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Words of Wisdom

Re. Effect of Robot-assisted Radical Cystectomy with Intracorporeal Urinary Diversion vs Open Radical Cystectomy on 90-Day Morbidity and Mortality Among Patients with Bladder Cancer: A Randomized Clinical Trial

Catto JWF, Khetrapal P, Ricciardi F, et al.

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Expert's summary:

A prospective randomized study comparing robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion versus open radical cystectomy was performed by 29 surgeons in nine high-volume centers in the UK over a period of 3 yr. Competence in robotic surgery (but not for open surgery) was required, defined as 30 RARC procedures with an intracorporeal urinary diversion. The distribution of the type of urinary diversion performed in these hospitals or by the surgeons outside the study is not known. Of the 1121 patients assessed for eligibility, 338 were randomized, of whom 317 were surgically treated, but only 306/317 of those randomized underwent either robotic cystectomy and intracorporeal urinary diversion (iRARC, 157 patients + 4 patients not randomized) or open surgery (ORC, 149 patients + 7 patients not randomized). The statistically recommended number of 170 patients in each group was not achieved.

For the primary outcome, defined as the cumulative number of days not in hospital within the 90 d following surgery, the median result was 82 d in the iRARC group versus 80 d in the ORC group; the difference was statistically significant (p = 0.01). Among the surgical metrics there were lower rates of blood loss, wound complications (5.6% vs 17.3%), and thromboembolic complications (1.9% vs 8.3%) in the iRARC group versus the ORC group. Quality of life (QoL) according to self-reported questionnaires, available for only 35% (110/317) of the patients, was significantly better in the iRARC group within the first 5 wk (EQ-5D-5L and EORTC QLQ-C30) and at 12 wk (EORTC QLQ-C30 only) postoperatively, but did not differ from the ORC group at 26 wk postoperatively. The same trend was observed for physical activity assessed using various measures, but with data only available for 24% (76/317) to 29% (92/317) of the patients.

There was no difference between the groups in all-cause mortality or cancer recurrence after minimum follow-up of 18 mo.

Expert's comments:

Although only a secondary endpoint in this study, the main goal of cystectomy is the oncological outcome, which was noninferior for the iRARC group, similar to the MSKCC [1] and RAZOR [2] prospective randomized studies of robotic versus open cystectomy, both of which included open urinary diversion. These studies revealed no significant differences [1] or noninferiority [2] in terms of recurrence-free survival, positive surgical margins, and complication rates (except for blood loss).

The authors are to be congratulated on extending their study by considering not only the ablative component of cystectomy but also the reconstructive element by comparing robotic intracorporeal to open urinary diversion. Owing to the COVID-19 pandemic and an apparent lack of motivation, the recommended number of patients in each group was not achieved, and only a minority of the patients could be followed for physical activity and QoL. The only hard data remaining are surgical metrics and cumulative days in hospital within 90 d after the primary surgery. As was seen in previous studies, there was less blood loss in the iRARC group but longer operating time. The primary outcome—a reduction of 2 d in cumulative hospital stay within 90 d for the iRARC group—was significant from a statistical standpoint. But was it significant from a patient's perspective? For QoL at 12 wk, only one of the QoL instruments—EORTC QLQ-C30—showed a better result for the iRARC group, and this was not apparent at 26 wk. The same was observed for physical activity and disability in the admittedly small group of patients who could be evaluated: there was no difference at 26 wk for any of these variables.

Of concern is the type of urinary diversion used in both groups by surgeons in high-volume hospitals. Almost half of the patients in the study had non–muscle-invasive tumor, 75% overall had organ-confined disease, 81% were described as fully active, and 48% were younger than 70 yr, but only 11% were selected for an orthotopic neobladder or other continent diversion.

From a patient's view, a major surgical intervention such as cystectomy should lead to both longer and better survival. Cure and thus survival for many years should be expected in at least 80% of patients [3] with organ-confined disease. With longer disease-free survival, QoL becomes increasingly important. Patients tumor-free after 18 mo will have higher QoL and more possibilities for physical activity with a continent diversion [4]. The question is whether many patients with knowledge of these data might accept 2 d more in the hospital within 90 d and even higher blood loss to avoid a wet stoma for the rest of their life.

Conflicts of interest: The author has nothing to disclose.

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Re: Neoadjuvant PD-L1 plus CTLA-4 Blockade in Patients with Cisplatin-ineligible Operable High-risk Urothelial Carcinoma

Gao J, Navai N, Alhalabi O, et al.

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Experts' summary:

In this phase 1 trial (NCT02812420; n = 28) [1], cisplatin-ineligible patients with invasive (cT1–4a N0 M0) high-risk urothelial carcinoma (UC) were treated with neoadjuvant tremelimumab (anti-CTLA4) plus durvalumab (anti-PD-L1) followed by surgery. In patients who underwent surgery (24/28), a complete pathological response (pCR; ypT0 N0) and overall downstaging ($\leq$ypT1 N0) were observed in 38% and 58% of patients, respectively. Grade 3–4 immune-related adverse events (irAEs) occurred in 21% of patients. At 1 yr, the overall survival (OS) rate was 89%. The relapse-free survival rate after surgery was 83%, whilst 11% experienced progression before surgery. Higher densities of B cells, $CD4^+$ T cells, $CD8^+$ T cells, and tertiary lymphoid structures in pretreatment tissue were associated with response.

Experts' comments:

This report provides promising data for cisplatin-ineligible patients with invasive UC, for whom treatment usually consists of upfront cystectomy associated with poor clinical outcomes [1]. The pCR rate was encouraging and toxicities were acceptable [1]. Of note, three patients (11%) experienced progression during neoadjuvant immune checkpoint inhibition (ICI) and did not undergo cystectomy. Hence, the pCR rate in the intention-to-treat population was 32%.

This study adds to other single-arm phase 1/2 trials of neoadjuvant ICI in invasive UC [2–4]. In the ABACUS trial, patients with mostly stage II UC (cT2 N0 M0; 85%) were treated with neoadjuvant atezolizumab, resulting in a pCR rate of 31% [3]. In the PURE-01-trial, the pCR rate was 42% for cT2 N0 M0 and 58% for cT3 N0 M0/cT2–3 N1 M0 UC treated with neoadjuvant pembrolizumab [4]. Similar to the trial by Gao et al., patients with locally advanced UC (cT3–4a N0 M0 or cTany N1–3 M0) treated with combination ICI in the NABUCCO trial had a pCR rate of 46% [2]. The rate of grade 3–4 irAEs was higher for combination ICI [1,2] than for ICI monotherapy [3,4] (21–55% vs 6–11%). On the basis of these small trials, it is currently unknown what the optimal neoadjuvant ICI dosing regimen is in terms of efficacy and tolerability. Nevertheless, neoadjuvant ICI (monotherapy and ICI combinations) is a promising option for patients who are cisplatin-ineligible, and may even compete with cisplatin-based NAC. A comparative study using a retrospective cohort of groups treated with platinum-based combination NAC versus combination ICI in NABUCCO suggested an OS benefit with ICI (hazard ratio 0.05, 95% confidence interval 0.007–0.41) [5]. Interestingly, OS appeared to be better among nonresponders to ICI than among nonresponders to NAC [5].

In conclusion, the first results for neoadjuvant ICI in invasive UC are promising. It is time to move forward to prospective comparative clinical trials to show whether neoadjuvant ICI is indeed superior to NAC and to elucidate which patients are most likely to benefit.

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