World Journal of Urology (2019) 37:1557–1570
https://doi.org/10.1007/s00345-019-02708-8

INVITED REVIEW

# Oncologic outcomes after robot-assisted versus open radical cystectomy: a systematic review and meta-analysis

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Received: 25 January 2019 / Accepted: 26 February 2019 / Published online: 11 April 2019


## Abstract

**Purpose** The efficacy of RARC in oncologic outcomes compared ORC is controversial. We assess potential differences in oncologic outcomes between robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC).

**Methods** We performed the literature search systematically according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement. A pooled meta-analysis was performed to assess the difference in oncologic outcomes between RARC and ORC, separately in randomized controlled trials (RCTs) and non-randomized studies (NRCTs).

**Results** Five RCTs and 28 NRCTs were included in this systematic review and meta-analysis. There was no difference in the rate of overall positive surgical margin (PSM) in RCTs, while NRCTs showed a lower rate for RARC. There was no difference in the soft tissue PSM rate between RARC and ORC in both RCTs and NRCTs. There was no difference in the lymph node yield by standard and extended lymph node dissection between RARC and ORC in both RCTs and NRCTs. There was no significant difference in survival outcomes between RARC and ORC in both RCTs and NRCTs.

**Conclusions** Based on the current evidence, there is no difference in the rate of PSMs, lymph node yield, recurrence rate and location as well as short-term survival outcomes between RARC and ORC in RCTs. In NRCTs, only PSM rates were better for RARC compared to ORC, but this was likely due to selection and reporting bias which are inherent to retrospective study designs.

**Keywords** Oncologic outcome · Open radical cystectomy · Positive surgical margin · Robot-assisted radical cystectomy

## Introduction

Radical cystectomy (RC) with pelvic lymph node dissection and urinary diversion is the standard treatment for muscle-invasive (MIBC) and very high-risk non-muscle invasive bladder cancer (NMIBC) [1, 2]. Advances in technology have facilitated the adoption of minimally invasive surgery such as robot-assisted radical cystectomy (RARC). With its first description in 2003 [3], it has found increasing adoption worldwide for the treatment of advanced bladder cancer. For example, in the United States, the rate of RARC has increased from 0.6% of all RCs in 2004 to 18.5% in 2012 [4, 5].

Somewhere between 30 and 50% of patients treated with radical cystectomy experience local and/or distant recurrence despite adequate surgery [6, 7]. Various quality criteria have been identified to reflect the oncologic effectiveness of RC such as soft tissue surgical margins (STSM), numbers of lymph nodes removed and early disease recurrence [8–10].

Despite several randomized-controlled trials (RCTs) and non-randomized studies (NRCTs) reporting on the short-term as well as long-term oncologic outcomes of RARC and ORC, there is still no consensus on the differential comparative oncologic effectiveness of RARC versus ORC [11–15]. We, therefore, conducted an up-to-date systematic review and meta-analysis of the literature comparing oncologic outcomes of patients treated with RARC to those treated with ORC.

Takehiro Iwata and Shoji Kimura contributed equally to this project.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00345-019-02708-8) contains supplementary material, which is available to authorized users.

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## Materials and methods

The protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018109437).

### Literature search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [16]. A completed PRISMA-P 2015 checklist and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist are shown to describe the methodology of our study regarding RCTs and NRCTs, respectively (Supplementary Tables 1, 2). We searched the electronic databases (MEDLINE, Web of Science, Cochrane Library and Scopus) on September 10th 2018 for studies comparing oncologic outcomes between RARC and ORC. After a first screening based on study title and abstract, all full text papers were assessed and excluded with reasons. Two reviewers carried out this process independently. All disagreements were resolved by a consensus or arbitration by third investigators. The following string terms were used in our search strategy: (robotic radical cystectomy OR robot-assisted radical cystectomy OR RARC) AND *bladder cancer* AND (surgical margin OR lymph node OR oncologic outcome).

### Inclusion/exclusion criteria

Studies were included if they compared RARC to ORC and reported surgical margin status, lymph node yield and/or survival outcomes between both arms in RCTs or NRCTs such as prospective and retrospective observational (or cohort) studies. We excluded review articles, editorials, comments, meeting abstracts and not in English. In case of the similar patient cohort publications, either the higher quality or the most recent publication was selected. We manually searched the reference lists of eligible studies to detect any potentially relevant articles.

### Data extraction

Two reviewers independently extracted and summarized the following data from the included studies: general study characteristics, patient demographics and oncologic outcomes. The outcomes of interest were PSM (overall, soft tissue and ureteral/urethral PSM) rates, mean lymph node yield (standard or extended lymph node dissection (LND)), disease recurrence (local and distant), recurrence-free survival (RFS) rate, cancer-specific survival (CSS) rate and overall survival (OS) rate. We defined the extent of LND as following based on the guideline [17] if there was no description of its definition in the article; standard LND was defined as the removal of nodal tissue cranially up to the common iliac with the ureter being the medial border, obturator, internal iliac, external iliac and presacral nodes. Extended LND was defined as a proximally up to the aortic bifurcation as well as the area described for standard LND. Any disagreement was resolved by the senior author.

