Impact of Lymphadenectomy on the Oncologic Outcome of Patients With Adrenocortical Carcinoma

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Objective: Adrenocortical carcinoma (ACC) is a rare malignancy with an unfavorable prognosis. The impact of a locoregional lymph node dissection (LND) has never been defined in this disease. We report the disease-specific outcome of patients treated with or without LND during primary adrenalectomy.

Methods: The medical records of patients followed by the German ACC Registry were retrospectively reviewed. Patients with incomplete resection or distant metastases were excluded. Only if the histologic analysis retrieved 5 or more lymph nodes, an intended LND was assumed (LND group). The predefined primary end point of the study was disease-specific survival.

Results: Of 283 included patients, 47 patients (16.6%) were treated with LND, whereas 236 patients (83.4%) underwent surgery without LND. Patients who underwent LND had a larger median tumor size (12.0 cm, range: 2.3–30 cm vs 10.0 cm, range: 4.0–39 cm, $P = 0.007$) and were more often treated by multivisceral resection (LND: 47.8% vs no-LND: 18.1%; $P < 0.001$). The other baseline characteristics (age, sex, endocrine activity, Weiss score, Ki-67 index, and adjuvant treatment) did not differ significantly. Median follow-up of all patients still alive was 40 months (range: 6–326). Multivariate analysis adjusted for age, tumor stage, multivisceral resection, adjuvant treatment, and lymph nodes status on preoperative imaging demonstrated a significantly reduced risk for tumor recurrence (hazard ratio: 0.65; 95% confidence interval: 0.43–0.98; $P = 0.042$) and for disease-related death (hazard ratio: 0.54; 95% confidence interval: 0.29–0.99; $P = 0.049$) in LND patients when compared with no-LND patients.

Conclusions: Our retrospective data indicate that locoregional LND improves tumor staging and leads to a favorable oncologic outcome in patients with localized ACC.

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Radical lymph node dissection (LND), first proposed by Moynihan et al[1] more than a century ago, has become standard practice in the attempted curative surgical treatment of most solid malignancies. Lymph node dissection permits refined tumor staging by histologic examination and in cases of lymph node (LN) involvement may guide the use of adjuvant treatment. Whether a locoregional LND is of prognostic benefit for the individual patient remains controversial.[2–8]

Adrenocortical carcinoma (ACC) is a rare endocrine neoplasm with a stage-dependent but generally poor prognosis,[9,10] mainly because of a high rate of recurrence. For localized disease, complete resection of the primary tumor is the mainstay of therapy and the only treatment that can offer a prospect of cure.[11–14] Thus, patient prognosis is highly dependent on radical initial surgery.[15–19] To date, there are no data available on whether or not tumor resection should include locoregional LND to improve disease control. Therefore, we analyzed the diagnostic and therapeutic impact of locoregional LND in patients with complete resection for ACC in Germany.

PATIENTS AND METHODS

Clinical data of all patients included in the German ACC Registry (www.nebennierenkarzinom.de) were retrospectively reviewed. The German ACC Registry is a nationwide database established in 2003.[20] The registry obtains detailed information on patient demographics, symptoms at primary diagnosis, tumor characteristics, surgical, adjuvant, or palliative treatment modalities, and outcome. The German ACC Registry is approved by the Ethics Committee at the University of Würzburg, Würzburg, Germany, and all patients gave written informed consent.

At the time the database was closed for analysis (December 2009), the German ACC Registry contained data sets of 563 patients. For detailed information on the extent of LND, all surgical protocols and pathology reports were critically reviewed. Tumor staging at primary diagnosis was based on imaging studies and intraoperative findings and is reported according to the European Network for the Study of Adrenal Tumors (ENSAT) classification[9]: stage I, a tumor diameter of 5 cm or less; stage II, a tumor diameter greater than 5 cm; stage III, a tumor of any size with infiltration into surrounding tissue, invasion into adjacent organs, LN involvement or tumor thrombus in the renal vein or vena cava; and stage IV, metastatic disease. The tumor stage distribution at primary diagnosis was the following: ENSAT stage I, 31 patients (5.5%); ENSAT stage II, 220 patients (39.1%); ENSAT stage III, 147 patients (26.1%); and ENSAT stage IV, 160 patients (28.4%). For 5 patients, there were insufficient data to assess exact tumor stage.

