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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Patterns of Lymph Node Recurrence in Adrenocortical Carcinoma: Possible Implications for Primary Surgical Treatment

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ABSTRACT

Background. In the surgical treatment of adrenocortical carcinoma (ACC), lymphadenectomy may improve oncologic outcome. However, patterns of metastatic lymphatic spread in ACC are unknown.

Methods. Clinical data of patients included in the European Network for the Study of Adrenal Tumors (ENSAT) registry were retrospectively reviewed. Inclusion criteria were: nonmetastatic ACC, complete resection of the primary tumor, a disease-free time of > 3 months, and lymph node metastases as the first disease relapse. The retroperitoneal lymphatic drainage area was evaluated by using follow-up imaging.

Results. Of 971 patients from the ENSAT registry, 56 patients were included. In left-sided ACC ($n = 36$), lymphatic recurrence was detected in the left renal hilum (50%), in the perirenal fat tissue cranial to the renal hilum (ventral, 47%; dorsal, 55%), para-aortic (47%), interaorto-caval (22%), and/or in the perirenal fat tissue caudal to the renal hilum (ventral, 20%; dorsal, 17%). In right-sided ACC ($n = 20$), lymph node metastases were detected in the perirenal fat tissue cranial to the renal hilum (dorsal, 55%; ventral, 45%), interaorto-caval (35%), in the area of the right renal artery (10%), and/or paracaval (15%). Patients with right-sided ACC showed left-paraaortic lymph node recurrences in 10% of cases.

Conclusion. Metastatic lymphatic spread appears to be more extensive than previously thought. The distribution pattern of lymph node metastases described in our study could be used as a guide for a more extended lymph node dissection.

Adrenocortical carcinoma (ACC) is a rare disease with a basically poor prognosis, partly due to a high recurrence rate.[1–4] In the nonmetastatic tumor stage the sole therapeutic option with a prospect of success is complete surgical resection of the primary tumor, but the extent of surgery is debated.[5–12] Moreover, the prognostic impact of a prophylactic locoregional lymphadenectomy during primary tumor resection is inadequately described in the literature and remains a matter of controversy. Recently, we could show a prognostic benefit of lymphadenectomy in ACC, and locoregional lymphadenectomy is now recommended in the recent European guidelines on the management of ACC.[13,14] However, our previous study had significant limitations, and thus, so far no standard for such a procedure has gained acceptance and it is unknown which regional lymph nodes should be removed.[13]

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Furthermore, reliable data on the anatomy of the lymphatic drainage of the adrenal glands are limited. From an anatomical point of view, the celiac lymph nodes, renal hilum lymph nodes, para-aortic, and paracaval lymph nodes between the aortic hiatus and the renal pedicle ipsilateral to the tumor are defined as first-order drainage nodes.[15] It is almost impossible, however, to predict the lymphatic drainage route of a malignant adrenal lesion, because the usually large primary tumors (e.g., > 10 cm) often possess lymphatic vessels that are then occluded by lymphangiosis carcinomatosa, and tumors may therefore metastasize "extra-anatomically." The purpose of the present study was to investigate the patterns of lymph node recurrence following initial curative resection of an ACC to possibly guide the extent of lymph node removal in this disease.

PATIENTS AND METHODS

Patients diagnosed with lymph node metastases after initial curative surgery for ACC between January 2000 and December 2013 were analyzed. Data of patients were retrospectively extracted from the German part of the European Network for the Study of Adrenal Tumors (ENSAT) registry.[16,17] The ENSAT registry is approved by our local ethics committee, and all patients included gave their written, informed consent. At the time of analysis (October 2014), 971 patients were registered within the ENSAT registry.

