

Re: Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial

Gschwend JE, Heck MM, Lehmann J, et al

Eur Urol. 2019;75:604–11

Experts' summary:

This multicenter, nationwide, randomized trial investigated the impact of extended (eLND) versus limited lymph node dissection on recurrence-free survival (RFS) in invasive ($\geq T1$) bladder cancer (BC). There was no significant difference in the primary endpoint, although a trend towards superior outcomes from eLND was noted [1].

Experts' comments:

The results of this study were keenly awaited for many years to clarify the prognostic role of eLND at RC. However, urologists are still confronted with the same questions this study intended to answer. It has to be stated that randomized studies on critical topics in BC surgery are difficult to conduct, for many reasons. Therefore, the authors should be commended for their efforts. Nonetheless, some results deserve further discussion.

Although the accrual period lasted from 2006 to 2010, the study results were published some 8 yr later. This is surprising given the fact that RFS was the primary endpoint. As the median time to recurrence after RC is approximately 12 mo [2], the results should have been mature enough for publication years ago. So what was the reason for the delay?

One reason might be the primary endpoint itself, which was defined as a 15% benefit in RFS for eLND. Admittedly, this level is ambitious and even questionable, as patients with T1 disease (12–16% in both arms) were eligible for inclusion, a group of patients with a risk of <10% of lymph node-positive disease [2,3]. With regard to the study design, the authors refer to Leissner et al. [4]. However, in this study the mean lymph node yield was almost 30% higher for eLND. So a question inevitably arises about the meticulousness of lymph node sampling and processing during the study period.

Strikingly, given the fact that only experienced surgeons were considered for the study, the rate of positive margins was relatively high (8–9%) in both groups, a finding that might have diminished any long-term benefit of eLND since the majority of patients with positive margins usually experience recurrence very early after RC [3].

So, is this a “negative” study on the prognostic benefit of eLND and should we refrain from performing eLND at RC in

the future? The answer is a definitive “no”. The subanalysis on the role of adjuvant chemotherapy reveals that the detection of positive lymph nodes translates into beneficial postoperative treatment decisions. Thus, the “diagnostic” benefit of eLND becomes “therapeutic” regardless of the primary endpoint analysis. This study also unravels another “myth” with regard to the morbidity of eLND: eLND did not result in higher complication rates per se, as has been claimed by a number of retrospective series and surgeons in the past [3].

In summary, given the inadequacy of the current radiological modalities for reliable detection of regional lymphatic spread in muscle-invasive BC (MIBC) [5], the standard of diagnostic care should be eLND, as this will allow more MIBC patients to be considered for (hopefully curative) adjuvant systemic treatment modalities.

Conflicts of interest: The author has nothing to disclose.

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Re: Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Rini BI, Plimack ER, Stus V, et al

N Engl J Med. 2019;380:1116–27

Experts' summary:

An open-label, phase 3 trial was performed in patients with previously untreated advanced clear-cell renal cell carcinoma

(RCC) to receive pembrolizumab (200 mg) plus axitinib (5 mg) or sunitinib (50 mg). The primary endpoints were overall survival (OS) and progression-free survival (PFS) in the intention-to-treat population. The main secondary endpoint was the objective response rate. Treatment with pembrolizumab plus axitinib resulted in significantly longer OS and PFS and a higher objective response rate when compared to treatment with sunitinib.

Experts' comments:

Immunotherapy is rapidly shifting the paradigm for urological cancer management. The seminal discoveries of CTLA-4 and PD-1 immune checkpoint receptors, recently awarded the 2018 Nobel Prize in Physiology or Medicine, led to significant improvements in the management of a range of solid tumours including RCC [1]. These immunogenic tumours are readily recognised by the immune system, and respond to the removal of immune checkpoint “breaks” which has generated a new pillar in cancer treatment and resulted in the integration of immunotherapy into routine clinical use. RCC is an immunogenic tumour and is characterised by resistance to cytotoxic chemotherapy but susceptibility to both immunotherapeutic and anti-angiogenic treatment approaches [2,3]. Guidelines for the treatment of metastatic RCC have changed dramatically to target these two major pathways. It was demonstrated that tyrosine kinase inhibitors (TKIs) with potent VEGF inhibition are superior to interferon- α , and consequently sunitinib became the new standard of care as first-line therapy [4].

However, it appears that this standard of care is about to change. Results from two large phase 3 trials comparing combinations of agents targeting immune checkpoint inhibitors and TKIs versus sunitinib have recently been reported [5,6]. The trial by Motzer et al compared the efficacy of avelumab, a PD-L1 inhibitor, plus axitinib, a small-molecule TKI, with that of sunitinib [6]. Both manuscripts were published in the same issue of the *New England Journal of Medicine*, and represent landmark papers in the field of metastatic RCC. The trial by Rini et al evaluated slightly different endpoints, and it is noteworthy that the two trials had positive outcomes and showed superiority over sunitinib in terms of PFS and the objective response rate. These new combinations are expected to become the new standard of care and be incorporated into future guidelines.

While targeted therapies can extend PFS and OS, this must be balanced against the significant rate of adverse events reported; adverse events of any cause occurred in 98.4% of the 429 patients in the pembrolizumab-axitinib group who received the assigned treatment and in 99.5% of the 425 patients in the sunitinib group who received the assigned treatment. These events were not insignificant, and led to more frequent discontinuation of any treatment

because of adverse events in the pembrolizumab-axitinib than in the sunitinib group.

Nonetheless, significant progress has been made in the field of immunotherapy and targeted therapy, with practice-changing implications. Exploring the applicability of these novel treatments remains a high priority; however, longer follow-up to determine optimal combinations and monitor side effect profiles is warranted. Regardless, a new standard of care for patients with metastatic RCC is now within reach.

Conflicts of interest: The authors have nothing to disclose.

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Re: Conservative Management Following Complete Clinical Response to Neoadjuvant Chemotherapy of Muscle Invasive Bladder Cancer: Contemporary Outcomes of a Multi-institutional Cohort Study

Mazza P, Moran GW, Li G, et al

J Urol 2018;200:1005–13

Experts' summary:

This retrospective multicenter study reported long-term outcomes for 148 patients with nonmetastatic muscle-invasive bladder cancer (MIBC) who opted for bladder

preservation after achieving a complete clinical response (cCR) following radical transurethral resection of bladder (TURB) followed by neoadjuvant chemotherapy (NAC). All patients refused radical cystectomy (RC) and elected for active surveillance. The median follow-up was 55 mo.

Intravesical recurrence was observed in 48% of patients; MIBC recurrences (23%) occurred earlier than noninvasive recurrences (77%) with a median time to recurrence of 33 versus 17 mo. Patients with MIBC relapse had significantly worse survival ($p < 0.015$). The 5-yr recurrence-free survival rate in the entire cohort was 64%. Of note, the