The criteria for patients included in this study were the following: ENSAT stage I to III, complete resection (R0 by histology), and a follow-up of at least 6 months (except for tumor-related death within 6 months). Laparoscopic procedures were also included in the analysis. Surgery was performed in more than 100 departments of surgery and urology throughout Germany. Patients with uncertain resection status, incomplete resection (R1, R2), or distant metastases at the time of primary diagnosis, and patients who did not undergo surgery, were excluded (Fig. 1).

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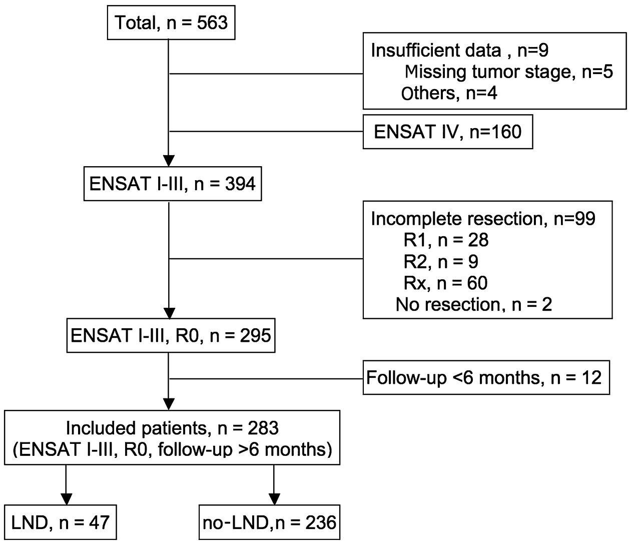

FIGURE 1. Flowchart for patient selection. ENSAT, tumor stage according to the European Network for the Study of Adrenal Tumors classification.[9]

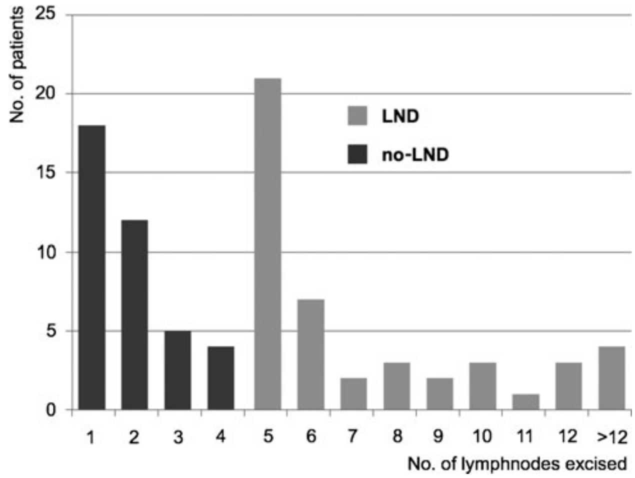

FIGURE 2. Distribution of the number of LN excised in 85 patients who had undergone resection of at least 1 LN. Patients with fewer than 5 excised LN were considered, by definition, as no-LND patients. Not included 198 patients without excision of LN.

Definition of Lymph Node Dissection

Because current literature offers no definition of LND in ACC or provides guidance on the "adequate" number of LN to be retrieved, we aimed at a definition that retrospectively allowed, at best, to separate patients in whom LN were excised accidentally from patients with intended LND. This definition was based on the effort of the surgeon to perform an LND (according to the surgical protocol) and on the number of LN excised (according to the pathology report). Regarding the latter, after extensive discussion within the study group we decided—before any outcome analysis was performed—to choose a threshold of 5 LN, which was also the median number of LN excised (range: 1–53, Fig. 2). Accordingly, patients with at least 5 excised LN were considered as patients with intended LND (LND group), whereas patients with fewer than 5 excised LN were considered as patients without intended LND (no-LND group).

Outcome

The predefined primary end point of the study was disease-specific survival in patients with or without intended LND using multivariate analysis adjusting for potentially prognostic factors. Secondary end points were recurrence-free survival, postoperative hospital stay, and 30-day mortality.