Tumor staging at primary diagnosis was based on the ENSAT classification: stage ENSAT I, tumor size ≤ 5 cm without any risk factors (T1N0M0); stage ENSAT II, tumor size >5 cm but still without risk factors (T2N0M0); stage ENSAT III, tumor of any size with at least 1 of the following factors: tumor infiltration in surrounding tissue (T3), tumor invasion into adjacent organs or venous tumor thrombus in the vena cava or renal vein (T4), positive lymph node (N1), but no distant metastasis (M0); stage ENSAT IV, the presence of distant metastases irrespective of tumor size or lymph node status (T1-T4N0-N1M1).[1] The inclusion criteria for patients in the current study were the following: nonmetastatic ACC (ENSAT I-III), complete resection (R0) of the primary tumor, a disease-free interval > 3 months, and lymph node metastases as the first disease relapse during the course of the disease (Fig. 1). For diagnosis of lymph node metastases, follow-up imaging (CT and/or MRI scan, FDG-PET/CT) was evaluated by a radiologist blinded to clinical information of the respective patients (for exemplary imaging, see Fig. 2). The retroperitoneal lymph node basin was evaluated separately to assess the patterns and percentage distribution of lymph node metastases. Histological confirmation of the lymph node metastases was not an inclusion criterion. However, it had been obtained in about half of the evaluated patients with samples derived from biopsy or surgery on the locoregional recurrence.

Definition of the Anatomic Recurrence Site

The regions in vicinity of the large retroperitoneal vessels were defined and evaluated for frequency of lymph node metastases (Supplemental Table 1; Figs. 3, 4). In addition, the perirenal soft tissue was subdivided with respect to the renal hilum, resulting in a cranial or caudal, as well as a ventral or dorsal compartment.

RESULTS

Of the 971 patients registered by our center within the ENSAT registry (October 2014), 56 (19 males, 37 females) underwent primary surgery between January 2000 and December 2013 in 48 different institutions and met all inclusion criteria (Fig. 1). The primary ACC tumor site was on the right side in 20 patients (36%) and on the left in 36 patients (64%). Detailed patient and treatment data are given in Table 1. The median time to lymph node recurrence was 17.5 (range 4–74) months. According to the surgical report, an intended lymphadenectomy during primary surgery had been performed in 6 of 56 patients (11%). These patients underwent primary surgery in six different institutions, and the comparison of the surgical report and later recurrence pattern showed that three of six patients (50%) recurred in an area already dissected during primary surgery (Supplemental Table 2). Imaging procedures detected distant metastases concurrent with the lymphatic recurrence in 32 of 56 patients (57%). In 29 of 56 patients (52%), tissue from radiologically conspicuous areas were obtained by biopsy or resection. Subsequent histological workup confirmed malignancy in all these cases.

In left-sided ACC tumors (Fig. 3), lymphatic recurrence occurred mainly in the left renal hilum (around the left renal artery; 50.0%), in the perirenal fat tissue cranial to the renal hilum (ventral, 47.2%; dorsal, 55.6%), para-aortic (47.2%), interaorto-caval (22.2%), and/or in the perirenal fat tissue caudal to the renal hilum (ventral, 20.0%; dorsal, 17.1%). In these 36 tumors, lymphatic recurrence was detected on the right side of the inferior vena cava in only 1 patient (2.8%). In right-sided ACC (Fig. 4), the majority of lymphatic recurrences were detected in the perirenal fat tissue cranial to the renal hilum (dorsal, 55.0%; ventral, 45.0%), interaorto-caval (35.0%), in the perirenal fat tissue dorso-caudal to the renal hilum (25.0%), paracaval (cranial or caudal to the renal hilum, each 15.0%), or in the area of

