



## Platinum Priority – Editorial

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# Lymphadenectomy Combined with Radical Nephrectomy: To Do or Not to Do?

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In this issue of *European Urology*, the European Organization for Research and Treatment of Cancer (EORTC) Genito-urinary Group presents the final results of a randomized phase 3 trial started 20 yr ago comparing radical nephrectomy with lymphadenectomy to radical nephrectomy alone [1]. Seven hundred and thirty-two patients with preoperatively staged N0 M0 tumors were eligible. The 4% incidence of unsuspected lymph node metastases was (expectedly) low, and thus, no survival advantage of a regional lymph node dissection in conjunction with radical nephrectomy could be demonstrated.

Because this is the first and only randomized study addressing the role of regional lymph node dissection in conjunction with radical nephrectomy for renal cell cancer (RCC), the results deserve much attention. The study raises the question of whether regional lymph node dissection can be safely omitted in the treatment of RCC; the answer is probably no because the results of this EORTC study are not necessarily applicable to many patients who undergo radical nephrectomy for RCC today.

There are several reasons for this lack of applicability:

1. The low (4%) incidence of positive nodes suggests that the investigators primarily included patients who would most likely not require lymph node dissection and, therefore, would not be harmed if they were randomized to the no-lymphadenec-

tomy arm. Indeed, approximately 70% of all patients had stage T1 and T2 tumors. These tumors are known to have a low incidence of positive nodes and suggest that the selection of low-risk patients for lymph node metastasis worked out well.

2. Despite the respectable number of patients included in EORTC trial 30881, the number of patients with positive nodes is too small to allow for the conclusion that the outcomes would be equivalent. As acknowledged by the authors, the study is underpowered for such a conclusion. Furthermore, besides the pT stage, nuclear grade, and presence or absence of lymph node metastases, other criteria such as the type of RCC (eg, clear cell, papillary, chromophobe, sarcomatoid), which is known to be an independent prognostic factor, would have to be taken into account in a study aiming to compare equivalents [2].
3. The number of regional lymph nodes resected and the number of positive nodes is not known for the patients enrolled into EORTC trial 30881. This information is crucial if the clinical relevance of regional lymph node dissection is to be assessed. As we know from other urologic cancers, the fewer nodes removed, the less likely it is that positive nodes are found. The lower the ratio of positive nodes or the total number of nodes removed, the better the prognosis. Unfortunately, this important information is not available.

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4. Over the past 20 yr, the importance of nephron-sparing surgery has become increasingly apparent; thus, the majority of the patients included in this EORTC trial would probably undergo partial nephrectomy today. A radical nephrectomy is still mandatory for patients with large, aggressive tumors invading the perivesical fat. These patients are the most likely to have regional lymph node metastasis, but they were seldom included in EORTC trial 30881. Therefore, the results of this trial are not necessarily applicable to patients currently undergoing radical nephrectomy.

In the absence of randomized trials in patients at high risk for having lymph node metastases, we have only indirect evidence that a regional lymphadenectomy in patients requiring a radical nephrectomy for advanced RCC may be beneficial for the following reasons:

1. A regional lymphadenectomy allows for more accurate staging and may occasionally decrease the local recurrence rate.
2. Data from the University of California Los Angeles (UCLA) suggest that the outcome of node-positive patients is better if the nodes are removed [3]; however, the results are based on a retrospective analysis. It might be that complete nodal removal was performed in patients with smaller, resectable lymph node metastases.
3. A recent retrospective analysis from pooled data of 171 RCC patients with positive nodal metastases but no evidence of distant metastases shows a projected 10- to 15-yr cancer-specific survival of approximately 30%. This finding strongly suggests that the removal of metastatic nodal disease in patients undergoing radical nephrectomy for RCC may be beneficial for some patients [2]. Data from M.D. Anderson institution point in the same direction. Patients with single nodal involvement in the absence of clinically evident distant metastases have a projected 10-yr recurrence-free survival of >50%. Although the absolute number of patients (12) is small, the data again suggest that regional lymph node resection may benefit some patients with minimal metastatic disease [4].
4. If indeed regional node resection is beneficial for patients with minimal metastatic spread, then one would not only have to look at the outcome of patients with histologically positive nodal disease but also at the outcome of high-risk patients with pN0 disease. Some patients may have metastatic disease that is detectable only by means of

molecular biology, as has already been shown in bladder and prostate cancer [5,6].

A factor that makes it difficult to assess the true value of regional lymph node dissection is the fact that lymph node dissection has been performed to various extents with various templates at various institutions, probably also within the framework of EORTC trial 30881. As long as we have no truly hard data that either prohibits or obliges us to do a regional lymph node dissection, it is imperative that the complications of this procedure are kept low. The apparent absence of a difference in post-operative morbidity between patients with or without lymph node dissection in EORTC trial 30881 is encouraging. The reported absence of a difference, however, could also be due to incomplete data or to a lack of vigorous postoperative search for hematomas, lymphoceles, thrombosis, and so forth. Occasional vascular injury, chylous ascites, or even death after regional lymph node dissection for RCC have been reported [7]. A reasonable compromise to avoid the complications from extensive lymph node dissection and to still give the patient the chance of removing the one or two regional nodes that might harbor micrometastasis, which might be beneficial to the patient, would probably be to remove all nodes on the lateral aspect (from the anterior to the posterior midline) of either the aorta or the vena cava from the crus of the diaphragma distally to the offspring of the inferior mesenteric artery or, respectively, to the confluents of the gonadal vein with the vena cava. This procedure can be done within 10–15 min of operative time.

In conclusion, EORTC trial 30881 is a landmark study. It is the only randomized study addressing the role of regional lymphadenectomy in combination with radical nephrectomy for RCC. The results, however, are not necessarily applicable to patients undergoing radical nephrectomy today for locally advanced disease. Therefore, if radical nephrectomy (instead of partial nephrectomy) is truly indicated, a limited regional lymph node dissection still seems reasonable. Morbidity is minimal, staging is more accurate, and there are reports that the removal of lymph nodes containing microscopic metastases may be beneficial to some patients.

**Conflicts of interest:** The authors have nothing to disclose.

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