Follow-Up

Follow-up data and information on any relevant change in the course of the disease were provided from the participating physicians and the patients themselves at least every 6 months. Usually every 3 months a thoracic and abdominal computed tomography was performed. The median follow-up of all patients still alive was 40 months (range: 6–326).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc, Chicago, IL). Continuous variables are presented as the median values and range. Characteristics between both patient subgroups were compared by Mann-Whitney *U* test (continuous variables) and Fisher exact test (categorical variables). Survival analysis was calculated according to the method of Kaplan-Meier, and differences between groups were assessed with log-rank statistics. Recurrence-free survival was defined as the time interval between initial surgery and the date of radiologic evidence of disease relapse. Disease-specific survival was defined as the time interval between initial surgery and tumor-related death. Patients alive at the time of the analysis and patients who died unrelated to ACC ($n = 7$) were censored. The Cox proportional hazards regression model was used for multivariate analysis to adjust for the following presumed prognostic factors: age, ENSAT tumor stage, multivisceral resection, adjuvant treatment, and LN status on preoperative imaging. A $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Characteristics of the Study Cohort

Of the 563 patients included in the German ACC Registry (December 2009), 283 patients (median age: 47 years, range: 1–87) who had primary surgery between 1981 and 2009 met all inclusion criteria (Fig. 1). Forty-seven of the 283 patients (16.6%) underwent LND during primary tumor resection (≥5 LN excised, LND group). Within this group, the median number of LN taken did not differ between the tumor sites (right: 5.5, range: 5–12 vs left: 6, range: 5–53; $P = 0.47$) but was significantly higher in patients who had undergone multivisceral resection, when compared with patients after adrenalectomy only (median: 9, range: 5–53 vs median: 5, range 5–15; $P < 0.01$). Detailed patient characteristics are given in Table 1. Both groups were comparable with regard to sex and age distribution, Weiss score, the proliferation marker Ki-67, and adjuvant treatment. Patients who underwent LND showed a larger tumor size at primary diagnosis (12.0 cm vs 10.0 cm, $P < 0.001$), had a higher rate of locally advanced carcinomas (ENSAT stage III, LND: 51.1% vs no LND: 27.1%; $P = 0.002$), and were more frequently subject to multivisceral resection (LND: 46.8% vs no LND: 17.8%; $P < 0.001$) (Table 1). Postoperative hospital stay was comparable for patients with and without LND (12 vs 11 days, $P = 0.76$). Three patients within the no-LND group (1.3%) and none of the LND patients died within 30 days after surgery ($P = 1.0$).

TABLE 1. Baseline Characteristics and Data on Surgical and Adjuvant Treatment in 283 Patients Treated With or Without Lymphadenectomy During Primary Tumor Resection for ENSAT Stage I to III Adrenocortical Carcinoma

	no-LND (<5 Excised LN)	LND (≥5 Excised LN)	*P*
Total	236	47	
Male, n (%)	85 (36.0)	21 (44.7)	0.32
Female, n (%)	151 (64.0)	26 (55.3)	
Median age, years (range)	47 (1–87)	45 (1–84)	0.69
Median tumor size, cm (range)	10.0 (2.3–30.0)	12.0 (4.0–39.0)	0.007
Tumor stage, ENSAT			
Stage I, n (%)	21 (8.9)	2 (4.2)	0.39
Stage II, n (%)	151 (64.0)	21 (44.6)	0.02
Stage III, n (%)	64 (27.1)	24 (51.1)	0.0018
Positive LN*	13/64 (20.3)	12/24 (50.0)	
Adjacent tissue infiltration*	48/64 (75.0)	16/24 (66.7)	
Venous tumor thrombus*	12/64 (18.8)	3/24 (12.5)	
Weiss score (range)†	5 (2–9)	5 (4–8)	0.73
Ki-67, % (range)‡	10 (1–70)	10 (1–60)	0.81
Functional tumor status			0.66§
Secreting tumors, n (%)	111 (47.0)	17 (36.1)	
Glucocorticoid	78 (33.1)	13 (27.6)	
Sex hormones	60 (25.4)	5 (10.6)	
Mineralocorticoid	10 (4.2)	4 (8.5)	
Nonsecreting tumors, n (%)	53 (22.4)	10 (21.2)	
Missing data, n (%)	72 (30.5)	20 (42.5)	
Surgery			<0.001¶
Adrenalectomy only, n (%)	194 (82.2)	25 (53.2)	
Laparoscopic	25 (10.6)	0	
Converted	6 (2.5)	0	
Multivisceral resection, n (%)	42 (17.8)	22 (46.8)	
Nephrectomy	21 (8.9)	16 (34.0)	
Splenectomy	11 (4.7)	6 (12.7)	
Liver resection	6 (2.5)	1 (2.1)	
Others	12 (5.1)	7 (14.9)	
Lymph nodes			
Patients with suspect LN on Preoperative imaging, n (%)	14 (5.9)	7 (14.9)	0.06
LN per patient identified by histology, median, n (range)	0 (0–4)	6 (5–53)	<0.001
Patients with LN metastases proven by histology, n (%)	13 (5.5)	12 (25.5)	<0.001
Adjuvant treatment			
Mitotane, n (%)	46 (19.5)	12 (25.5)	0.33
Tumorbed irradiation, n (%)	20 (8.5)	3 (6.4)	0.78
Recurrence at the time of registration (%)	108/143 (75.5)	23/32 (71.9)	0.66
Postoperative hospital stay, days (range)	11 (4–39)	12 (6–70)	0.76
Mortality within 30 days, n (%)	3 (1.3)	0	1.0

