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Research Letter



New Evidence and Innovative Approaches to Blinding in Robot-assisted Radical Cystectomy

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Open radical cystectomy (ORC) and robot-assisted RC (RARC) with intracorporeal (iRARC) or extracorporeal (eRARC) urinary diversion are the mainstays of treatment for localized muscle-invasive bladder cancer. No clear superiority of either approach has been shown in meta-analyses of randomized controlled trials (RCTs) [1,2]. Since then, a pilot RCT (BORARC trial) by Maibom et al. [3] that focused on blinding techniques and an interim analysis of a larger RCT by Mastroianni et al. [4] have been published. Remarkably, in contrast to all previous RCTs, all patients in these two trials underwent iRARC.

The aim of this letter is to provide an updated meta-analysis comparing ORC and RARC using data from all available RCTs and with consideration of the type of urinary diversion. Results for the trial endpoints were quantitatively summarized and pooled. For dichotomous data, the odds ratio was calculated using the Mantel-Haenszel model. For continuous data, differences are presented as the mean difference and 95% confidence interval calculated using the inverse variance model. The random effects model was used to address heterogeneity among studies.

Our analysis of seven unique RCTs showed no significant differences in major or minor complications or positive surgical margins. Operating time was significantly longer in the RARC group. There were significantly fewer transfusions, lower blood loss, and shorter hospital stay in the RARC group. There were no subgroup differences between eRARC and iRARC. All the data are presented in Fig. 1.

The benefits of minimally invasive surgery have been shown in many surgical fields and seem to be valid for RC too. Nevertheless, according to evidence from seven RCTs, RARC still fails to prove major benefits in terms of surgical complications. However, previous trials did not include intracorporeal urinary diversion or such meticulous blinding as the newly published trials.

The authors of the BORARC trial performed blinding of all postoperative caregivers and patients with the help of nontransparent wound dressings applied to cover both RARC and ORC wounds. The operating room was booked for the same slot for all procedures and personnel did not to leave the theater during this time. Operating surgeons were not involved in postoperative care and only nurses from neighboring wards changed the wound dressings, while patients were blinded by placing a pillow on their chest during wound dressing. Successful blinding was verified by asking caregivers and patients about their opinion on which technique was used. Only 26% of patients were unblinded before discharge and physicians, patients, and nurses did not guess the intervention correctly in 44-54% of cases. Interestingly, there seems to be a learning curve for treating blinded patients, as 44% of the initial 25 patients but only 8% of the last 25 patients were unblinded. The lessons learned from this trial should be applied in future trials as evidence-based concepts develop further in surgical urology.

Regarding iRARC, the final results from the study by Mastroianni et al [4] and the ongoing iROC trial [5] should give a good overview of the postulated benefits of intracorporal diversion. Meanwhile, both ORC and RARC represent valuable options.

Conflicts of interest: The authors have nothing to disclose.