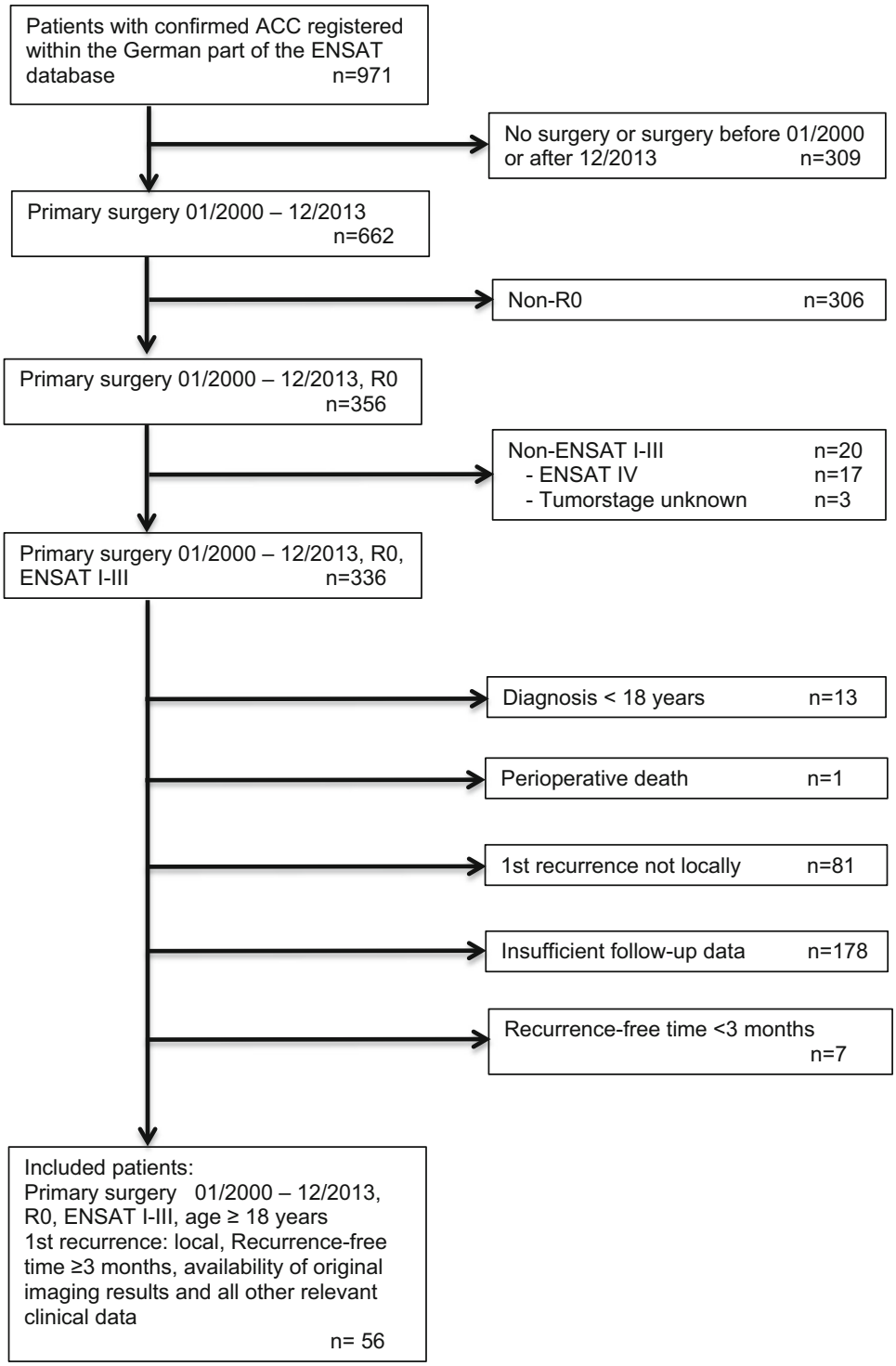

FIG. 1 Flowchart for patient selection. ENSAT, tumor stage according to the European Network for the Study of Adrenal Tumors classification

the right renal artery (10%). Of note, 2 of the 20 patients (10.0%) with right-sided ACC had lymph node metastases left of the aorta. Locoregional recurrence or lymph node metastases in the respective contralateral renal fat tissue were not seen in any patient.