*Percentages exceeding 100% due to multiple risk factors in some patients.
†Weiss score is available for 39% of LND patients and 48% of no-LND patients.
‡Ki-67 available for 59% of LND patients and 55% of no-LND patients.
§Secreting versus nonsecreting tumors.
¶Adrenalectomy versus multivisceral resection.

Follow-Up and Oncologic Outcome

The median follow-up time was 59 months (range, 8–273) for LND patients and 39 months (range, 6–326) for no-LND patients ($P = 0.026$). During follow-up, recurrence was documented in 32 of 47 LND patients (68.1%) and in 143 of 236 no-LND patients (60.6%). For patients with disease relapse, median time to first recurrence was 14.2 months: 20.1 months for LND patients and 12.8 months for no-LND patients ($P = 0.36$). Eighty-six patients had died from ACC: 14 patients (29.8%) in the LND group and 72 patients (30.5%) in the no-LND group. Seven patients had died of other causes. One hundred one patients were free of recurrence at the time of last follow-up: 14 patients (29.8%) in the LND group and 87 patients (36.8%) in the no-LND group.

For patients with tumor relapse, treatment for recurrent disease in LND and no-LND patients included surgery (68.7% vs 55.2%, $P = 0.17$), mitotane and/or cytotoxic chemotherapy (53.1% vs 61.5%, $P = 0.42$), or radiotherapy (9.4% vs 7.7%, $P = 0.72$). Treatment modalities were often used in combination. Eight patients with recurrent disease received no specific treatment.

The outcome was worse for patients with histologic proven LN metastases (n = 25), when compared with patients with uninvolved nodes (n = 258) (median time to recurrence: 12.5 months vs 31.3 months, $P = 0.002$; median disease-specific survival: 86.4 months vs 135 months, $P = 0.058$). Within the group of patients with LN metastases (n = 25), the patients who underwent intended LND (n = 12) had a superior median recurrence-free survival (20.4 vs 9.9 months, $P = 0.086$) and disease-specific survival (>86 months [median not yet reached] vs 26.2, $P = 0.06$), when compared with node-positive patients who had not undergone LND (n = 13).

Because important prognostic parameters like tumor size, tumor stage, and frequency of suspected LN involvement on preoperative imaging were not equally distributed between the groups, a predefined multivariate analysis was performed, adjusting for age, ENSAT tumor stage, multivisceral resection, adjuvant treatment, and LN status on preoperative imaging as covariates. This analysis revealed a significant reduction in both the risk of recurrence (hazard ratio: 0.65; 95% confidence interval [CI], 0.43-0.98; $P = 0.042$) and disease-related death (hazard ratio: 0.54; 95% CI, 0.29-0.99; $P = 0.049$) for LND patients when compared with no-LND patients (Fig. 3, Table 2). Results were the same when only patients at a higher risk of tumor recurrence (ENSAT stage III: LND, n = 24; no-LND, n = 64) were included in this multivariate model. Again, for LND patients, a considerable reduced risk of recurrence (hazard ratio: 0.57; 95% CI, 0.32-1.01; $P = 0.05$) and for disease-related death (hazard ratio: 0.37; 95% CI, 0.16-0.87; $P = 0.02$) was observed (Fig. 4, Table 3).

DISCUSSION

This is the first study analyzing on the impact of LND in ACC. Our results suggest a clinical benefit of LND in patients undergoing curative intended surgery for localized disease. This finding is of clinical importance, considering the high rate of tumor recurrence even after seemingly complete resection.[13] Lymph node dissection was associated with a reduction of the risk of recurrence by 35% and for tumor-related death by 46%. This prognostic benefit of LND was apparent when analyzing both the whole study cohort and the subgroup of patients with high risk of tumor recurrence (ENSAT stage III).