### Statistical analysis

The relative risk (RR) and weighted mean difference (WMD) were used as the summary statistic for dichotomous and continuous variables, respectively. All results were reported with 95% confidence intervals (CIs). For studies that presented continuous data as median and range or interquartile range, the means and standard deviations were calculated using the technique described by Hozo et al. [18]. We analyzed the data from RCTs and NRCTs separately to reduce bias. Statistical heterogeneity between studies was assessed by the Chi-square test with $p < 0.10$ and the $I^2$ test with $I^2 < 50\%$ used for statistical significance. A random-effect model was used for outcomes in cases of significant heterogeneity; otherwise, the fixed-effect model was used. Statistical analyses were performed using Review Manager Version 5.3 (RevMan-Computer program, Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

### Risk of bias

Two reviewers independently assessed the risk of bias (RoB) of each individual study. An evaluation of RoB of the included studies was performed according to the Cochrane handbook [19]. For RoB assessment, selection, performance, detection, attrition, reporting bias and other potential sources of bias were assessed as "yes", "no", or "unclear" in each of the included RCTs (Supplementary Table 3). The RoB assessment of NRCTs was evaluated according to The Risk of bias in non-randomized studies of interventions. This tool is based on seven domains that included bias due to confounding, participant selection, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes and selection of the reported result (Supplementary Table 4).

## Result

### Quantity of evidence identified and characteristics of included studies

A total of 543 articles were identified by the initial search (Fig. 1). After removal of duplicates, 270 remained for the screening of titles and abstracts. We excluded 161 articles based on our inclusion and/or exclusion criteria. Then, we assessed the full texts of the remaining selection leaving 33 studies for the qualitative and quantitative analyses. The general characteristics of the included studies are summarized in Table 1. Five studies were RCTs [11, 12, 20–22] comprising 501 patients and 28 studies were NRCTs [13–15, 23–47] comprising 25,991 patients. These studies were published between 2006 and 2018 with 19 being from North America, eight from Europe and five from Asia. Twenty-three studies reported neoadjuvant chemotherapy (NAC) rates (RARC: 2.0–100%, ORC: 0–100%). Pooled rates of NAC were 26.8% for RARC and 36.5% for ORC in RCTs and 21.9% for RARC and 19.1% for ORC in NRCTs, respectively. In one study [14], patients who received NAC were excluded. Thirteen studies reported adjuvant chemotherapy rates (RARC: 4.5–36.9%, ORC: 1.5–46.3%). Pathological outcomes are summarized in Table 2. PSM rates and lymph node yield were reported in 33 and 31 studies, respectively. Standard and extended LND were performed in 13 and nine studies, respectively. Other studies included mix cohorts with standard/extended LND or did not report the extent of LND. Oncologic outcomes are summarized in Table 3. The duration of follow-up in RARC and ORC arms varied from 8 to 58.8 months and from 12 to 59.1 months, respectively. Eight studies reported local and/or distant recurrence. Estimated RFS, CSS and OS rates were reported in seven, five and seven studies, respectively. It was not possible to perform meta-analysis of survival outcomes in eligible studies, due to the lack of data availability.

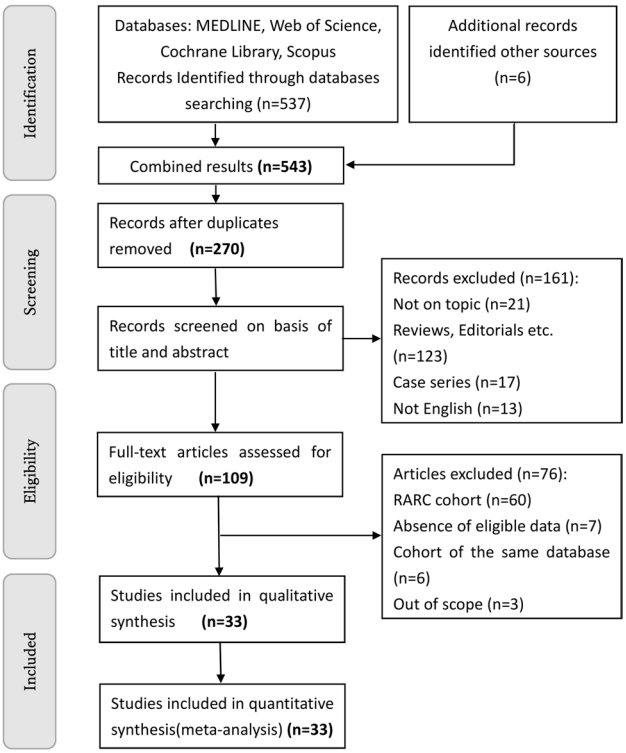


**Fig. 1** Flow chart for article selection process to analyze oncologic outcomes in patients treated with robot-assisted radical cystectomy (RARC) compared to those treated with open radical cystectomy (ORC)

### Meta-analysis

#### Comparison of PSM rates between RARC and ORC

Four RCTs including 500 patients and 27 NRCTs including 25,881 patients reported differences in PSM rates between RARC and ORC. The forest plot (Fig. 2a) showed that there was no significant difference in PSM rates (RR: 1.16, 95% CI 0.56–2.37, $p=0.69$) between RARC and ORC in RCTs. Conversely, in NRCTs, RARC was associated with lower PSM rates (RR: 0.84, 95% CI 0.77–0.91, $p<0.0001$) compared to ORC.