DISCUSSION

To our knowledge, this is the first study to analyze the clinical patterns of lymph node metastases in ACC. Our results are clinically relevant, because the incidence of locoregional and lymphatic recurrences remains unacceptably high even after curative primary tumor

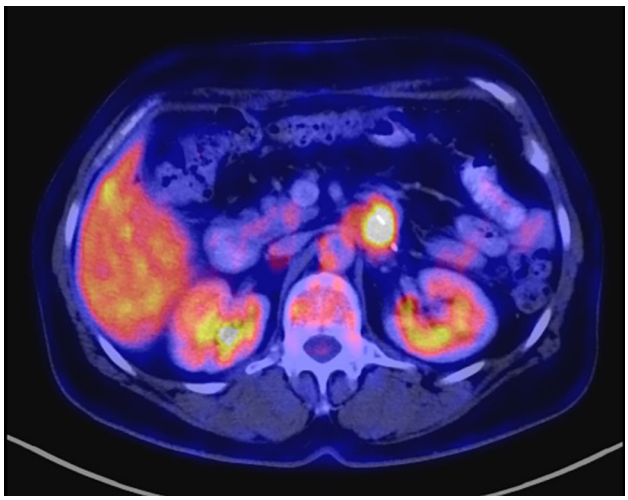

FIG. 2 PET-CT of a patient with lymph node recurrence in the area of the left renal hilum, 4 years after adrenalectomy for adrenocortical carcinoma

resection.[18–20] Some authors even describe local recurrence as the most frequent site of recurrence (in up to 65% of cases).[21]

The role of lymph nodes and the importance of lymphadenectomy in ACC has most recently been highlighted.[22] Based on an analysis of patients from the National Cancer Database between 2004 and 2013, Panjwani et al. clearly showed that patient's lymph node status represents an independent predictor of overall survival with patients with positive nodes having a threefold increased risk of death. Thus, in their analysis, involved lymph nodes were an even stronger negative prognostic factor than a positive resection margin. The authors also worked out that at least four lymph nodes should be resected and analyzed to determine accurately the lymph node negativity.

Well compatible with this observation, the two recently published guidelines recommend that in case of a highly suspected or proven ACC a routine locoregional lymphadenectomy at index surgery should be performed.[14,23] Based on a review of all relevant anatomic and clinical literature, the panel proposed that this lymphadenectomy should (as a minimum) include the periadrenal and renal hilum nodes as well as all suspicious or enlarged lymph nodes identified on preoperative imaging. Furthermore, lymph node clearance in the area of the celiac axis, the superior mesenteric artery, paraaortic and/or paracaval ipsilateral to the tumor should be additionally considered.[23]

Taking into account the published date and our own results, a special attention should be paid to the removal of the perirenal fat in continuity to the tumor, because this seems to be the most frequent side of recurrence (> 50% of cases). Furthermore, lymph node dissection in the interaorto-caval space also should be considered, because both left- and right-sided ACC showed interaorto-caval recurrence in 22.2% and 35.0% of cases, respectively. However, *isolated* interaorto-caval recurrence seems to be exceptional, because 14 of 15 patients (93%) with interaorto-caval lymph node recurrence also had metastases in other compartments at the same time. Of particular interest is the

