Reply to Letter: "Regional Lymphadenectomy for Adrenocortical Carcinoma"

Reply:

We are pleased to read the letter from Miller and Doherty and are delighted that our study on lymphadenectomy in adrenocortical carcinoma (ACC) gives rise to an intensive discussion. The German ACC Registry is a comprehensive database and is maintained prospectively since 2003. However, relevant data for the current study were retrieved retrospectively from pathology reports, surgical protocols, and patient charts. As indicated in our publication, such data are limited in terms of their explanatory power and should be interpreted with some caution.[1] Nevertheless, regarding the issue of lymphadenectomy in ACC, a higher level of evidence (eg, prospective data) has not yet been published and can probably not be expected in the near future.

It is plausible to assume that a (early) lymphatic invasion indicates aggressive tumor biology and is associated with a poor prognosis. This is clearly demonstrated for lymph node–positive patients, not only in our current series but also in other series.[2–4] As suggested by Miller and Doherty, we performed an analysis including all patients for which both the lymph node status and Ki67 were available. This analysis showed that lymph node–positive patients (n = 14) had significantly higher Ki67 values (median = 20% vs 10%, $P = 0.018$) than patients without involved lymph nodes (n = 144). However, we cannot reliably answer the question on intratumoral lymphatic invasion. Because the included patients were treated in more than 100 institutions in Germany, the pathology reports were not standardized. Furthermore, intratumoral lymphatic invasion is not an established criterion to evaluate adrenocortical tumors and was therefore not reported by the German reference pathologist, Prof Wolfgang Saeger, who reviewed about half of the samples. Thus, information on intratumoral lymphatic invasion was available for only 78 patients and an invasion was present in only 8 patients, precluding a meaningful analysis.

In our study, we intentionally decided not to refer to subgroup analysis in terms of tumor recurrence, which would have resulted in small patient numbers (in each subgroup) for this rare condition. As requested by Miller and Doherty, we have now performed this analysis. It became apparent that the rate of local recurrence was comparable for patients who had undergone lymph node dissection (LND patients) and those who had not undergone lymph node dissection (noLND patients, 68.7% vs. 65.5%). However, LND patients experienced local recurrence somewhat later than noLND patients (19.6 months vs 15.5 months, $P = 0.08$). Taking into account a significantly higher rate of locally advanced tumors in the LND group at primary diagnosis and the reduced sample sizes, we interpret these results as a trend to a better local tumor control in patients undergoing locoregional lymph node dissection. Nevertheless, further studies are necessary to better define subgroups of patients who specifically benefit from such an approach.

We are well aware that our definition of "regional lymphadenectomy" according to the total number of excised lymph nodes is arbitrarily chosen and prone to some criticism. We also agree that the number of reported nodes strongly depends on the completeness of the pathological examination. We can exclude neither the possibility that some of our LND patients underwent lymph node dissection only by chance nor the fact that in some cases the reported lymph nodes came from outside of the lymph node basin of the adrenal gland or the demarcated area of Figure 5 of our publication.[1] This scenario might particularly apply for those patients who underwent a multivisceral resection. However, surgeons and pathologists are confronted with such an "inaccuracy" in lymph node evaluation in most specimens after extended tumor surgery, not only in ACC. The fact that our patients underwent surgery in multiple institutions and the operative data was retrieved retrospectively precludes a more precise definition of regional lymphadenectomy in our series. Obviously, much more work is needed before the quality of oncological surgery in terms of the total number of excised lymph nodes (and fields of dissection) can be defined for ACC. However, besides the total number of excised nodes (which is influenced by the resection of adjacent organs), the definition of lymphadenectomy in our series was also based on the efforts of the surgeon to perform a locoregional lymph node dissection in the periadrenal region. Provided that only those patients who underwent an "intended" locoregional lymphadenectomy according to the surgical protocol *and* presented 5 or more lymph nodes in the pathology report were considered as LND patients in our series, we strongly assume that in the majority of cases the reported lymph nodes came from the locoregional lymph node basin of the adrenal gland. However, we acknowledge that a "more precise definition of regional lymphadenectomy," as requested by Miller and Doherty, requires the results of prospective trials with standardized surgery and pathological workup. Therefore, the proposed fields for lymphadenectomy (see Figure 5 of our publication[1]), which are based on the pattern of recurrence in ACC patients,[5] should be regarded as plausible suggestions.

In summary, our study on lymph node dissection in ACC covered an issue that has not been addressed before. We are aware that the retrospective design of our study is prone to some bias. Moreover, a single study cannot cover such an approach exhaustively and, inevitably, questions will remain until prospective data are available. We, therefore, propose to initiate a study with the surgical colleagues from Ann Arbor and other centers to further define the role of lymphadenectomy in ACC.

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