Editorial Commentary

Minimally invasive versus open radical cystectomy: long term oncologic outcomes compared

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Provenance and Peer review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article did not undergo external peer review.

Comment on: Khan MS, Omar K, Ahmed K, *et al.* Long-term Oncological Outcomes from an Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). Eur Urol 2020;77:110-8.

Submitted Apr 05, 2020. Accepted for publication Apr 22, 2020.
doi: 10.21037/tau-2020-03
View this article at: http://dx.doi.org/10.21037/tau-2020-03

Radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion is the standard surgical treatment for either muscle invasive bladder cancer (MIBC) or for recurrent high-risk nonmuscle-invasive bladder cancer (HRNMIBC) (1,2). Traditionally, RC is considered as a high complexity surgical procedure burdened by a high rate of intra- and postoperative complications, long hospital stay and a no negligible mortality rate (3). Minimally invasive approaches have been proposed in order to lessen the perioperative morbidity attributed to open RC (ORC), which still remains the standard approach (4). Among minimally invasive treatments, Robot-assisted RC (RARC) has precociously replaced laparoscopic RC (LRC) due to improved ergonomics, better dexterity and consequent faster learning curve (5). Large interest on RARC has risen from the urologic community and the rate of RARC has increased in the last decades (6). Comparative studies have reported better surgical perioperative outcomes after RARC or LRC, relative to ORC, such as reduced blood loss, shorter hospitalization and fewer complications, without affecting early oncologic outcomes (i.e., lymph node yield and positive surgical margins) (7). However, some concerns still remain for late oncologic safety. In particular, an increased risk of port site recurrences and peritoneal carcinomatosis has been supposed in RARC and LRC due to a possible tumour cells spillage and seeding as consequence of pneumoperitoneum, excessive manipulation of the cystectomy specimen, and breach of the specimen bag. Only a few prospective randomized controlled trials (RCT) reported oncologic results of either LRC *vs.* ORC (8) or RARC *vs.* ORC (9,10). All these studies did not show major differences in oncologic outcomes when either LRC or RARC have been compared with ORC.

After a preliminary prospective dual-centre study comparing ORC *vs.* LRC *vs.* RARC (11), in 2016 Khan *et al.* reported the early results of their single-centre prospective RCT (the Cystectomy Open Robotic and Laparoscopic [CORAL] Trial) (12). In this study between 2009 and 2012, Authors enrolled a total of 60 patients out of the 164 initially selected with MIBC or HRNMIBC, and allocated 20 patients in each of the three study arms (ORC *vs.* LRC *vs.* RARC). Authors reported reduced blood loss and shorter hospitalization after LRC or RARC, relative to ORC. Moreover, they found no significant differences in late complication rates and early oncological outcomes. Major biases of this study were: possible miscalculation of sample size and underpowered analyses, surgical biases and a significant crossover between arms.

More recently, the same group reported long term oncologic outcomes from the CORAL Trial (13). Similar rates of five-year recurrence free survival, cancer specific and overall survival were found when the three treatment modalities (ORC *vs.* LRC *vs.* RARC) were compared. Noteworthy, both intentions to treat and per-treatment analyses were performed to minimize the bias created by the initial patient crossover among arms. Moreover,

univariable Cox regression analyses and competing risks models did not reveal any significant difference. However, as stated also by the Authors, the results of these predictive analyses should be interpreted with caution due to the small sample size. It is unfortunate that the exact survival rates have not been reported, which instead have to be deduced from the Kaplan-Meier plots. In consequence, it is difficult to derive direct comparisons between the results of the current study and those reported in previous RCTs (8-10). Furthermore, due to small sample size, often these RCT studies lacks of multivariable adjustments or specific survival analyses stratified according to tumour characteristics, such as T-stage, N-stage or PSM, or according to patients comorbidities and demographic characteristics. Last, it is remarkable that none of the patients enrolled in the CORAL study developed peritoneal carcinomatosis or port site metastasis. These results are encouraging and validate those of previous RCTs (8,9), where the oncologic safety of minimally invasive RC (MIRC) has been investigated. Despite this, due to the small population, no definitive conclusion could be derived in light of other studies where the MIRC oncologic safety has not been confirmed for this particular aspect (10,14).

The effort of Khan *et al.*, as well as the effort of other authors who tried to give answers to concerns raised on MIRC oncologic safety, has to be commended. Nowadays, we have solid data regarding the advantages of minimally invasive treatments in terms of lower perioperative morbidity, relative to traditional open surgery. In the last decades, these advantages have been confirmed also for RC. In consequence, we agree with Khan *et al.* that the quest for reducing the morbidity of RC should not stop, particularly in light of the non-inferiority of MIRC in terms of oncologic results reported in recent RCTs', relative to ORC.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-2020-03). The authors have no conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Mistretta FA, Luzzago S, Musi G, de Cobelli O. Minimally invasive versus open radical cystectomy: long term oncologic outcomes compared. Transl Androl Urol 2020;9(3):1006-1008. doi:10.21037/tau-2020-03