Point of Focus Debate: Con

Extended Lymph Node Dissection for Bladder Cancer: Do Clinical Trials Rule Out a Benefit?

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Lymph node dissection (LND) during radical cystectomy (RC) is a crucial staging procedure in bladder cancer (BCa) patients. Lymph node (LN) metastases are detected in 20–25% of patients and represent one of the main prognostic risk factors for poor oncologic outcome [1,2]. Nevertheless, prognosis can be improved with adjuvant cisplatin-based chemotherapy, resulting in a 23% reduction in mortality [3,4].

Besides the clear diagnostic value of LND, there is controversy regarding its therapeutic role. Contemporary RC series without systemic treatment support a prognostic benefit of LND: 10-yr recurrence-free survival (RFS) rates of 15–35% have been reported for node-positive patients [1,2]. However, the optimal anatomic extent of LND for removal of local metastases and the corresponding therapeutic benefit are unclear. From a diagnostic point of view, it seems sufficient to perform LND that includes the obturator and external and internal iliac nodes. Mapping studies have revealed that it is uncommon to find metastatic LNs above the common iliac bifurcation if this field is free of tumor [5–8]. However, lymphatic landing sites of early metastatic BCa up to the level of the inferior mesenteric artery have been described [6,7,9]. Up to now, evidence from trials investigating the extent of LND with regard to its therapeutic benefit is controversial.

Definitions of the anatomic extent of LND used in the literature are not consistent. To standardize the nomenclature, the European Association of Urology guideline defines LND templates as follows [10]:

- Standard LND comprises LNs cranially up to the common iliac bifurcation, with the ureter as the medial border, and includes the internal iliac, presacral, obturator fossa, and external iliac nodes.
- Extended LND comprises LNs in the region of the aortic bifurcation and the presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, and caudally the circumflex iliac vein, the lacunar ligament, and the LN of Cloquet, as well as the area described for standard LND.
- Superextended LND extends cranially to the level of the inferior mesenteric artery.

In 2014 a systematic review summarized the results of 22 retrospective and one prospective, nonrandomized study including more than 19 000 BCa patients treated with RC [11]. Limited by evidence mainly based on retrospective studies, the authors stated that the data were of poor quality, with significant risks of bias and confounding. However, they concluded that any kind of LND was advantageous over no LND and that a more extended LND including at least the common iliac region might be superior to lesser degrees of dissection, although extending the dissection beyond the aortic bifurcation was unlikely to yield any further benefit. The only prospective, albeit nonrandomized study included in the review compared superextended with standard LND in 400 BCa patients undergoing RC [12]. The authors reported a significant absolute improvement of 11.9% in 5-yr disease-free survival (from 54.7% to 66.6%) in the superextended LND group ($p = 0.04$). However, since this trial had high risk of selection bias without randomization, it is not possible to recommend superextended LND on the basis of the results. Moreover, approximately half of

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the patients included in the trial had nonurothelial BCa, which represents a further limitation.

We recently reported results from the first prospective, randomized phase 3 trial (LEAU AUO AB 25/02) comparing superextended versus standard LND in patients undergoing RC for urothelial BCa [13]. The trial failed to show a therapeutic advantage of superextended LND over standard LND at 5 yr for the primary endpoint recurrence-free survival (RFS; 65% vs 59%; hazard ratio [HR] 0.84; $p = 0.36$) and the secondary endpoints cancer-specific survival (CSS; 76% vs 65%; HR 0.70; $p = 0.10$) and overall survival (OS; 59% vs 50%; HR 0.78; $p = 0.12$). Although all time-to-event analyses showed a trend towards better survival with superextended LND, conventional levels of significance were not reached.

Notably, patients with neoadjuvant treatment were excluded from this trial and the use of adjuvant treatment was low: only 28% of patients with pT3/4 or pN + BCa (equally distributed in both study arms) received platin-based adjuvant chemotherapy. Thus, the study results were not influenced by neoadjuvant or adjuvant treatment.

So, why was this a negative trial? First, it was designed to show an absolute improvement of 15% in 5-yr RFS with superextended LND on the basis of retrospective data [14]. However, the difference observed between the limited and super-extended and standard LND groups was smaller than expected. We recently considered the patient numbers that would have been needed to reach statistical significance and calculated that 1225 patients per study arm (2250 in total) would have been needed for 80% power for the RFS endpoint or 450 patients per study arm (900 in total) for power of 80% for OS as a primary endpoint.

Second, we included pT1G3 BCa, which was the maximum tumor extent in 14% of the patient cohort. However, detection of LN metastases in these patients is rare and the recurrence rate is low.

Third, a median of 19 LNs were removed in the standard LND group, compared to 31 LNs in the superextended LND group. Several retrospective studies have shown a beneficial prognostic impact of a high LN count, whereas the recommended number of LNs to dissect varies between nine and 16 [14–18]. As these numbers were far exceeded in the study, we speculate that standard LND in the control arm might have been too excessive, resulting in a lower survival difference than expected when compared to superextended LND. A smaller LND template in the control group might have led to a greater survival difference between the two study arms.

The Southwest Oncology Group initiated another prospective, randomized phase 3 trial evaluating standard versus extended LND (with optional dissection of the paracaval and para-aortal LNs) in BCa patients treated with RC which has recently completed accrual but is still ongoing (SWOG S1011; NCT 01224665). The trial includes 650 patients with predominantly urothelial BCa and was powered to detect a 10% improvement in 3-yr disease-free survival (from 55% to 65%). In favor of this trial, the preplanned patient number is higher and the expected survival difference is smaller compared to the LEA trial. Moreover, only patients with T2-T4a BCa were included and pT1G3 tumors with a low risk of recurrence were excluded.

It is noteworthy that both neoadjuvant and adjuvant chemotherapy are allowed in this trial, as they are the gold standard in a multimodal approach for BCa patients undergoing RC with curative intent. However, subsequent perioperative systemic treatment might influence the trial results, diluting the potential survival benefits achieved from extended LND.

Despite several retrospective studies and one prospective nonrandomized study indicating a therapeutic benefit from superextended or extended LND in BCa patients undergoing RC, the first prospective randomized trial could not demonstrate a significant benefit. This was mainly because the survival difference was smaller than expected and the sample size was not sufficient to reach a conventional level of significance for the difference. Results of another prospective randomized trial from SWOG are awaited before we can draw a final conclusion. However, with multimodal approaches combining neoadjuvant or adjuvant systemic chemotherapy with RC as a gold standard, it might become even more difficult to demonstrate survival benefits from superextended or extended LND.

Conflicts of interest: The authors have nothing to disclose.

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