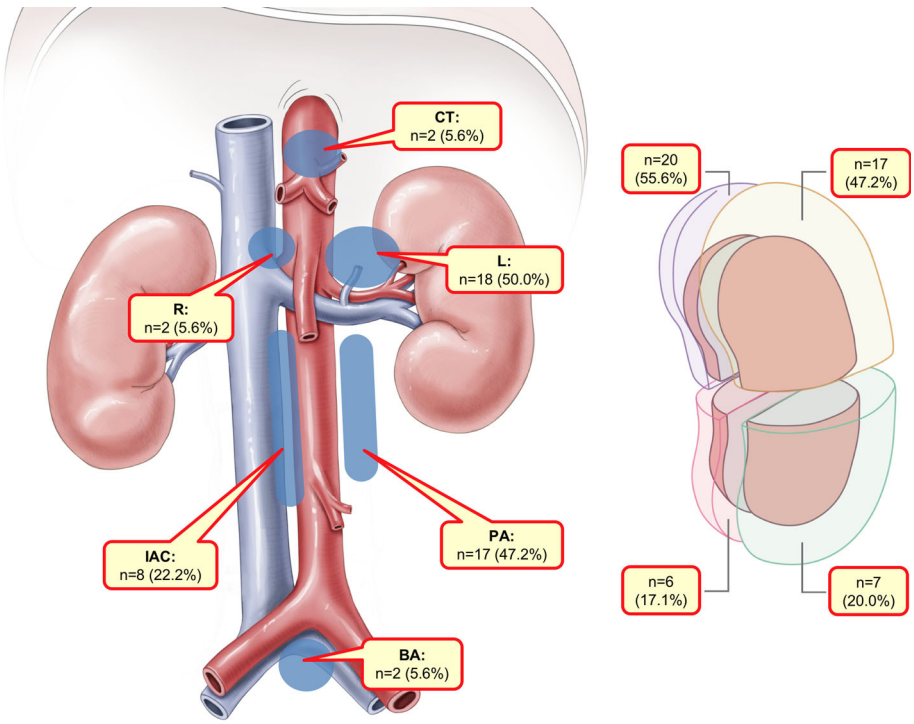

FIG. 3 Percentage distribution of the lymph node metastases in patients with ACC located on the left side. The sum of more than 100% is due to the fact that in many cases the tumor has metastasized into several compartments simultaneously. Recurrence in the perirenal fat tissue of the contralateral side was not seen. (*CT* coeliac trunk, *L* left renal hilum, *R* right renal artery, *PA* paraaortic, *IAC* interaorto-caval, *BA* aortic bifurcation)

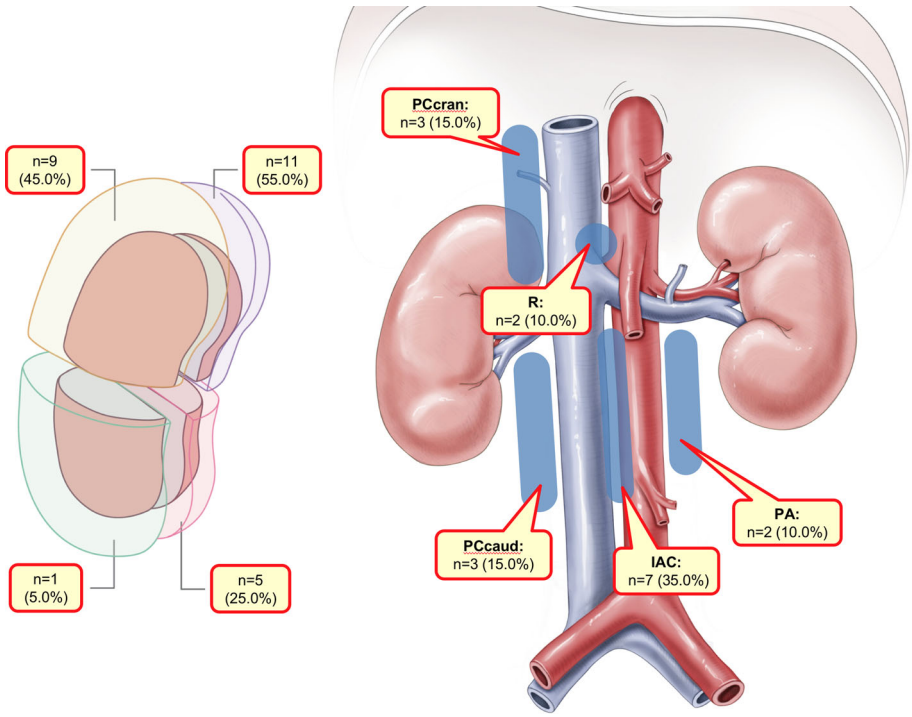

FIG. 4 Percentage distribution of the lymph node metastases in patients with ACC located on the right side. The sum of more than 100% is due to the fact that in many cases the tumor has metastasized into several compartments simultaneously. Recurrence in the perirenal fat tissue of the contralateral side was not seen. (*R* right renal artery, *PA* paraaortic, *IAC* interaorto-caval, *PCcran* paracaval cranial, *PCcaud* paracaval caudal)

finding that in a high percentage of cases (47.2% in left-sided and 40% in right-sided ACC), lymph node metastases were detected *caudal* to the ipsilateral renal hilum along the large vessels, so that these regions might be eligible for a prophylactic lymph node dissection. However, this pattern of recurrence has not been described in any former study.[24] In contrast to findings published by Gaujoux et al., we found only a few cases with lymph node metastases in the area of the aortic hiatus, celiac trunk, or the superior mesenteric artery (0–5% of cases).[15] Therefore, following our results, these latter compartments do not need to be routinely dissected.

