Editorial

Robotic-assisted *vs.* open radical prostatectomy: an update to the never-ending debate

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Radical prostatectomy (RP) remains a standard of care surgical management for localized prostate cancer (PCa). However, with the introduction of robotic-assisted techniques, the surgical management of PCa has changed drastically. With uptake varying by country, depending on cost, insurance coverage, government healthcare approval, and patient preference, there have been frequent reports assessing its safety, perioperative outcomes, functional outcomes and oncologic outcomes, as compared to traditional open radical retropubic prostatectomy. While robotic-assisted radical prostatectomy (RARP) has generally been accepted to have lower estimated blood loss and shorter hospital stays (1,2), and in some series, lower incidence of bladder neck contractures/anastomotic strictures (3) and lower intraoperative adverse event rate (1), there is conflicting evidence regarding its effect on functional outcomes and no reliable data on oncologic outcomes.

In the study by Sooriakumaran *et al.* (4), the authors present the results of the LAPPRO study, a prospective non-randomized study. While they have previously reported on perioperative outcomes (5) and urinary continence outcomes with shorter 12-month follow-up (6), in this manuscript they focus primarily on erectile function (EF) recovery and oncologic outcomes.

Specifically, 2,545 Swedish men with PCa underwent either robotic-assisted radical prostatectomy (RARP) or open radical retropubic prostatectomy (ORP) at 14 different Swedish institutions by 50 experienced surgeons over a 3-year period [2008–2011]. The surgical technique was primarily determined by the patient's location of residence; hence, patient residence determined surgical technique, which the authors state substitutes for true randomization. Only surgeons who had performed greater than 100 procedures (either RARP or ORP) were included, to help reduce the influence of surgeon learning curves. Men <75 years old who had D'Amico low, intermediate or high-risk PCa without evidence of metastases on standard staging evaluation were included in the study.

Primary outcomes were erectile function recovery, positive surgical margins (PSMs) and prostate specific antigen (PSA) relapse rates at 3, 12 and 24 months post-prostatectomy. EF recovery was assessed using validated questionnaires, focusing on two domains: penile stiffness and morning erections. Postoperative recovery was considered positive when patients responded "stiff enough less than half the time", "stiff enough more than half of the time," or "stiff enough every time" on either of the two domains. PSA relapse was defined as PSA 0.2 ng/mL post-prostatectomy. Importantly, in this study, unlike other similar studies, surgeon input regarding completeness of bilateral neurovascular bundle sparing was surveyed at the time of surgery, and then correlated to EF recovery.

Despite no formal randomization and a higher number undergoing RARP (1,792 RARP and 753 ORP), the two

groups were well balanced, across all risk classifications. Response rates to surveys exceeded 90% through the 24-month follow-up period in both arms. When specifically comparing EF recovery across the entire cohort, RARP patients had better recovery through 24 months than ORP patients, with differences noted as early as 3 months (P<0.01). This benefit is primarily seen in the patients with D'Amico low and intermediate risk disease (P<0.01). While there is a slightly higher rate of recovery at 24 months in the high-risk cohort, it was not statistically significant (P>0.05). Importantly, in both groups, the rate of EF recovery (defined as having any mild return of function) at 24 months did not exceed 51% (51% for RARP and 39% for ORP). Potent EF recovery (defined as having erections every time) was much lower for both groups: 14% in ORP patients and 21% in RARP patients. The authors present this data as a follow-up to their own study with longer follow-up (5,6). In the original reported results with 12-month follow-up, RARP was moderately associated with improved EF recovery, but it appears that with longer follow-up, the improvement is more distinctly favoring RARP.

A unique finding in this study is the correlation between surgeon reported neurovascular bundle sparing and patient reported EF recovery. The correlation was much higher for the RARP arm than the ORP arm at all three time points, suggesting a surgeon's ability to visualize and complete adequate nerve sparing is better in RARP than ORP. It also further supports the importance of neurovascular bundle sparing to EF recovery.

