



Role of pelvic lymph node dissection in bladder cancer: is it better to do more?

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Radical cystectomy (RC) is frequently used for the treatment of muscle invasive bladder cancer (MIBC) (1). Typically, this is accompanied by a pelvic lymph node dissection (PLND), which certainly allows for accurate nodal staging (2) and may even have therapeutic effect, especially in those with small volume disease (3). This has to be weighed against the drawbacks of PLND including increased operative time and added risks of surgery. The decision-making on PLND for MIBC is further complicated by a lack of high-level evidence (4). A systematic review of the available retrospective series suggested a survival benefit to performing PLND, but found the evidence for a greater extent of dissection to be equivocal (5). Thus, although PLND with RC is recommended by guidelines (6), the optimal extent of PLND for MIBC remains uncertain (4,7).

The LEA AUO AB 25/02 study by Gschwend *et al.* is a multi-centre phase-III randomised controlled trial aiming to assess whether extending the PLND improves recurrence-free survival (RFS) (8). This prospective trial was conducted between 2006 and 2010 at 16 high volume RC centres in Germany. Patients were included if they had locally resectable T1 or MIBC. Those with bony or visceral metastases on staging computed tomography as well as those who underwent neoadjuvant chemotherapy were excluded. The primary outcome was 5-year RFS with secondary outcomes including 5-year overall survival (OS), 5-year cancer specific survival (CSS) and post-operative complications. Overall, 401 of 458 potential patients were randomised to undergo either extended or limited PLND with RC. It should be noted that the nomenclature of

PLND templates often varies between studies, thus further complicating interpretation of the literature. Thus, what is described as a limited PLND in this study can also be considered a standard PLND (obturator, internal and external iliac groups), whereas the extended PLND study group might be better described as having undergone a super-extended PLND to distinguish from an extended PLND that terminates at the aortic bifurcation (4,6).

The trial found no statistically significant differences in the primary endpoint of 5-year RFS (64.6% *vs.* 59.2%), or secondary endpoints of 5-year CSS (75.9% *vs.* 64.5%) and 5-year OS (58.9% *vs.* 49.7%) between extended and limited PLND (8). These findings appear to suggest that there is no oncological benefit to performing a more extensive PLND with RC for MIBC, but need to be interpreted cautiously. Although the study was powered on the assumption of a 5-year RFS of 50% in the limited PLND group, the actual survival was much better at 59%. This may be a consequence of including patients with T1 disease (12% in the limited and 16% in the extended PLND group), who have a low risk of node positive disease. Meta-analysis of previous retrospective studies suggests that the improvement in RFS from extending the PLND may be seen only in patients with T3 to 4 bladder cancer, not in those with stage T2 or lower (9).

There have been a number of studies that suggest improved recurrence free survival in those patients who have more lymph nodes removed at PLND (10,11). In the study by Gschwend *et al.*, the median number of lymph nodes removed was 19 in the limited PLND group and

31 in the extended PLND group (8). This is quite high in both groups, but more in those that underwent extended PLND, as might be expected. However, this did not result in a higher rate of node positivity, as is usually seen with a more extensive PLND (9). Possible explanatory factors may include a high number of lymph nodes removed even in the limited PLND group and an imbalance in T-stage between the two groups, given that there were slightly more patients with T1 disease and less patients with T4 disease in the extended PLND group. To what extent this might have also contributed to the lack of impact of extended PLND on RFS is unclear.

Interestingly, although there was no difference between the two groups in terms of node-positivity, within the extended PLND group, 21 (11%) had positive nodes within the extended field of dissection, including 4 (2%) in whom the limited PLND fields were negative. Thus, an understanding of which sites are likely to be involved is also important in determining what extent of PLND is required. Leissner and colleagues demonstrated that the majority of nodal metastases occurred in the obturator spaces and adjacent to the iliac vessels, while metastases in the inter-aorto-caval and paracaval regions were far less likely (12). Conversely, a number of studies have also confirmed that a substantial proportion of metastatic lymph node deposits are outside the boundaries defining the limited PLND in the AUO trial (12-14). Thus, it may be concluded that the optimal PLND template should lie somewhere between those defined as limited and extended in this trial, i.e., extending up to the aortic bifurcation.

Of course, PLND is not without risk, specifically including lymphocele formation, vascular injury and thrombo-embolic sequelae (4,7). Increasing the extent of PLND raises the concern of potentially increasing these risks. Reassuringly, the AUO study found comparable rates of major morbidity and mortality between the two groups, with the only difference being a higher rate of lymphoceles requiring intervention in the extended compared to the standard PLND group (8.6% *vs.* 3.4%, $P=0.04$) (8).

An interesting secondary analysis in this study relates to the use of adjuvant chemotherapy (AC), in the form of 4 cycles of Gemcitabine and Cisplatin, delivered at physician discretion. Only 58 patients received AC, being 14.5% of the overall study population, but 28% of the 205 patients with high-risk pathology (T3 and 4 or node-positive), who were principally considered for treatment. The impact of AC, assessed as a prespecified secondary endpoint in this subgroup, was to improve median RFS from 11.5 to 35.4 months

(hazard ratio 0.56, 95% CI: 0.38–0.83; $P=0.004$). Although this finding needs to be interpreted with caution, based as it is on a non-randomised comparison, it adds support to the evidence that AC after RC may improve outcomes for bladder cancer (15).

Overall Gschwend *et al.* should be congratulated on their study—surgical trials are notoriously difficult to accrue. The standardisation of PLND templates and the thorough dissection evidenced by high lymph node yields in both groups are particular strengths of the study. The inclusion of patients with T1 disease, the exclusion of neo-adjuvant and low use of adjuvant chemotherapy represent some limitations. Further research is required to address the interaction of peri-operative chemotherapy with PLND and determining how the extent of PLND can be optimised. The SWOG 1011 trial is another large randomised controlled trial currently underway in multiple centres in the United States, comparing extended *vs.* standard PLND with RC for MIBC with the primary outcome being disease-free survival and secondary outcomes including lymph node counts, operative time and OS (16). Accrual is planned for 620 participants and expected to be completed in August 2022—results from this study will be crucial to further inform the surgical management of MIBC.

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Footnote

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