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A Major complication		E Blood loss
Study or RARC ORC Odds Ratio Subgroup Events Total Events Total Weight MH, Random, 95% CI extracorporeal	Odds Ratio MH, Random, 95% CI	Study or RARC ORC Mean Difference Mean Difference Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Bocher 2015 13 60 12 58 21.9% 1.06[10.44] 2.57] Khan 2016 7 20 4 20 8.3% 2.15[10.52] 9.00] Nix 2010 1 21 1 20 2.1% 0.95[10.66;16.29] - Pareka 2013 1 20 1.2% 2.1% 1.00[10.06;17.18] - Pareka 2018 31 150 34 152 5.7% 0.08[0.57;1.68] Total (95%, C) 271 270 92.4% 1.07 [0.70; 1.65]	**************************************	extracorporeal Nama 2016 585:00 618:00 20 808:00 329:00 20 14:2% -223:00 [-529:83; 83:83] Parekh 2013 400:00 342:59 20 800:00 537:04 19 15:2% -400:00 [-684:5,-115:65] Parekh 2018 300:00 222:22 150 700:00 370:37 15:2 26:1% -400:00 [-468:29; 33:121] Total (95% CI) 190 191 55:5% -391:98 [-457:30; -326:65] Heterogenety, Tau ² = 0, Ch ² = 1.22, df = 2 (P = 0.54), l ² = 0%
Intracorporeal 3 25 2 25 4.8% 1.57 [0.24; 10.30] Mastroianni 2021 2 0 1 28 28% 1.93 [0.17; 22.53] Total (9% C1) 55 55 7.6% 1.89 [0.38; 7.54] Heterogenety: Tax ² = 0, CR ² = 0.02, df = 1 (P = 0.90), f ² = 0% 1.89 [0.38; 7.54]		Intracorporeal Maibom 2021 200 00 166 67 25 850 00 385 19 25 21 6% 450 00 [.814 52; .485 48] = Bochner 2015 516.00 427.00 60 676.00 338 00 58 23.0% 180 00 [.208 71; .21 29] = Total (95% CI) 215 .19.2; .21 10.2; .215; .Ch ² 19.9; .21 10.2; .215; .216 .274 100.0% .373.74 [.539.92; .207.55]
$ \begin{array}{cccc} \textbf{Total} \left(\textbf{95\% CI}\right) & \textbf{326} & \textbf{323} & \textbf{100.0\%} & \textbf{1.11} \left[\textbf{0.73}; \textbf{1.68}\right] \\ \text{Heterogenety}, Tau^2 = 0, Ch^2 = 1.38, df = 6 (P = 0.97), f^2 = 0\% \\ \text{Residual heterogenety}, Tau^2 = NA, Ch^2 = 1.05, df = 5 (P = 0.96), f^2 = 0\% \\ \text{Test for overall effect } Z = 0.49 (P = 0.62) \\ \end{array} \right. $	0.1 0.5 1 2 10 Favors RARC Favors ORC	Heterogeneity, Tau ² = 26289 9072; Chr ² = 21.34, df = 4 (P < 0.01); f ² = 81%, Residual heterogeneity; Tau ² = N4; Chr ² = 21.14, df = 3 (P < 0.01); f ² = 86% 500 0 500 Test for overall effect. Z = 4.41 (P < 0.01) Favors RARC Favors ORC
B Minor complication Study or RARC ORC Odds Ratio	Odds Ratio	F Operating time
Study or Subgroup Events Total Verents Total Weight MH, Random, Sv% CI extracorporal Rhan 2016 4 20 10 20 7.8% 0.25 [0.06; 1.02] — Nx 2010 6 21 9 20 9.2% 0.49 [0.13; 1.78] Parekh 2013 4 20 6.5% 1.00 [0.21; 4.71] Parekh 2018 68 150 71 152 51.8% 0.95 [0.06; 1.49] Parekh 2018 68 150 71 122 75.3% 0.95 [0.06; 1.49] Parekh 2018 68 150 71 122 75.3% 0.92 [0.06; 1.49] Parekh 2018 68 150 71 122 75.3% 0.92 [0.06; 1.49] Parekh 2018 68 150 71 122 75.3% 0.92 [0.06; 1.49] Parekh 2018 68 150 71 122 75.3% 0.92 [0.06; 1.49] Parekh 2018 6.00 [0.12] 72 74.3% 72 74.11 121 75.3% 72 74.11 12 75.3% 72 74.11 12.5% 74.2% 74.3% 72 74.11 72.1% 74.11 74.3%	MH, Random, 95% CI	Study or Subgroup RARC Mean Difference (V, Random, 95% CI Mean Difference (V, Random, 95% CI Mean Difference (V, Random, 95% CI 8c/hne 2705 456.00 62.00 60.292.00 77.00 58 17.8% 127.00 95% CI Pareka 2016 389.00 98.00 29.293.00 66.00 20 12.9% 96.00 14.22; 147.78 14.366; 63.56 Pareka 2013 300.00 93.30 26.256; 06.22 19.14.3% 14.56; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56 14.366; 63.56; 76.76 17.366; 63.56; 76.76; 77.96;
Intracorporeal Maibom 2021 1 1 25 10 25 11.9% 1.18 [0.38; 3.63] Masticianni 2021 9 30 14 28 12.9% 0.43 [0.15; 1.26] Total (95% Cl) 55 53 24.7% 0.70 [0.28; 1.89] Heterogenety: Tau ² = 0.1964; Clu ² = 1.62; df = 1 (P = 0.20); l ² = 38%		Intracorporeal Malbom 2021 263.00 34.81 25 136.00 22.22 25 20.2% 127.00 [110.81; 143.19] Mastroianni 2021 303.00 57.00 30 204.00 49.00 28 18.1% 99.00 [71.70; 128.30] Total (15%, CI) 5 5 38.3% 115.25 [88.16; 142.33] Heterogeneby: Tau ² = 260.8570; Ch ² = 2.99, df = 1 (P = 0.06), f ² = 87%
	0.1 0.5 1 2 10 Favors RARC Favors ORC	Total (95% CI) 305 302 100.0% 92.28 [62.94; 121.62] Heterogenety: Tau ² = 1042.9090; Ch ² = 28.81, df = 5 (P < 0.01); l ² = 83% -150.100.50 0 50.100.150 Test for overall effect. 2 = 61 (P < 0.01); l ² = 81% -150.100.50 0 50.100.150 Test for overall effect. 2 = 61 (P < 0.01); l ² = 81% Favors RARC Favors RC Favors RARC Favors RC
C Positive margin Study or RARC ORC Odds Ratio Subgroup Events Total Events Total Weight MH, Random, 95% Cl	Odds Ratio MH, Random, 95% Cl	G Length of hospital stay Study or RARC ORC Mean Difference Mean Difference Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Bochner 2015 2 60 3 58 15.7% 0.63(0,10,393) Khan 2016 3 20 2 14.4% 1.59(0,24,10.70) Nix 2010 0 21 0 20 0.0% Parekh 2013 1 20 1 20,65% 1.00(0,6(7,18)) Parekh 2018 9 150 7 152 50.9% 1.32(0,48;365) Total (95% Cl) 271 270 87.5% 1.17(0,54;2.64) Heterogenety, Tau ² = 0, Ch ² = 0.6, off = 3 (P = 0.90), i = 0%		extracorporeal Bochner 2015 & 8.00 3.00 & 60 8.00 5.00 58 7.8% 0.00[-1.49, 1.49] Nan 2016 11.90 6.20 20 14.40 5.90 20 1.4% -2.50[-6.25, 1.25] Nar 2010 5.10 2.40 21 6.00 2.40 20 8.0% -0.90[-2.37, 0.57] Parekh 2013 6.60 1.10 20 6.80 0.80 20 27.4% -0.20[-0.80, 0.40] Parekh 2018 6.00 0.80 150 7.00 0.70 152 48.7% -1.00[-1.17, -0.83] Total (95% CT) 271 271 270 93.3% -0.67[-1.22; -0.11] Heterogenety, Tax ² = 0.1702; Ch ² = 8.5 d; d = 4 (P = 0.37); ²⁴ = 55%
Intracorporeal 2 2 2 2 1.00 [0.13; 7.72] Matiom 2021 0 30 0 28 0.0% Total (95% Cl) 55 53 12.5% 1.00 [0.13; 7.72] Heterogeneity: not applicable 53 12.5% 1.00 [0.13; 7.72]		Intracorporeal Maibom 2021 5.00 2.96 25 6.00 2.99 25 6.6% -1.00 [-2.65; 0.65] Mastroiann 2021 10.00 11.00 30 15.00 32.00 28 0.1% -5.00 [-17.49; 7.49] Total (95% CI) 55 55 6.7% -1.07 [-2.70; 0.57] Heterogenety: Tau ² = 0; Ch ² = 0.39; df = 1 (P = 0.53); t ² = 05
	0.1 0.5 1 2 10 Favors RARC Favors ORC	Total (95% CI) 326 323 100.0% -0.72 [-1.17; -0.27] Heterogeneity: Tau ² = 0.1015; Ch ² = 8.99; df = 6 (P = 0.17); l ² = 33% -15 -10 -5 0 5 10 15 Residual heterogeneity: Tau ² = N4; Ch ² = 8.97; df = 5 (P = 0.11); l ² = 44% -15 -10 -5 0 5 10 15 Test for overal effect - 2 - 3.13 (P < 0.01)
D Transfusion rate Study or RARC ORC Odds Ratio Subgroup Events Total Events Total Weight MH, Random, 95%	Odds Ratio CI MH, Random, 95% CI	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		
Intracorporeal Maibom 2021 1 25 5 25 3.7% 0.17 [0.02, 1.55] Mastroinam 2021 6 30 12 28 13.3% 0.33 [0.10, 107] Total (95% CI) 55 53 17.0% 0.29 [0.10; 0.81] Heterogenety: Tau ² = 0; Chi ² = 0.29, df = 1 (P = 0.59); F = 0%		
$\begin{array}{c cccc} \textbf{Total (95\% CI)} & 218 & 216 & 100.0\% & 0.39 [0.26; 0.60] \\ Heterogeneity, Tau \tilde{i}=0, Ch^{2}=1.33, df=3 (P=0.72), \tilde{f}=0\% \\ Residual heterogeneity, Tau ^{2} HAC Ch^{2}=0.91, df=2 (P=0.64), \tilde{f}=0\% \\ Test for overall effect; Z=4.30 (P<0.01) \end{array}$	0.1 0.5 1 2 10 Favors RARC Favors ORC	