Lastly, the authors assess the rate of PSM and PSA-recurrence. In men with pT2 tumors, the rates of PSM were slightly higher in the RARP group than those undergoing ORP, but this did not translate into a higher PSA-relapse rate. On the other hand, in men with pT3/4 tumors, the PSM rate was 15% higher in the ORP arm, which translated to higher PSA-relapse rates within 2 years (21.5% *vs.* 13.5%). Adjusted for pT-stage, post-operative Gleason score, and PSA, this represented a 1.66 relative risk (RR) of developing PSA-relapse in men undergoing RP in men with pT3/4 disease.

While this study presents some novel findings and reinforces results previously known, there are some important limitations that need to be discussed. First, it should be noted that the definition of EF recovery used in the original study utilized IIEF-5 score as well as the two domains from this study (6). It is unclear why the IIEF-5 was no longer assessed for longer follow-up, especially as it is a validated questionnaire for EF. Second, as the authors note in their discussion, the correlation between PSM and PSA-recurrence is difficult to define. Specifically, the lack of detail regarding the location and extent of PSM limits the utility of this analysis, as not all PSM are equivalent in terms of oncologic outcomes (7-9). This appears to be reflected in the lack of PSA-relapse in patients with pT2 disease and PSMs. However, the short 2-year follow-up may also limit the ability to capture PSA-relapse and local recurrence.

In the only randomized controlled trial (RCT) assessing RARP and ORP (1), the initial report of early 12-week results suggested no significant difference in the 6- and 12-week urinary continence and erectile function recovery between the two groups. Similarly, there was no significant difference in the PSM rates between the two arms, though PSM rates were higher in the pT3/4 cohort than in the pT2 cohort. Unfortunately, due to the short follow-up in the initial reporting of the data, PSA-relapse or biochemical recurrence rates could not be reported. However, this study has significantly fewer patients (n=308) compared to the current study and was performed entirely at a single institution under the care of two surgeons, making the generalizability a little less reliable. Structured to follow patients through 24 months, final results are still pending and yet to be reported.

Outside of RCTs, there are numerous population-based analyses and retrospective analyses that have attempted to compare functional and oncologic outcomes following RARP and ORP. Gershman *et al.* (10) similarly evaluated patient-reported functional outcomes in men undergoing RARP or ORP by high-volume surgeons at two high-volume centers in the USA (Massachusetts General Hospital, Boston, MA and Mayo Clinic, Rochester, MN). High-volume surgeon was defined as a surgeon performing greater than 25 cases per year. Functional outcomes were captured using the Expanded Prostate Cancer Index Composite short-form (EPIC-26) questionnaire at 1 and 2 years postoperatively. While their survey capture rate (59.7%) was significantly lower than the current study, they were still able to capture 1,686 men who underwent RARP, ORP or laparoscopic RP (LRP). However, in this study, there was no randomization, and selection bias for surgical technique was evident—patients undergoing ORP were more likely to have higher stage (pT3/4) and higher grade (Gleason score >6) disease, and were also more likely to undergo adjuvant radiotherapy (RT) or androgen deprivation therapy (ADT). Despite these differences, surgical technique was not associated with either urinary or sexual function outcomes. Pre-operative sexual function was an important modifier of postoperative sexual function, as expected. Other retrospective series suffer from the same

limitations (11).