We analyzed separately PSM rates in patients with pathological T1–2 and T3–4 tumors. One RCT including 208 patients and four NRCTs including 6082 patients reported PSM rates in patients with pathological T1–2 tumors between RARC and ORC. Three RCTs including 148 patients and ten NRCTs including 6462 patients reported PSM rates in patients with pathological T3–4 tumors between RARC and ORC. The forest plots (Supplementary Fig. 1a, b) showed that there was no significant difference in PSM rates of patients with pathological T1–2 and T3–4 tumors between RARC and ORC in both RCTs (RR: 1.00, 95% CI 0.14–6.97, $p=1.00$ and RR: 1.15, 95% CI 0.50–2.66, $p=0.75$, respectively) and NRCTs (RR: 1.11, 95% CI 0.81–1.52, $p=0.52$ and RR: 0.90, 95% CI 0.79–1.02, $p=0.09$, respectively). The Chi-square and $I^2$ test did not show any heterogeneity in any of the pooled analyses (Supplementary Fig. 1a, b).

Additionally, we analyzed separately the soft tissue positive surgical margin (STSM) and ureteral/urethral PSM rates. Three RCTs including 460 patients and eight NRCTs including 1280 patients reported STSM rates between RARC and ORC. One RCT including 302 patients and five NRCTs including 517 patients reported ureteral/urethral PSM between RARC and ORC. The forest plots (Fig. 3a, b) showed that there was no significant difference in STSM and ureteral/urethral PSM rates between RARC and ORC in

**Table 1** Characteristics of the included studies

| Author | Region | Arm | No. pts. | Age (mean/median) | Male (%) | BMI (mean/median) | ASA (mean/median) | Neo bladder rate (%) | NAC rate (%) | AC rate (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Randomized studies | | | | | | | | | | |
| Nix 2010 [21] | US | RARC/ORC | 21/20 | 67.4/69.2 | 66.7/85 | 27.5/28.4 | 2.7/2.7 | 33.3/30 | NR | 28.6/40.0 |
| Parekh 2013 [22] | US | RARC/ORC | 20/20 | 69.5/64.5 | 90/80 | 27.6/28.3 | 3.0/3.0 | NR | NR | NR |
| Khan 2016 [20] | UK | RARC/ORC | 20/20 | 68.6/66.6 | 85/90 | 27.5/27.4 | 1.9/1.9 | 10/15 | 10/15 | NR |
| Bochner 2018 [11] | US | RARC/ORC | 60/58 | 66/65 | 85/72 | 27.9/29.0 | 2.7/2.7 | 55/55 | 32/45 | NR |
| Parekh 2018 [12] | US | RARC/ORC | 150/152 | 70/67 | 84/84 | 27.8/28.2 | NR | 24/20 | 27/36 | 17/11 |
| Non-randomized studies | | | | | | | | | | |
| Galich 2006 [27] | US | RARC/ORC | 13/24 | 70/70.5 | 77/75 | 25.1/26.5 | NR | 0/0 | NR | NR |
| Rhee 2006 [44] | US | RARC/ORC | 7/23 | 60/67 | 86/61 | 25/28 | NR | 0/0 | NR | NR |
| Pruthi 2007 [42] | US | RARC/ORC | 20/24 | 62.3/68.2 | 100/100 | NR | NR | 50.0/20.8 | 10/NR | NR |
| Abaza 2012 [23] | US | RARC/ORC | 35/120 | 69.8/67.3 | 89/79 | NR | NR | NR | 36/31 | NR |
| Gondo 2012 [29] | Japan | RARC/ORC | 11/15 | 68.9/69.7 | 82/87 | NR | NR | 36.4/40.0 | 0/0 | NR |
| Khan 2012 [32] | UK | RARC/ORC | 48/52 | 66.5/65 | 85/77 | 29.8/29.6 | 19/48% (≥3) | 12.5/9.6 | NR | NR |
| Styn 2012 [46] | US | RARC/ORC | 50/100 | 66.6/65.6 | 84/84 | 29.8/29.6 | 54/57% (≥3) | 28/28 | 46/42 | 18/11 |
| Kader 2013 [31] | US | RARC/ORC | 100/100 | 67/67 | 72/72 | 26.5/27.1 | 78/73% (≥3) | 3.0/12.0 | 10/10 | NR |
| Knox 2013 [33] | US | RARC/ORC | 58/84 | 65.9/67.1 | 79/70 | 28.6/28.9 | 88/90% (≥3) | 8.6/10.7 | 15.5/22.6 | 17.2/14.3 |
| Maes 2013 [35] | US | RARC/ORC | 14/14 | 71.0/67.6 | 78.6/100 | 27.3/27.2 | NR | 0/0 | NR | NR |
| Nepple 2013 [39] | US | RARC/ORC | 36/29 | 72/67 | 86/55 | 27.7/26.2 | NR | 16.7/37.9 | 6/14 | 22/14 |
| Ahdoot 2014 [24] | US | RARC/ORC | 51/51 | 72.0/70.0 | 67/67 | 28.0/26.5 | NR | NR | NR | NR |
| Musch 2014 [37] | Germany | RARC/ORC | 100/42 | 71.4/69.0 | 76/64 | 27/27 | NR | 22.0/16.7 | 2.0/0 | NR |
| Atmaca 2015 [25] | Turkey | RARC/ORC | 32/42 | 62.2/61.4 | 91/98 | 25.7/24.8 | 41/14% (≥3) | 100/100 | NR | NR |
| Nguyen 2015 [40] | US | RARC/ORC | 263/120 | 72/69 | 79/71 | 25/24 | 52/54% (≥3) | 20.9/27.5 | 24/23 | 17/18 |
| Cusano 2016 [26] | US | RARC/ORC | 121/92 | 65.9/67.8 | 79/79 | 28.2/28.4 | 3/3 | 30.0/25.0 | 31.4/22.8 | NR |
| Gandaglia 2016 [28] | Belgium | RARC/ORC | 138/230 | 70/70.9 | 83/83 | 26.1/26.0 | 39/39% (≥3) | 15.2/62.5 | 19.9/0 | 8.7/19.5 |
| Iwamoto 2016 [30] | Japan | RARC/ORC | 20/40 | 73/72.5 | 70/73 | 23.1/21.7 | NR | 15.0/22.5 | NR | NR |
| Matulewicz 2016 [36] | USA | RARC/ORC | 2397/9639 | 67.7/68.1 | 78/74 | NR | NR | NR | 20.9/14.5 | 16.6/17.9 |
| Tan 2016 [47] | UK | RARC/ORC | 90/94 | 64.3/66.4 | 77/72 | NR | NR | 33.4/13.8 | 34.4/22.3 | 10.0/7.4 |
| Koie 2017 [34] | Japan | RARC/ORC | 29/196 | 65/69 | 93/74 | NR | NR | NR | 100/100 | NR |
| Necchi 2017 [38] | Italy | RARC/ORC | 85/603 | 62.0/63.4 | 77/79 | NR | NR | 27.7/22.8 | 63.9/60.1 | 36.9/46.3 |
| Sharma 2017 [45] | USA | RARC/ORC | 65/407 | 70.9/70.2 | 73/97 | 27.8/28.0 | 49/56% (≥3) | 10.8/13.8 | 21.5/39.3 | NR |
| Hanna 2018 [14] | USA | RARC/ORC | 2048/7513 | 69/70 | 79/74 | NR | NR | NR | Excluded | 15.8/15.1 |
| Niegisch 2018 [13] | Germany | RARC/ORC | 89/59 | 68.0/71.7 | 84/83 | 25.6/27.1 | 2/3 | NR | 3.5/3.5 | 4.5/1.5 |