Fig. 1 – Meta-analysis results. (A) Major complications; (B) minor complications; (C) positive margin; (D) transfusion rate; (E) blood loss; (F) operating time; and (G) length of hospital stay. CI = confidence interval; df = degrees of freedom; IV = inverse variance; MH = Mantel-Haenszel model; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

References

- [1] Satkunasivam R, Tallman CT, Taylor JM, Miles BJ, Klaassen Z, Wallis CJ. Robot-assisted radical cystectomy versus open radical cystectomy: a meta-analysis of oncologic, perioperative, and complication-related outcomes. Eur Urol Oncol 2019;2:443-7.
- [2] Rai BP, Bondad J, Vasdev N, et al. Robotic versus open radical cystectomy for bladder cancer in adults. Cochrane Database Syst Rev 2019;2019:CD011903.
- [3] Maibom SL, Røder MA, Aasvang EK, et al. Open vs robot-assisted radical cystectomy (BORARC): a double-blinded, randomised feasibility study. BJU Int. In press. https://doi.org/10.1111/bju.15619.

[4] Mastroianni R, Tuderti G, Anceschi U, et al. Comparison of patientreported health-related quality of life between open radical cystectomy and robot-assisted radical cystectomy with intracorporeal urinary diversion: interim analysis of a randomised controlled trial. Eur Urol Focus. In press. https://doi.org/10.1016/j. euf.2021.03.002.

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[5] Catto JW, Khetrapal P, Ambler G, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy (iROC): protocol for a randomised controlled trial with internal feasibility study. BMJ Open 2018;8: e020500.

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