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# What is the Standard of Care for Pelvic Lymphadenectomy Performed at the Time of Radical Cystectomy?

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Gschwend and colleagues [1] report results from a prospective multicenter randomized trial conducted in Germany (LEA AUO AB 25/02) comparing extended versus "limited" pelvic lymphadenectomy (LND) at the time of radical cystectomy (RC). The extended LND during RC investigated in this trial is well supported by observational cohort studies. As reported by Skinner in 1982 [2], a meticulous bilateral pelvic LND provides optimal local control of invasive bladder cancer and is associated with local pelvic recurrence rates of 5–15% in patients with N0 and N+ disease, respectively. There is strong evidence that an extended pelvic and iliac LND identifies more lymph nodes and therefore increases the sensitivity for identification of pathologic lymph node metastasis [3]. Mapping studies of lymph node metastasis demonstrate orderly progression of node metastasis from the true pelvis proximally to the common iliac and presacral nodes, with infrequent skip metastasis in $<$10% of patients [4,5]. Patients with N+ disease are curable with RC and pelvic LND, and outcomes are stratified by N1 versus N2–3 and pathologic tumor stage [6–8].

The LEA trial tested the hypothesis that bilateral extended LND up to the inferior mesenteric artery is associated with better recurrence-free survival (RFS) compared to bilateral "limited" LND. The term "limited" has been associated with incomplete node dissection and may be confusing to the reader and broader urologic community, but in this trial included the external and internal iliac nodes and the obturator nodes anterior to the obturator nerve. With the exception of omitting dissection of the "deep" obturator nodes, what the authors refer to as "limited" includes the anatomic regions specified in what the American Urologic Association (AUA) guidelines refer to as a "standard" node dissection [9]. However, with a median of 19 lymph nodes removed in the limited arm, this is less than the 25 nodes that we propose provides 75% sensitivity for detection of nodal metastasis [10]. Interestingly, however, the proportion of patients with N+ disease was higher in the limited than in the extended group (28% vs 22%), as was the proportion of those N+ patients with N2 disease (20% vs 15%). One might expect the reverse, as the authors showed that patients in the extended arm had a higher total number of lymph nodes, and studies have shown that extended LND results in a higher proportion of patients with $\geq$N2 disease [10]. The number of nodes identified is vulnerable to several factors, including presentation in packets, processing, and pathologic interpretation. However, it is most likely that the anatomic extent and the completeness of the LND are the primary determinants of regional nodal cancer control.

This study is noteworthy as the first phase 3 trial to address the extent of node dissection in the management of patients with bladder cancer. Although the trial did not meet its primary endpoint for both the intent to treat and per protocol analyses, it is a highly relevant surgical question and the results are an important step in furthering our understanding of outcomes for patients treated with RC. Similar experiences have been reported for esophageal, gastric, and pancreatic cancer, for which retrospective and level 2 evidence suggested a benefit from more extensive dissection that failed to be validated in phase 3 trials [11–13]. While the gastric and pancreatic trials suggested worse overall survival (OS) with extended LND, the LEA trial demonstrates a trend favoring all three endpoints with

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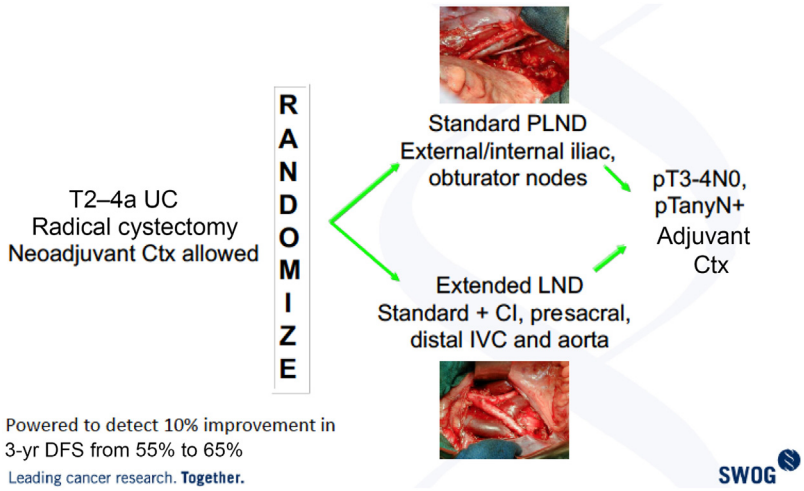


**Fig. 1 – Schema for trial S-1011. UC = urothelial carcinoma; Ctx = chemotherapy; LND = lymphadenectomy; PLND = pelvic LND; CI = common iliac; IVC = inferior vena cava; DFS = disease-free survival.**

extended LND, although this did not reach statistical significance and is therefore interpreted as a negative trial. An unplanned subset analysis that suggested a benefit in patients with pT2N0 disease is hypothesis-generating and requires prospective validation.