**Table 1** (continued)

| Author | Region | Arm | No. pts. | Age (mean/median) | Male (%) | BMI (mean/median) | ASA (mean/median) | Neo bladder rate (%) | NAC rate (%) | AC rate (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Panwar 2018 [41] | India | RARC/ORC | 24/54 | 57/58 | NR | 23.2/23.1 | NR | 33.3/11.1 | 4.2/14.8 | 25/27.8 |
| Ram 2018 [43] | India | RARC/ORC | 125/45 | 61.8/60.1 | 87/89 | 24.2/23.9 | NR | 36.0/28.9 | 17.6/17.8 | NR |
| Simone 2018 [15] | Italy | RARC/ORC | 64/46 | 62.5/63.6 | 78/83 | 26.1/26.7 | 13/13% (≥ 3) | 100/100 | 25/17.4 | NR |

*AC* adjuvant chemotherapy, *ASA* American Society of Anesthesiologists physical status classification, *BMI* body mass index, *NAC* neoadjuvant chemotherapy, *NR* not reported, *ORC* open radical cystectomy, *RARC* robot-assisted radical cystectomy, *US* United States of America, *UK* United Kingdom

both RCTs (RR: 1.00, 95% CI 0.40–2.47, $p = 1.00$ and RR: 0.76, 95% CI 0.17–3.34, $p = 0.72$, respectively) and NRCTs (RR: 0.68, 95% CI 0.43–1.07, $p = 0.09$ and RR: 1.30, 95% CI 0.68–2.50, $p = 0.42$, respectively). The Chi-square and $I^2$ test did not show any heterogeneity in any of the pooled analyses (Fig. 3a, b).