However, it remains uncertain—and cannot be definitively answered by the available data—which lymph node compartments should at long last be prophylactically removed. There is no sufficient evidence as to which percentage of lymph node recurrences in a given compartment a lymph node dissection is justified, as no such risk-benefit analysis has been performed to date. Currently, it seems unrealistic to reach a general consensus. This applies in particular to the interaorto-caval space; lymph node dissection in this area is challenging and conceivably risky for the patient. In addition, according to common experience, an intended lymph node dissection in this area often is reflected by a very low actual lymph node yield. Therefore, we recommend that each center defines an individual strategy based on its own data on surgical morbidity and the respective patients' risk profile. Based on our clinical experience and assuming that a risk rate of >20% for a locoregional recurrence would justify a prophylactic lymph node/soft tissue dissection in a given compartment, lymphadenectomy during index surgery should be considered in all compartments with a presumed recurrence rate $> 20\%$ (Figs. 3·4). Because 82% of our patients had initial primary tumor stage ENSAT I or II (limited disease) and still developed lymph node metastases comparatively early during the course of the disease, we would not limit this recommendation for lymphadenectomy to locally advanced tumors (ENSAT III). We also would not restrict lymphadenectomy to special subtypes of tumors (poorly differentiated, high Ki67 index, lymphovascular invasion, etc.), because this information is not available at the time of index surgery. Furthermore, although our study did not analyze specific oncologic follow-up data, the observation that in half of our patients the lymphatic recurrence occurred at a limited time interval (within 18 month after index surgery) makes it seem reasonable to pursue lymphadenectomy at the time of primary surgery.

We are aware that a recommendation for (an extended) lymphadenectomy would lead to a critical reexamination of the indication for a primary laparoscopic tumor resection/lymphadenectomy, although some authors (including ourselves) regard this approach as a possible option in small, localized ACC.[25–28] Mainly, such considerations must regard the technical limitations of performing an extended retroperitoneal lymphadenectomy and soft tissue dissection laparoscopically.

The present study has certain limitations. A histological workup of the radiologically conspicuous areas was only done in half of the patients included, as in the remaining

TABLE 1 Baseline characteristics and treatment data of 56 ACC patients with lymph node metastases during the course of the disease

Patients (*n*)	56
Male, *n* (%)	19 (34)
Female, *n* (%)	37 (66)
Age (year), median (range)	49.5 (25–79)
Primary tumor location (right/left), *n* (%)	20 (36)/36 (64)
Tumor size (cm), median (range)	9.8 (3–24)
Primary tumor stage (ENSAT)	
ENSAT I, *n* (%)	6 (11)
ENSAT II, *n* (%)	40 (71)
ENSAT III, *n* (%)	10 (18)
Ki-67 (%), median (range)*	10 (1–40)
Surgery for the primary tumor	
Adrenalectomy only, *n* (%)	49 (88)
Open, *n* (%)	35 (71)
Laparoscopic, *n* (%)	11 (22)
Converted, *n* (%)	3 (6)
Partial adrenalectomy, *n* (%)	2 (4)
Multivisceral resection, *n* (%)	5 (9)
Adrenalectomy along with splenectomy, *n* (%)	2 (4)
Adrenalectomy along with nephrectomy, *n* (%)	3 (5)
Adrenalectomy along with partial nephrectomy, *n* (%)	1 (2)
Surgery including lymphadenectomy, *n* (%)**	6 (11)
Distant metastases concurrent with lymph node metastases (within 4–6 weeks), *n* (%)	32 (57)
Liver metastases, *n* (%)	10 (31)
Pulmonary metastases, *n* (%)	20 (63)
Bone metastases, *n* (%)	2 (6)
Peritoneal carcinosis, *n* (%)	8 (25)
Others, *n* (%)	5 (16)
Time interval between surgery and detection of lymphatic recurrence	
$\leq$ 18 months, *n* (%)	31 (55)
$>$ 18 months, *n* (%)	25 (45)
Imaging procedure for detection of lymphatic recurrence	
CT or MRI scan, *n* (%)	43 (77)
FDG-PET/CT, *n* (%)	13 (23)
Adjuvant treatment	
Mitotane, *n* (%)	14 (25)
Tumor bed irradiation, *n* (%)	2 (4)