The median follow-up was 43 mo, which should have been sufficient to identify the majority of RFS events. However, 5-yr RFS in the control arm was 61.5%, whereas the sample size calculations were based on an estimate of 50%, suggesting that the patient population had a more favorable prognosis than anticipated. Examination of the difference in RFS between the two arms revealed a hazard ratio (HR) of 0.84. The 95% confidence interval for the RFS primary endpoint (0.58–1.22) includes clinically meaningful relative differences that cannot be ruled out by this trial. If we were to design a trial for the same population as the LEA trial with a HR of 0.84 (assuming similar $\alpha$ and $\beta$ as in the manuscript), a sample size of more than 2000 patients would be required, which is not feasible (Cathy Tangen, personal communication). Thus, the study was underpowered for detection of a smaller benefit attributed to the extended LND. Nevertheless, in treating our patients today, we must make decisions based on the best available data. Importantly, the trial found no difference in complications between the two groups with the exception of symptomatic lymphoceles. There is some clinically significant separation in the Kaplan-Meier curves between the treatment groups for all three endpoints, and perhaps the largest is for OS. Follow-up should continue for these patients to determine if longer follow-up will provide any additional insights.

The Southwest Oncology Group (SWOG) initiated a similar trial in 2011 (S-1011) and completed enrollment of 659 patients in February 2017 (Fig. 1). The primary endpoint is RFS and we estimate that patients in the extended LND arm will have a 10% improvement in 3-yr RFS compared to an estimated 55% RFS for patients in the control arm (HR 0.72). There are several differences between these two trials (Table 1). Eligible patients had ≥T2 disease; neoadjuvant chemotherapy (NAC) was allowed and was used in more than half of the patients (Table 2). Randomization was

**Table 1 – Comparison of the LEA and S-1011 trials**

| | LEA | S-1011 |
|---|---|---|
| Eligibility | T1–4a | T2–4a |
| Neoadjuvant chemotherapy | Not allowed | Allowed (56%) |
| Planned randomization | 400 | 564 |
| Randomization timing | Before surgery | Intraoperative |
| Registered (*n*) | 438 | 659 |
| Randomized (*n*) | 433 | 620 |
| Drop out/ineligible | 71 (16.4%) | Assume 10% ineligible |
| Intent to treat | 362 | Estimate 576 |
| LND control arm | Limited | Standard |
| ePLND | IMA | Aorta bifurcation up to IMA |
| Primary endpoint | Recurrence-free survival at 5 yr | Recurrence-free survival |
| Effect size | 15% (from 50% to 65%) | 10% improvement (from 55% to 65%) at 3 yr |
| Power | 90% | 85% |
| Hazard ratio | 0.80 (final result) | 0.72 |

LND = lymphadenectomy; ePLND = extended pelvic LND.

**Table 2 – Prerandomization factors in the S-1011 trial**

| | No NAC | NAC |
|---|---|---|
| Total patients randomized, *n* (%) | 267 (44) | 346 (56) |
| Randomized arm | | |
| Extended LND (302/49%) | 133 (44) | 169 (56) |
| Standard LND (311/51%) | 134 (43) | 177 (57) |
| Median age (yr) | 71.9 | 67.1 |
| Sex, *n* (%) | | |
| Male | 204 (76) | 281 (81) |
| Female | 63 (24) | 65 (19) |
| Clinical stage, *n* (%) | | |
| cT2 (431/70%) | 215 (81) | 216 (62) |
| cT3–4a (182/30%) | 52 (19) | 130 (38) |
| NAC, *n* (%) | | |
| Cisplatin-based | – | 303 (88) |
| Carboplatin-based | – | 22 (6) |
| Other | – | 21 (6) |

NAC = neoadjuvant chemotherapy; LND = lymphadenectomy.

stratified on the basis of NAC, clinical stage, and performance status. Surgeons interested in participating underwent a credentialing process requiring completion of accredited residency training, performance of ≥50 RCs in the past 3 yr, operating in hospitals performing >30 RCs annually, and meeting specified standards in submitted operative and pathology reports and intraoperative photos for five cases. To prevent unplanned crossover and mimize the number of ineligible patients, randomization occurred intraoperatively after establishing that the bladder was resectable and that no grossly enlarged nodes in the external template were positive (on the basis of frozen sections).

For those who advocate extended LND during RC, the LEA trial provides evidence that this approach does not increase complications and does not appear to provide inferior outcomes. The trial was not designed to determine if limited LND is not inferior to extended LND and therefore these remain important surgical and oncologic questions to address in ongoing and future trials.

***Conflicts of interest:*** The authors have no conflicts of interest directly related to this research. Seth P. Lerner has participated in clinical trials for Endo, FKD Therapies, JBL (SWOG), Roche/Genentech (SWOG), and Viventia; is a consultant for Anchiano Therapeutics, UroGen, and Vaxiion; is on advisory boards for Anchiano Therapeutics, miR Scientific, QED Therapeutics, and UroGen; and is a speaker for MSD Korea and Dava Oncology. Robert S. Svatek is a consultant for Ferring and receives research support from Japanese BCG Laboratories, MDxHealth, and FKD Therapies.

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