low incidence that should lend credence to the general consensus of low incidence of ACC in small adrenal masses (14).

PLN were strong predictors of CSD in our analysis. In fact, adding PLN to the model rendered all other variables insignificant. These results corroborate findings from the few studies that investigated LND in ACC. Bilimoria *et al*. used another national database from the United States and identified 3,982 patients with ACC. He then examined the effect of disease characteristics on patient's survival in surgically-treated patients and found PLN status to be associated with a significant 56% excess mortality in that population (3). Reibetanz *et al*. studied a well-characterized group of 283 patients from the German ACC registry and found the outcome to be worse for patients with histologically-proven LN metastases when compared to patients having uninvolved nodes (median time to recurrence=12.5 months *vs*. 31.3 months, p=0.002; median disease-specific survival=86.4 months *vs*. 135 months, p=0.058) (7). While having one PLN was not significantly associated with CSD in our study, we feel that considering the aggressive nature of ACC, and the small number of patients with LND in SEER, patients with any level of PLN findings should be treated as having poor prognosis for the purpose of active adjuvant therapy if it becomes available. Having emphasized the importance of LND in predicting prognosis of ACC, we recognize recent advances in molecular biology of ACC. Risk stratification *via* biomarker assessment is now routinely performed in modern practices leaded by endocrine pathologists. Routine microscopic assessment (angioinvasion, tumor grade) along with immunochemical (p53, β-catenin, MIB1) and molecular approaches (transcriptome profiling, gene-expression profile) are now distinguishing aggressive tumors from non-aggressive ACCs. Therefore, the assessment of lymph node status may not continue to add any superiority to risk stratification derived from the evaluation of the primary tumor, especially when the tumor is confined to the adrenal gland.

There are several limitations to this study. First, the study is observational, and thus suffers all the limitations of observational studies. Second, the SEER database is limited

Table II. *Results of the univariate analysis for the association between lymph node dissection and primary tumor size, cancer stage, and cancer-specific death (CSD).*

Variable		Lymph node dissection (frequency)	No lymph node dissection (frequency)	p-Value
Size (cm)	<3	0	26	0.018
	>3	56	955	
Stage	Localized	8	261	0.163
	Regional	10	111	
	Distant	6	100	
CSD	Yes	36	538	0.002
	No	22	441	

Table III. *Results of the univariate analysis for the association of lymph node positivity with cancer stage, and cancer-specific death (CSD).*

Variable		Lymph node-positive (frequency)	Lymph node-negative (frequency)	p-Value
Stage	Localized	0	8	0.787
	Regional	4	6	
	Distant	3	3	
CSD	Yes	16	20	0.005
	No	2	16	

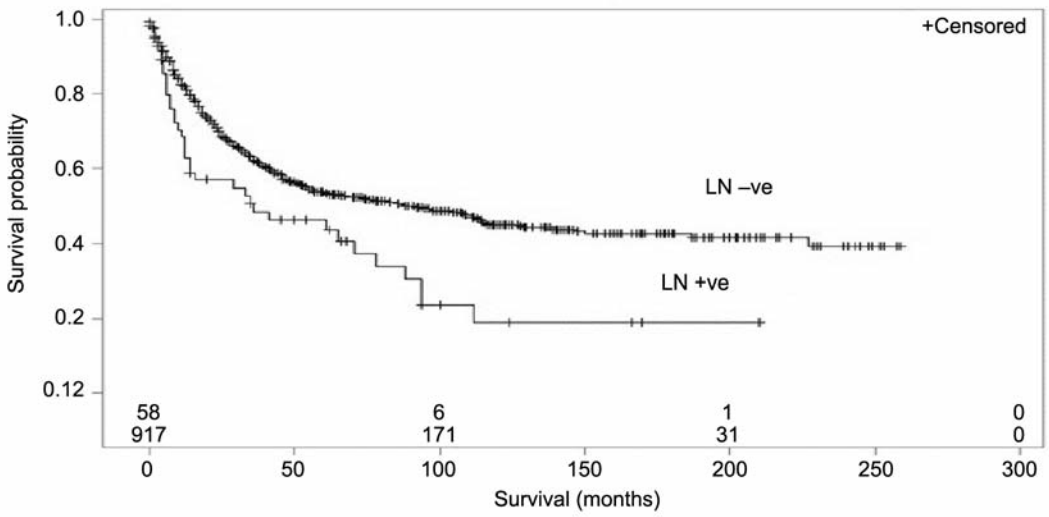

Figure 1. *Kaplan–Meier curve for the association of lymph node (LN) positivity with cancer-specific survival in patients with adrenocortical carcinoma ($p<0.05$).*

Table IV. *Significant predictors of lymph node dissection (LND), of cancer-specific death (CSD) in patients treated with lymph node dissection, and of cancer specific death in patients found to have positive lymph nodes on multivariate analysis controlling for age, sex, race, disease stage, and tumor size.*

Predictors of LND	Odds ratio	95% Confidence interval
Regional disease *vs*. localized	3.061	1.158-8.091
Predictors of CSD in patients treated with LND	Hazard ratio	
LND *vs*. no LND	1.741	1.214-2.496
Regional	1.727	1.224-2.436
Distant	6.644	4.690-9.413
Radiation therapy	1.400	1.006-1.948
Predictors of CSD in patients treated with LND and found to have PLN	Hazard ratio	
One PLN *vs*. none	2.471	0.080-76.323
Two or more PLN *vs*. none	3.130	1.233-7.950

as to the clinical factors that are coded, and clinical features such as other organ involvement, and treatment with chemotherapy, are not coded in SEER, and cannot be accounted for in our models. Third, comprehensive data related to the status of angioinvasion, lymphatic invasion, and Weiss Score are lacking in SEER; all prognostic factors determining the outcome of patients with ACC that we could not control for. Lastly, the small sample sizes necessitated by such a rare disease make it difficult to detect more subtle associations, and it is possible that other covariates could have reached statistical significance with larger numbers. Therefore, larger international studies will be necessary to address some of these shortcomings.

In conclusion, these findings highlight the low prevalence of LND in modern ACC treatment in the United States, and the importance of lymph node status in the staging process. Specifically, the presence of PLN could better-determine the need for adjuvant therapy, in conjunction with other clinical and pathological factors.

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Received June 7, 2015
Revised July 10, 2015
Accepted July 13, 2015