*Ki-67 missing for 7 patients

**Details see Supplemental Table 2

patients biopsy or resection was clinically not indicated. However, in these patients the radiological diagnosis of recurrence was clear and was made at a multidisciplinary team meeting. Moreover, even histological workup of the local tumor recurrence in most patients could not finally confirm that it was a true lymph node metastasis (in contrast to a locoregional soft tissue metastasis). Therefore, we cannot exclude the possibility that some of what was recorded as lymph node metastases may have been drop metastases from the primary tumor, which occurred during resection even if the margins of the specimen were negative (R0). We also realize that even a meticulous lymph node dissection will never safely prevent a locoregional or lymphatic recurrence. This is clear from the observation that our study included 6 of 56 patients (11%) with intended lymphadenectomy in a given area, and at least three of them (50%) suffered a lymphatic relapse in this compartment. Moreover, appropriate preoperative staging is important to select which patients have only locoregional disease and thus are candidates for prophylactic

lymphadenectomy. In addition, in the literature, it is still not conclusively elucidated whether lymphadenectomy is indicated in localized ACC at all. Before the current analysis, we had already observed a prognostic benefit from lymph node dissection in patients from the German Adrenocortical Carcinoma Registry.[13] Furthermore, in a recent multicenter study on ACC, the surgeon's effort to dissect peritumoral lymph nodes was independently associated with improved overall survival.[29] However, other authors with similar study protocols could not reproduce this finding.[30,31] Therefore, we are convinced that a conclusive determination of the possible oncological benefit of a lymphadenectomy in ACC can only be based on a multicenter, prospective randomized study. Our present results, however, provide at least a viable discussion basis for definition of the relevant retroperitoneal lymph nodes needed for such studies.

On the contrary, the results of our study represent a comprehensive lymphatic metastasizing profile based on a sufficiently large patient cohort. With a median Ki-67 of 10% in our study, this value was on average for ACC. It therefore may be assumed that included patients are a representative cohort in terms of tumor aggressiveness (including the risk of lymph node metastases). Another strength of our analysis is that all imaging procedures were re-reviewed by the same interdisciplinary team of a radiologist and a surgeon.

CONCLUSIONS

Our study describes for the first time, the favored retroperitoneal regions of locoregional recurrence and lymph node metastases in ACC. In right-sided ACC, these recurrences were observed in the perirenal fat tissue cranial-ventral, cranial-dorsal, and caudal-dorsal to the renal hilum, paracaval-right, and in the interaorto-caval space. In left-sided ACC, the left renal hilum, the perirenal fat tissue cranial-ventral, cranial-dorsal, and caudal-ventral to the renal hilum as well as the para-aortal and interaorto-caval space were favored regions of locoregional and/or lymphatic recurrence. Our results, together with published guidelines, allow first conclusions to be drawn on which retroperitoneal compartments might reasonably be cleared during index surgery to possibly reduce the risk of lymph node or locoregional recurrence in ACC.[14,23] Whether or not such an approach has a prognostic benefit for the individual patient is still controversially discussed in the literature and can only be definitively established in a multicenter, prospective, randomized study that also includes oncologic follow-up data.[13,30,31] Until then, we invite other working groups to assess this important question of lymph node recurrence in ACC based on their own data.

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