### Comparison of lymph node yield between RARC and ORC

Two RCTs including 83 patients and eight NRCTs including 1404 patients reported standard LND data comparing RARC to ORC. The forest plot (Supplementary Fig. 2a) showed that there was no significant difference in lymph node yield between RARC and ORC in both RCTs (WMD: 4.81, 95% CI −4.74–14.36, $p = 0.32$) and NRCTs (WMD: −2.08, 95% CI −5.84–1.67, $p = 0.28$). The Chi-square and $I^2$ test showed significant heterogeneity in all pooled analyses (Supplementary Fig. 2a). Two RCTs including 116 patients and five NRCTs including 864 patients reported extended LND data comparing RARC to ORC. The forest plot (Supplementary Fig. 2b) showed that there was no significant difference in lymph node yield between RARC and ORC in both RCTs (WMD: −1.21, 95% CI −3.91–1.49, $p = 0.38$) and NRCTs (WMD: −1.56, 95% CI −4.31–1.18, $p = 0.26$). The Chi-square and $I^2$ test showed significant heterogeneity in NRCTs pooled analyses (Supplementary Fig. 2a, b).

### Comparison of disease recurrence between RARC and ORC

Two RCTs including 340 patients and five NRCTs including 748 patients reported local recurrence data. Three RCTs including 458 patients and five NRCTs including 767 patients reported distant recurrence data. The forest plots (Supplementary Fig. 3a, b) showed that there was no significant difference in local and distant recurrence rates between RARC and ORC in both RCTs (RR: 1.19, 95% CI 0.39–3.65, $p = 0.75$ and RR: 0.94, 95% CI 0.69–1.30, $p = 0.73$, respectively) and NRCTs (RR: 0.72, 95% CI 0.46–1.12, $p = 0.15$ and RR: 0.79, 95% CI 0.58–1.06, $p = 0.12$, respectively). The Chi-square and $I^2$ test did not show any heterogeneity in any of the pooled analyses (Supplementary Fig. 3a, b).

### Comparison of survival between RARC and ORC

**Recurrence free survival** Two RCTs reported disease recurrence rates between RARC and ORC. Bochner et al. [11]. reported that 5-year risk of recurrence rates of 118 patients were 36% for RARC and 41% for ORC after a median follow-up of 58.8 months. Parekh et al. [12]. reported that 2-year progression-free survival rates of 302 patients were 72.3% for RARC and 71.6% for ORC ($p = 0.90$) with a minimum follow-up of 24 months. Five NRCTs reported RFS rates. 2-year RFS rates ranged from 67 to 87.8% for RARC

**Table 2** Pathological outcomes in RARC and ORC

| Author | Arm | Pathological T stage | | | PSM rate (%) all T stage | | | PSM rate (%) | | Extent of LND | Lymph node yields |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≤ pT2 (%) | ≥ pT3 (%) | Cis (%) | Soft tissue | Ureteral/urethral | Overall | ≤ T2 | ≥ T3 | | |
| Randomized studies | | | | | | | | | | | |
| Nix 2010 [21] | RARC/ORC | 66.7/40.0 | 33.3/60.0 | NR | 0/0 | NR | 0/0 | 0/0 | 0/0 | Extended | 19/18 |
| Parekh 2013 [22] | RARC/ORC | 50.0/65.0 | 50.0/35.0 | 10.0/30.0 | 5.0/5.0 | NR | 5.0/5.0 | 0/0 | 10.0/14.3 | Standard | 11/23 |
| Khan 2016 [20] | RARC/ORC | 70.0/70.0 | 30.0/30.0 | NR | NR | NR | 15.0/10.0 | NR | NR | Extended | 16.3/18.8 |
| Bochner 2018 [11] | RARC/ORC | 71.7/67.2 | 28.3/32.8 | 23.3/19.0 | 3.3/5.2 | NR | 3.3/5.2 | 0/0 | 11.8/15.8 | Standard Extended | 20/18 31/29 |
| Parekh 2018 [12] | RARC/ORC | 69.3/68.4 | 30.7/32.2 | NR | 4.0/3.3 | 2.0/2.6 | 6.0/4.6 | 1.9/1.9 | 15.2/10.2 | Standard Extended | 23.3/25.7 |
| Non-randomized studies | | | | | | | | | | | |
| Galich 2006 [27] | RARC/ORC | 53.8/37.5 | 46.2/62.5 | NR | NR | NR | 0/12.5 | 0/0 | 0/20.0 | Standard | NR |
| Rhee 2006 [44] | RARC/ORC | 85.7/43.5 | 14.3/56.5 | NR | 0/0 | 0/4.8 | 0/4.8 | NR | NR | Standard | NR |
| Pruthi 2007 [42] | RARC/ORC | 70.0/50.0 | 30.0/50.0 | NR | NR | NR | 0/4.2 | NR | NR | Standard | 19/16 |
| Abaza 2012 [23] | RARC/ORC | 60.0/45.0 | 40.0/55.0 | NR | 5.7/6.7 | NR | 5.7/6.7 | 0/0 | 14.3/12.1 | Extended | 37.5/36.9 |
| Gondo 2012 [29] | RARC/ORC | 90.9/53.3 | 9.1/46.7 | NR | NR | NR | 9.1/20.0 | 0/0 | 100/42.9 | Extended | 20.7/13.8 |
| Khan 2012 [32] | RARC/ORC | 75.0/50.0 | 25.0/50.0 | 6.3/1.9 | NR | NR | 0/9.6 | NR | NR | Extended | 16/11 |
| Styn 2012 [46] | RARC/ORC | 80.0/72.0 | 20.0/28.0 | 16.0/15.0 | 2.0/1.0 | 14.0/10.0 | 16.0/11.0 | NR | NR | Standard | 14.3/15.2 |
| Kader 2013 [31] | RARC/ORC | 58/53 | 42/47 | NR | NR | NR | 12.0/11.0 | 0/0 | 27.9/23.4 | Standard | 17.7/15.7 |
| Knox 2013 [33] | RARC/ORC | 66/43 | 34/57 | NR | NR | NR | 6.9/8.3 | 0/0 | 20.0/14.6 | Extended | 21.3/17.7 |
| Maes 2013 [35] | RARC/ORC | 35.7/28.6 | 57.1/42.9 | 7.1/7.1 | NR | NR | 21.4/14.3 | NR | NR | Extended | 11.9/9.5 |
| Nepple 2013 [39] | RARC/ORC | 52.8/58.6 | 47.2/41.4 | NR | 5.6/6.9 | 8.3/6.9 | 13.9/13.8 | 0/0 | 29.4/33.3 | Standard | 17/14 |
| Ahdoot 2014 [24] | RARC/ORC | 54.9/47.1 | 45.1/52.9 | 7.8/9.2 | 0/5.9 | 3.9/3.9 | 3.9/9.8 | NR | NR | Standard | 18/6 |
| Musch 2014 [37] | RARC/ORC | 61.0/57.1 | 39.0/42.9 | 21.0/14.3 | NR | NR | 2.0/2.4 | NR | NR | NR | 27.5/19.6 |
| Atmaca 2015 [25] | RARC/ORC | 59.4/61.9 | 40.6/38.1 | NR | 6.3/2.4 | NR | 6.3/2.4 | NR | NR | Standard Extended | 25.4/20.4 |
| Nguyen 2015 [40] | RARC/ORC | 65.8/57.5 | 34.2/42.5 | NR | NR | NR | 6.1/12.5 | NR | NR | Extended | 21/20 |
| Cusano 2016 [28] | RARC/ORC | 59.5/58.7 | 40.5/41.3 | NR | NR | NR | 8.3/5.6 | NR | NR | NR | 18/11.5 |
| Gandaglia 2016 [28] | RARC/ORC | 63.8/62.2 | 36.2/37.8 | 28.7/41.9 | NR | NR | 8.7/13.5 | 2.3/3.5 | 20.0/29.9 | NR | 12/13 |