Only few series have reported on the rate of LND in ACC patients and typically revealed a low-lymphadenectomy rate between 17% and 30%.[11,17] This contradicts surgical principles of other solid malignancies. It further highlights a yet undefined role of LND in the surgical treatment of ACC, although patients' LN status is an inherent component of all past and currently used staging systems for ACC.[9,21–23]

The majority of patients who underwent LND had stage III tumors, whereas for no-LND patients ENSAT II was the dominating tumor stage. A stage migration phenomenon is a reasonable explanation for this observation. Without LND, nodal status is beyond evaluation and a stage III carcinoma (due to LN involvement) can easily be missed. Thus, beside a prognostic benefit, LND in ACC patients permits a refined tumor staging and is therefore an important diagnostic tool. This "contamination" of stage II with locally advanced cancers may also explain the variable outcome that has been reported for stage II patients in different series.[9,15,17,19,24]

Because the frequency of multivisceral resections was higher in the LND group, it is likely that the surgical approach influenced on the number of excised LN. However, as all included patients experienced margin-free resection (R0), the imbalance in the extent of surgery (multivisceral resection vs adrenalectomy only) per se is unlikely to explain the different outcome. Indeed, the multivariate analysis confirmed that a more radical surgical approach would have rather favored an inferior outcome (Table 2). Similarly, Bilimoria et al[11] reported a worse prognosis for ACC patients undergoing resection of adjacent organs.

In our series, LN were histologically tumor affected in about 26% of LND patients, which largely resembles the incidence of LN metastases of previous reports.[11,25] It remains speculative whether LND facilitates complete tumor clearance in these patients. However, without LND, nodal staging might be incorrect. Even worse, residual tumor might have been left in situ implicating a high risk of local recurrence. Our data suggest that this scenario relates to up to every fourth patient.

Metastatic LN involvement is associated with both a higher likelihood of incomplete resection and an inferior outcome.[9,11] Therefore, accuracy of surgical LN staging is indispensable for determining patient prognosis and may further guide the use of adjuvant mitotane treatment.[26] Although there is evidence that adjuvant mitotane treatment is able to reduce the risk of recurrence,[27] the final answer concerning the efficacy of this therapy[28–31] awaits the results of a prospective randomized trial (www.adiuvo-trial.org). In addition, adjuvant radiotherapy might prolong recurrence-free survival in selected patients,[32,33] and radiotherapy in patients with LN metastases might be a reasonable approach.[34]

Tumor relapse in ACC patients is common,[16,18,32,35] and inadequate surgical treatment of the primary tumor without its lymphatic drainage might be a possible explanation for this phenomenon. The favorable outcome of LND patients in our series with a 5-year disease-specific survival rate of more than 70% strongly argues for an aggressive surgical approach including LND, and a close follow-up by specialized centers. On the basis of the lymphatic drainage of the adrenal gland[36] and a recent analysis of the patterns of recurrence in ACC patients,[34] we would propose excision of the connective tissue as shown in Figure 5. Ideally, such an operative approach would be tested in a prospective, randomized study. However, it is rather unlikely that such a trial will be launched in the near future. Therefore, a first step toward a better evidence could be a prospective trial