In a series of meta-analyses published in 2012, Novara, Ficarra and colleagues provided a snapshot into the differences in functional outcomes stratified by surgical technique (12,13). With regards to urinary continence, analyzing 51 articles, of which 9 compared RARP to ORP, they identified a mean urinary continence rate (no pad or safety pad only) of 91% at 12 months, with continence rates superior in men undergoing RARP compared to RP (OR =1.53; P=0.03) (12). With regards to potency, upon analyzing 15 case series, of which 6 compared RARP to ORP, they identified 12- and 24-month potency rates of 54–90% and 63–94%, respectively. Potency rates were significantly higher in men undergoing RARP at 12-months (OR =2.84; P=0.002), and trended towards significance at the 24-month mark (OR =1.89; P=0.21) (13). It is important to note that the analysis was dependent on case series from experienced centers during the early experience of RARP. With variable definitions of potency and lack of consistency in the quality of the studies, the results of the meta-analyses must be accepted with caution. They do, however, support the finding of earlier recovery of potency and urinary continence with RARP, though there has been no demonstrable difference in long-term recovery.

With regards to the oncologic outcomes in the study by Sooriakumaran *et al.* (4), the follow-up limits the ability to make any strong conclusions. Unfortunately, the lack of granularity regarding the location and extent of PSM ensures that even with longer follow-up, all results will have to be questioned regarding veracity and utility. At this point, patients with higher stage pT3/4 disease appear to have a PSM rate when undergoing ORP, which translated to higher PSA-relapse rates within 2 years (21.5% *vs.* 13.5%). However, the implications on subsequent therapy, such as radiotherapy, need for ADT, and cancer-specific survival is unclear. It is important to note the authors do not report the rate of lymphadenectomy in this cohort, nor do they report the rate of node-positive disease in each of the arms. It is therefore uncertain if the PSA-relapse is truly attributable to the PSM and local recurrence or due to distant disease. As such, no conclusions can be drawn regarding oncologic benefit based on surgical technique.

Novara *et al.* have previously provided some insight into the oncologic benefit of RARP (14). In their systematic review and meta-analysis of 79 papers, they identified a PSM rate of 15% for all RARPs, while the rate was reduced to 9% in patients with localized disease. All cumulative analyses comparing RARP to ORP demonstrated similar overall PSM rates (RARP *vs.* RP: OR 1.21, P=0.19), PSM rates in localized ≤ pT2 disease (OR =1.25; P=0.31) and in BCR-free survival (HR =0.9; P=0.526). As previously discussed, though, all of the data included in the analysis was from high-volume centers with experienced surgeons, thus limiting the generalizability of the analysis.

While the strength of the study by Sooriakumaran *et al.* lays in its size, generalizability, and functional outcome results, it cannot significantly add to the discussion regarding oncologic benefit. Despite that, it is an important addition to the comparison between two commonly used surgical techniques for the management of localized PCa, particularly in the setting of increased critical assessment of RARP from a cost-effectiveness standpoint.

More important than the comparison between the two surgical techniques, however, is the cumulative rate of functional recovery, specifically the overall rate of erectile function recovery. Even utilizing a liberal definition of EF recovery (defined as having any mild return of function), the recovery at 24 months did not exceed 51% (51% for RARP and 39% for ORP). Potent EF recovery (defined as having erections every time) was much lower for both groups: 14% in ORP patients and 21% in RARP patients (4). This highlights the significant work that is still required in understanding the mechanisms of erectile function recovery and methods to improve outcomes. We recently published our functional results after RP from a high-volume institution, where the 12-, 24-, and 36-month EF rates were 45%, 51%, and 53%, but reached up to 65.7% in preoperatively potent patients with bilateral nerve sparing (15). Historical series, based on surgeon-reported outcomes, often reported much higher rates of recovery. More recent series, focusing on patient-reported outcomes, have come to demonstrate the significant discrepancy between the two sources (16,17). Large multi-institution multi-surgeon analyses such as this represent a more generalizable functional outcome study than single-institution, single-surgeon studies of the past. When counseling patients on prostatectomy, these outcomes are more representative of real-world functional outcomes that patients can expect postoperatively (18).

In our opinion, the debate between RARP and ORP is unlikely to have any clear resolution, despite the completion of randomized controlled trials. The inherent biases in these trials, essentially comparing surgeons rather than technique, will limit the generalizability of the study results.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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