**Table 2** (continued)

| Author | Arm | Pathological T stage | | | PSM rate (%) all T stage | | | PSM rate (%) | | Extent of LND | Lymph node yields |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≤ pT2 (%) | ≥ pT3 (%) | Cis (%) | Soft tissue | Ureteral/urethral | Overall | ≤ T2 | ≥ T3 | | |
| Iwamoto 2016 [30] | RARC/ORC | 75.0/65.0 | 25.0/35.0 | 5.0/7.5 | NR | NR | 0/5.0 | NR | NR | Standard | 21/16 |
| Matulewicz 2016 [36] | RARC/ORC | 50.7/44.3 | 42.9/49.0 | NR | NR | NR | 10.8/13.2 | 3.7/3.4 | 19.6/21.8 | NR | 16/11 |
| Tan 2016 [47] | RARC/ORC | 70.0/58.5 | 30.0/41.5 | 5.6/1.1 | 8.2/19.3 | NR | 8.2/19.3 | NR | NR | Standard | 14.9/12.6 |
| Koie 2017 [34] | RARC/ORC | 75.9/78.6 | 24.1/21.4 | NR | NR | NR | 0/0.5 | NR | NR | Standard | 15/18 |
| Necchi 2017 [38] | RARC/ORC | 47.1/43.4 | 52.9/52.9 | NR | NR | NR | 14.6/12.2 | NR | NR | NR | 21/13 |
| Sharma 2017 [45] | RARC/ORC | 55.4/54.3 | 44.6/45.7 | NR | 10.8/12.0 | NR | 10.8/12.0 | 0/0.5 | 24.1/25.8 | Standard | 15/16 |
| Hanna 2018 [14] | RARC/ORC | 54.4/49.2 | 41.1/46.8 | NR | NR | NR | 9.3/10.7 | NR | NR | NR | 17/12 |
| Niegisch 2018 [13] | RARC/ORC | 59.6/52.5 | 40.4/47.5 | 9.0/1.7 | NR | NR | 8/14 | 5.7/3.2 | 11.1/25.0 | Standard | 17/21 |
| Panwar 2018 [41] | RARC/ORC | 87.5/68.5 | 22.5/31.5 | 8.3/3.7 | 4.2/3.7 | 0/0 | 4.2/3.7 | NR | NR | Standard Extended | 26.6/20.7 |
| Ram 2018 [43] | RARC/ORC | 36.0/42.2 | 64.0/57.8 | NR | 0/0 | 6.4/4.4 | 6.4/4.4 | NR | NR | NR | 23.6/20.8 |
| Simone 2018 [15] | RARC/ORC | 64.1/65.2 | 35.9/34.8 | 15.6/13.0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | Extended | 33.4/31.4 |

