Standard vs extended lymphadenectomy for muscle invasive bladder cancer

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Muscle invasive urothelial cancer of the bladder (MIBC) is often a lethal disease and its treatments, particularly radical cystectomy and urinary diversion, may cause considerable morbidity (including grade 5 = death), prolonged hospitalizations, high re-hospitalization rates, side effects (e.g., sexual dysfunction), complications (e.g., hydronephrosis), and significant long term body image issues. There have been attempts to improve efficacy (e.g., using neoadjuvant and adjuvant systemic therapy) and reduce short-term (e.g., enhanced recovery after surgery [ERAS] protocols, minimally invasive surgical approaches) and intermediate/ long-term (e.g., "nerve" and vaginal sparing cystectomies, continent urinary diversions) morbidity. Despite these efforts improvements in outcomes have only been modest and much of these attributable to improvements in perioperative and supportive care.

The recently published results of the SWOG S-1011 randomized trial of standard vs extended lymphadenectomy in patients with MIBC (stages T2-4a) undergoing cystectomy and urinary diversion adds to this literature.[1]

As background, a large population data base study reported that cancer specific survival was better in patients undergoing cystectomy who had pelvic lymph node dissection (LND) than in those who had no lymphadenectomy.[2] Subsequently, data from several retrospective series[3] and one prospective observational study[4] indicated that extended LND resulted in survival benefits, and 5–15 years ago it became adopted by many high-volume centers as the appropriate approach with no randomized prospective evidence supporting it.[5]

In the SWOG S-1011 trial, 658 patients with MIBC (57% of whom had received neoadjuvant chemotherapy [NAC]) were registered and 592 eligible patients were randomized intraoperatively to undergo radical cystectomy and "standard" bilateral pelvic LND (external iliac, internal iliac and obturator nodes up to the iliac bifunction[5]) vs "extended" LND (the "standard" LND template + common iliac, presciatic and presacral nodes, and if considered appropriate the dissection could continue up to the inferior mesenteric artery). Oncologic outcomes including disease-free and overall survival, local and distant recurrence rates as well as morbidities (up to grade 5) and surgical staging, margins and node yields were monitored.

This surgical trial had serval methodological features worth noting which tried to overcome the variability inherent with many surgeons taking part in a cooperative group study looking at surgical (and oncologic) outcomes. These included:

1- Preoperative credentialing of participating surgeons by a committee of experienced cystectomy surgeons including having performed at least 50 cystectomies over the previous 3 years, and review of operative and pathology reports and of intraoperative photographs of operative fields from five recent cystectomies demonstrating the completeness of the surgeries.
2- The randomized assignment of extended or standard dissection was made intraoperatively, with neither the patient nor surgeon knowing the assignment preoperatively.
3- 3. Lymph node packets were identified by location and sent separately for counts of number of nodes identified by the pathologist and number of positive nodes, in part as a form of quality control.
4- There was a peer review quality control assessment of 100 randomly selected patients including at least one patient per surgeon and 50 patients from each group by two experienced urological oncology surgeons who were not associated with the study.

Patients undergoing extended dissection had more lymph nodes removed (median 39) than those with the standard LND (median 24), and if any nodal metastases, a greater number of positive nodes (median 2 [range 1–35]) vs (median 1 [range 1–16]). However, the percentage of patients in each group with any positive node was similar (26% for extended LND vs 24% for standard). Most importantly disease-free survival (5 year estimated 60% for

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standard vs 56% for extended) and overall survival (63% standard vs 59% extended) were similar in both groups.

Moreover, there was a higher proportion of patients with grade 3–5 complications who underwent extended dissection (54% vs 44%, $p = 0.01$), including 19 deaths over the first three months in the extended group vs 7 in the standard group.

A similar trial has been conducted in Germany, differing in that clinical stage T1 patients were included and those who received NAC were not, also showed no significant differences in recurrence-free, cancer specific on overall survivals.[6] Additionally, randomized phase 3 trials of standard vs. extended LNDs in endometrial, gastric, and pancreatic cancers have not showed improved survival with extended dissections despite prior nonrandomized series and population-based data supporting extended dissections in those malignances.[5–7] There was also increased morbidity with the extended dissections in patients with gastric cancer.[7]

So, what we have learned from the SWOG S-1011 trial is that rigorous surgical studies can be performed in the cooperative group setting with careful attention to the screening of the participating surgeons (as well as patients) and strict performance monitoring during the study. However, the outcome results reinforce the conclusions that when it comes to LND for MIBC (as well as other abdominal/pelvic malignancies), "bigger" is not always "better" and is associated with higher morbidity.

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