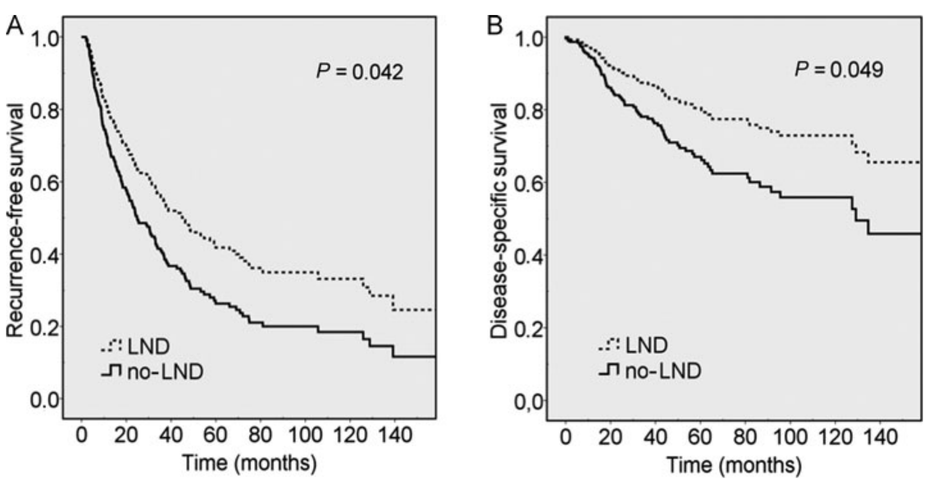

FIGURE 3. Survival analyses using multivariate Cox regression analysis: recurrence-free survival A, and disease-specific survival B, for patients undergoing LND versus no-LND. Adjustment for age, tumor stage, multivisceral resection, adjuvant treatment, and LN status on preoperative imaging was performed.

TABLE 2. Predictors of Recurrence-Free and Disease-Specific Survival Using a Cox Regression Multivariate Analysis

	Recurrence-Free Survival		Disease-Specific Survival	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Surgical modality				
no-LND (n = 236)*				
LND (n = 47)	0.65 (0.43–0.98)	0.042	0.54 (0.29–0.99)	0.049
Tumor stage				
ENSAT I*				
ENSAT II	1.32 (0.70–2.49)	0.39	3.56 (0.86–14.77)	0.08
ENSAT III	2.00 (1.01–3.98)	0.04	7.21 (1.69–30.69)	0.008
Multivisceral resection				
No (n = 219)*				
Yes (n = 64)	1.61 (1.09–2.38)	0.016	1.26 (0.73–2.16)	0.41
Adjuvant treatment				
No (n = 202)*				
Yes (n = 81)	0.99 (0.68–1.44)	0.96	0.92 (0.53–1.59)	0.77
LN status on preoperative imaging				
No suspicion of LN metastases (n = 262)*				
Suspicion of LN metastases (n = 21)	0.77 (0.76–2.20)	0.34	1.15 (0.39–1.93)	0.73
Age†	1.01 (1.00–1.03)	0.02	1.01 (1.00–1.02)	0.016

*Respective reference group.
†Continuous variable.
HR indicates hazard ratio.

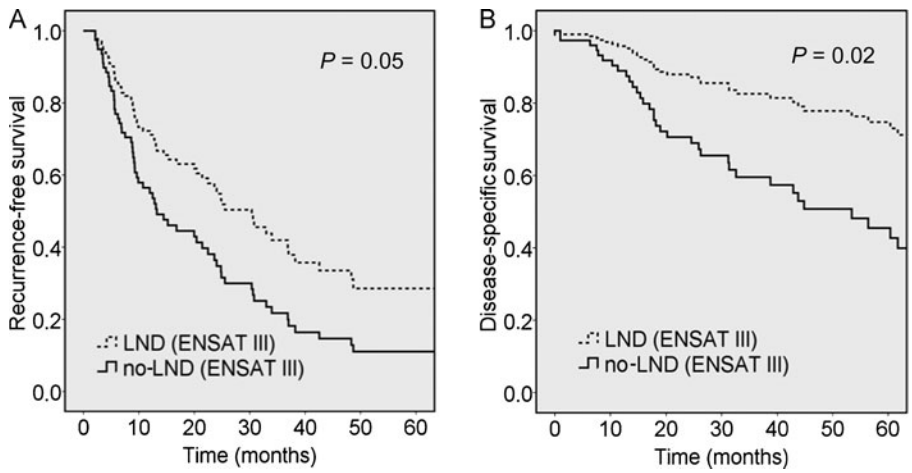

FIGURE 4. Survival analyses using multivariate Cox regression analysis: recurrence-free survival (A) and disease-specific survival (B) for stage III patients undergoing LND versus no-LND. Adjustment for age, multivisceral resection, adjuvant treatment, and LN status on preoperative imaging was performed.

without randomization using standardized preoperative imaging, surgical therapy (including predefined clearance of the lymphatic bearing tissue), and histologic workup by experienced pathologists.

Our study raises the question if a secondary surgery is indicated in patients with an ACC on final histology, initially operated for a suspected adenoma. We are very cautious to (generally) recommend secondary LND in such cases on the basis of our retrospective analysis, not only because final histology is often available not before 10 to 14 days after surgery, which is a period not suitable for reoperation.

Minimally invasive surgery for ACC is currently a matter of debate.[37–39] As in our series, none of the LND patients were treated by laparoscopy, the oncologic significance of laparoscopic LND remains unanswered. However, laparoscopic retroperitoneal LND is feasible[40] and therefore an intended LND would not a priori preclude minimally invasive surgery in a patient who otherwise could qualify for such an approach.