*Cis* carcinoma in situ, *NR* not reported, *ORC* open radical cystectomy, *PSM* positive surgical margin, *LND* lymph node dissection, *RARC* robot-assisted radical cystectomy

**Table 3** Oncologic outcomes after RARC and ORC

| Author | Arm | Recurrence local (%) | Recurrence distant (%) | Estimate RFS rate (%) | Estimate CSS rate (%) | Estimate OS rate (%) | Follow-up (months) |
|---|---|---|---|---|---|---|---|
| Randomized studies | | | | | | | |
| Khan 2016 [20] | RARC/ORC | 0/5.3 | 26.3/5.3 | NR | NR | NR | 12 |
| Bochner 2015 [11] | RARC/ORC | NR | 28.3/37.9 | 36/41 (5 years)[a] | NR | NR | 58.8 |
| Parekh 2018 [12] | RARC/ORC | 4.0/2.6 | 22.0/23.0 | 72.3/71.6 (2 years)[b] | NR | NR | ≥24 |
| Non-randomized studies | | | | | | | |
| Styn 2012 [46] | RARC/ORC | 2.0/10.0 | 12.0/13.0 | NR | NR | NR | 8/13.5 |
| Nepple 2013 [39] | RARC/ORC | 11/3 | 22/21 | 67/58 (2 years) | 75/63 (2 years) | 68/63 (2 years) | 12.3/12.2 |
| Nguyen 2015 [40] | RARC/ORC | 18/23 | 29/36 | NR | NR | NR | 23/30 |
| Gandaglia 2016 [28] | RARC/ORC | NR | NR | 54.2/57.1 (5 years) | 73.5/61.9 (5 years) | 59.2/58.4 (5 years) | 40.0/59.1 |
| Tan 2016 [47] | RARC/ORC | 7.8/9.6 | 6.7/13.8 | 75.2/65.9 (2 years) | 84.4/80.9 (2 years) | 79.2/72.5 (2 years) | 16.1/33.8 |
| Necchi 2017 [38] | RARC/ORC | NR | NR | 52.1/32.2 (5 years) | NR | 48.4/44.3 (5 years) | 27.6 |
| Hanna 2018 [14] | RARC/ORC | NR | NR | NR | NR | 70.2/62.5 (2 years) | 26.9 |
| Niegisch 2018 [13] | RARC/ORC | 2.2/5.1 | 10.1/13.6 | NR | 90/70.7 (2 years) | 80/65.3 (2 years) | 32/47.5 |
| Simone 2018 [15] | RARC/ORC | NR | NR | 87.8/84.4 (2 years)<br>79.3/84.4 (3 years)<br>79.3/73.4 (4 years) | 89.6/88.3 (2 years)<br>86.4/85.3 (3 years)<br>86.4/85.3 (4 years) | 85.2/86 (2 years)<br>82.1/83 (3 years)<br>82.1/79.6 (4 years) | ≥24 |

*CSS* cancer-specific survival, *NR* not reported, *ORC* open radical cystectomy, *OS* overall survival, *RARC* robot-assisted radical cystectomy, *RFS* recurrence-free survival

[a]Risk of recurrence rate

[b]Progression-free survival: disease progression was determined on the basis of radiographical or pathological evidence of disease or death from disease according to Response Evaluation Criteria in Solid Tumors criteria version 1.1

and 58 to 84.4% for ORC [15, 39, 47]. 5-year RFS rates ranged from 52.1 to 54.2% for RARC and 32.2 to 57.1% for ORC [28, 38]. All studies concluded that there was no significant difference regarding RFS rates between RARC and ORC.

### Cancer-specific survival

Five NRCTs reported CSS rates between RARC and ORC. Two-year CSS rates ranged from 75–90% for RARC compared to 63–88.3% for ORC [13, 15, 39, 47]. Gandaglia et al. [28], in the largest NRCT, showed that there was no difference in 5-year CSS with a median follow-up of 40.0 and 59.1 months, respectively [i.e. 73.5% for RARC and 61.9% for ORC ($p \geq 0.1$)]. All studies concluded that there was no significant difference regarding CSS rates between RARC and ORC.

### Overall survival

Seven NRCTs reported OS between RARC and ORC. Two-year OS rates ranged from 68–85.2% for RARC and 62.5–86% for ORC [13–15, 39, 47]. Five-year OS rates ranged from 48.4–59.2% for RARC and 44.3–58.4% for ORC [28, 38]. All studies concluded that there was no significant difference regarding OS rates between RARC and ORC.

## Discussion

The present systematic review and meta-analysis of five RCTs comprising 541 patients and 28 NRCTs comprising 25,991 patients aimed to compare differences in oncologic outcomes of patients treated with RARC to those treated with ORC.

