Bladder cancer

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Knockout of extended pelvic lymph node dissection during radical cystectomy

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Results from the SWOG S1011 and LEA trials show that extended pelvic lymph node dissection during radical cystectomy for muscle-invasive bladder cancer offers no survival benefit. Novel perioperative systemic therapies could lead to true survival improvement for patients with muscle-invasive bladder cancer undergoing radical surgery and have the potential to implement bladder-preserving strategies.

REFERS TO Lerner, S. P. et al. Standard or extended lymphadenectomy for muscle-invasive bladder cancer. *N. Engl. J. Med.* **391**, 1206–1216 (2024).

Over four decades ago, the uro-oncological community began wondering whether pelvic lymph node dissection (LND) is truly necessary in patients undergoing radical cystectomy for muscle-invasive bladder cancer (MIBC). Early evidence showed that LND enhanced histological staging and reduced pelvic recurrence rates[1]. For years, discussions centred on the potential benefits of extended or even super-extended lymphadenectomy, supported by large retrospective radical cystectomy series. Yet, until a few months ago, level 1 evidence was conspicuously absent.

The long-anticipated results of the SWOG S1011 trial have now been published, providing a definitive answer to this discussion. In this study, Lerner and colleagues[2] showed that an extended LND beyond the iliac bifurcation offers no survival benefit for patients undergoing radical cystectomy[2].

This conclusion echoes findings from the LEA trial, a large, prospective, randomized controlled study, which similarly failed to show a statistically significant survival advantage for extended LND during radical cystectomy[3].

Despite a shared conclusion, the SWOG S1011 (ref. 2) and LEA[3] trials differ substantially in design, patient populations and surgical protocols. Crucial distinctions lie in the use of neoadjuvant chemotherapy (NAC), patient recruitment periods and geographical origins.

The LEA trial (conducted between 2006 and 2010 in Germany) included no patients receiving NAC[3], reflecting the limited adoption of this treatment during the recruitment period. Conversely, in SWOG S1011 (conducted between 2011 and 2017 in the United States and Canada), 57% of patients included had received NAC[2], consistent with a frequent use of this treatment in North American high-volume centres. These differences underscore evolving treatment paradigms and highlight the impact of NAC on patient outcomes.

Interestingly, despite these differences, comparable pN0 rates were reported in these two trials, with a slightly higher proportion of pN1 versus pN2 and pN3 tumours reported in SWOG S1011 than in LEA[2,3]. These results reinforce the notion that platinum-based NAC alone is insufficient to eliminate lymph node metastases in patients with cN+ disease. Results from other clinical trials, such as NIAGARA, have shown the benefit of adding perioperative durvalumab to cisplatin-based NAC[4], whereas in the CheckMate 274 and AMBASSADOR trials, improved recurrence-free survival was shown with adjuvant nivolumab[5] and pembrolizumab[6], respectively.

In both trials, the iliac bifurcation was defined as the cranial boundary for standard LND[2,3], although in the SWOG S1011 study, the field was extended to include deep obturator nodes[2]. Extended LND in both studies included the common iliac vessels, presacral lymph nodes and the inferior mesenteric artery[2,3].

In the SWOG S1011 study, a higher median lymph node yield than in the LEA trial was reported (24 versus 19 nodes for standard LND and 39 versus 31 nodes for extended LND[2,3]). These variations might reflect procedural differences and highlight the importance of including crucial drainage sites, such as the deep obturator nodes, when standardizing surgical techniques.

The SWOG S1011 and the LEA trials also diverged in the perioperative outcomes. In the LEA trial, an increase in post-surgical lymphoceles requiring drainage with extended versus limited LND (8.6% versus 3.4%; $P = 0.04$) was reported, but no significant increase in 90-day major complications (Clavien grade ≥3) or 90-day mortality was shown[3]. Conversely, results from the SWOG S1011 trial showed higher rates of severe complications in patients receiving standard versus extended LND (44% versus 54%) and increased 90-day mortality (4.1% for extended LND versus 1.3% for standard LND)[2].

These findings raise important questions about the balance between surgical aggressiveness and patient safety, even in high-volume centres with experienced surgeons.

Results from both trials unequivocally showed that extending LND boundaries does not improve survival outcomes for patients with MIBC undergoing radical cystectomy[2,3]. These results underscore the systemic nature of lymph node metastases and the need for more effective perioperative systemic therapies.

Emerging evidence suggests that systemic treatment strategies might be more impactful than increasingly aggressive surgical interventions. For example, the combination of enfortumab vedotin and pembrolizumab has revolutionized first-line systemic treatment for metastatic urothelial cancer[7]. This combination is being assessed in the perioperative setting in ongoing trials, such as EV-303 (ref. 8) and EV-304 (ref. 9), potentially paving the way for new therapeutic paradigms.

In summary, clear evidence indicates that extended LND beyond the iliac bifurcation during radical cystectomy does not confer a survival benefit. As the field shifts towards personalized approaches, the

focus should be on optimizing perioperative systemic therapies rather than intensifying surgical interventions. These advances might even open the door to bladder-preserving strategies, indicating a move away from the invasive radical procedures that have long dominated the treatment landscape for MIBC.

This shift is a crucial opportunity for the uro-oncological community to reimagine treatment strategies and deliver effective, patient-centred care.

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Competing interests

The authors declare no competing interests.