Although we did not address the issue of perioperative morbidity in details, the comparable postoperative hospital stay of both patient groups suggests that LND in ACC patients is not a major source of an increased complication rate.

Our study has certain limitations. First, the retrospective study design could have influenced the results by unknown confounders. Second, our definition of LND is somewhat arbitrary, but currently there is no specific recommendation for locoregional LND in ACC we could have referred to. Third, the accurateness of the local pathologist in examining the excised LN may have affected our results. Finally, the performance and extent of LND might be a representative of a more experienced surgical treatment and may therefore have confounded the oncologic outcome.

Beside the large number of included patients, another strength of our study is the well-performed patient selection, including only patients with a margin-free resection (R0 by histology). We believe that this is mandatory to uncover delicate prognostic parameters, as patients with incomplete tumor resection will suffer an unfavorable prognosis.[41] However, this selection obviously contributes to the better-clinical outcome of our cohort in comparison to most published

TABLE 3. Predictors of Recurrence-Free and Disease-Specific Survival Using a Cox Regression Multivariate Analysis in ENSAT Stage III Patients

	Recurrence-Free Survival		Disease-Specific Survival	
	HR (95% CI)	P	HR (95% CI)	P
Surgical modality				
no-LND (n = 64)*				
LND (n = 24)	0.57 (0.32–1.01)	0.05	0.37 (0.16–0.87)	0.02
Multivisceral resection				
No (n = 47)*				
Yes (n = 41)	0.71 (0.42–1.20)	0.21	0.79 (0.40–1.56)	0.50
Adjuvant treatment				
No (n = 61)*				
Yes (n = 27)	1.18 (0.65–2.14)	0.59	0.93 (0.45–1.89)	0.83
LN status on preoperative imaging				
No suspicion of LN metastases (n = 74)*				
Suspicion of LN metastases (n = 14)	0.58 (0.30–1.12)	0.11	1.37 (0.52–3.63)	0.53
Age†	1.01 (0.99–1.02)	0.49	1.01 (0.99–1.03)	0.58

*Respective reference group.
†Continuous variable.

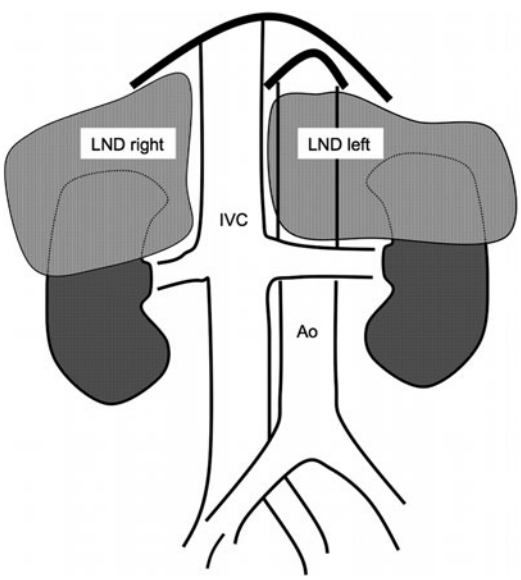

FIGURE 5. Proposed field for right- and left-sided LND. On the right side, the upper limit of LND is the lower edge of the liver, the left-lateral limit is the edge of the inferior vena cava (IVC), and the lower limit is the renal pedicle. On the left side, the upper limit of the dissection is the diaphragmatic crus, the right-lateral limit is the edge of the aorta (Ao), and the lower limit is the renal pedicle.

series that included a relevant number of patients with incomplete or uncertain resection. Baseline and tumor characteristics were evenly distributed between both groups. Furthermore, both patients groups were highly comparable regarding the presence of recurrence at the time of registration in the registry, as this has been shown to be of major prognostic relevance in retrospective series.[42] Finally, the participation of more than 100 surgical and urologic departments throughout Germany makes the results of this study generalizable.

In conclusion, our data suggest that locoregional LND contributes to a refined tumor staging and improves the prognosis in patients with localized ACC. Lymph node dissection should therefore be considered as part of the surgical treatment in patients undergoing surgery for ACC. We are aware that a final recommendation for such an approach needs the results of a prospective randomized trial. However, the results of this study are the most accurate level of evidence on this issue available at present.

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