Surgical margin status is pathologically diagnosed by the absence or presence of tumor in the margin of soft tissue, ureter or urethra. Positive surgical margin (PSM) was

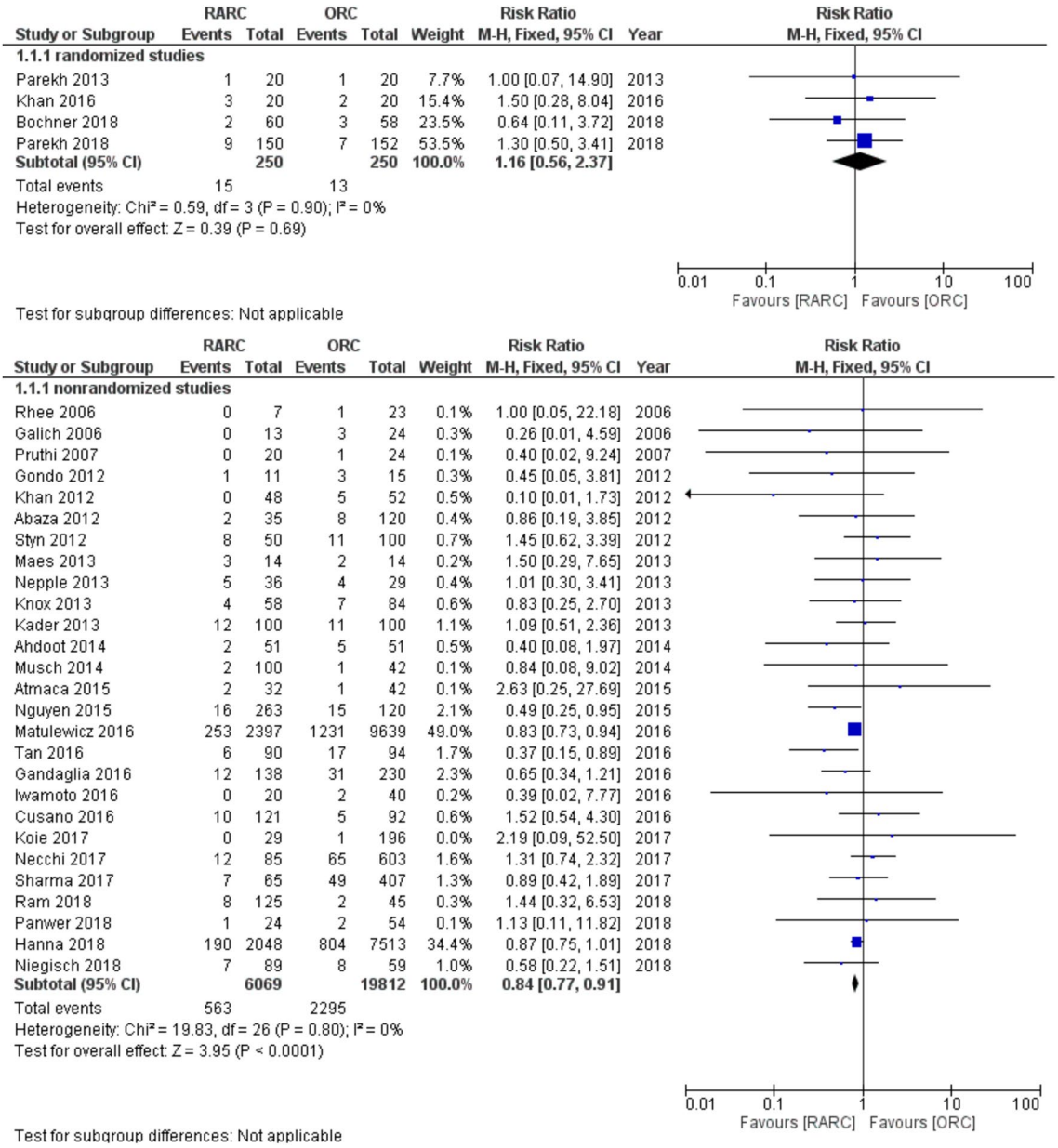


**Fig. 2** Forest plots showing the comparison of overall positive surgical margin between RARC and ORC. *CI* confidence interval, *M–H* Mantel–Haenszel test, *ORC* open radical cystectomy, *RARC* robot-assisted radical cystectomy, *SD* standard deviation

reported as one of independent predictors of disease recurrence [48]. PSM rates in open radical cystectomy (ORC) were reported in around 2% of patients with pathological T1-2 tumors with higher rates in patients with pathological T3–4 tumors [48, 49]. Wide dissection of the peri-vesical tissue would theoretically minimize PSM rates especially in patients with clinical non-organ confined disease [50]. We analyzed RCTs and NRCTs separately to decondition several potential biases that are inherent to NRCTs. We failed to find any difference in PSM rates between RARC and ORC in RCTs. Interestingly, NRCTs found a higher rate of PSM for ORC compared to RARC. For example, Tan et al. [47]. reported that RARC was superior to ORC regarding PSM rates (8.2% vs 19.3%). However, NRCTs are limited in validity due to their design issue leading to selection, reporting and detection bias among others [51]. For example, patients with higher pathological stage were more likely to receive ORC [24, 29, 32, 40, 47]. Therefore, RCTs are necessary to ensure equality or superiority of one method over another. Our meta-analysis of RCTs showed no difference in PSM rates between RARC and ORC. However, the type of PSM confers a different prognosis based on location. Soft tissue

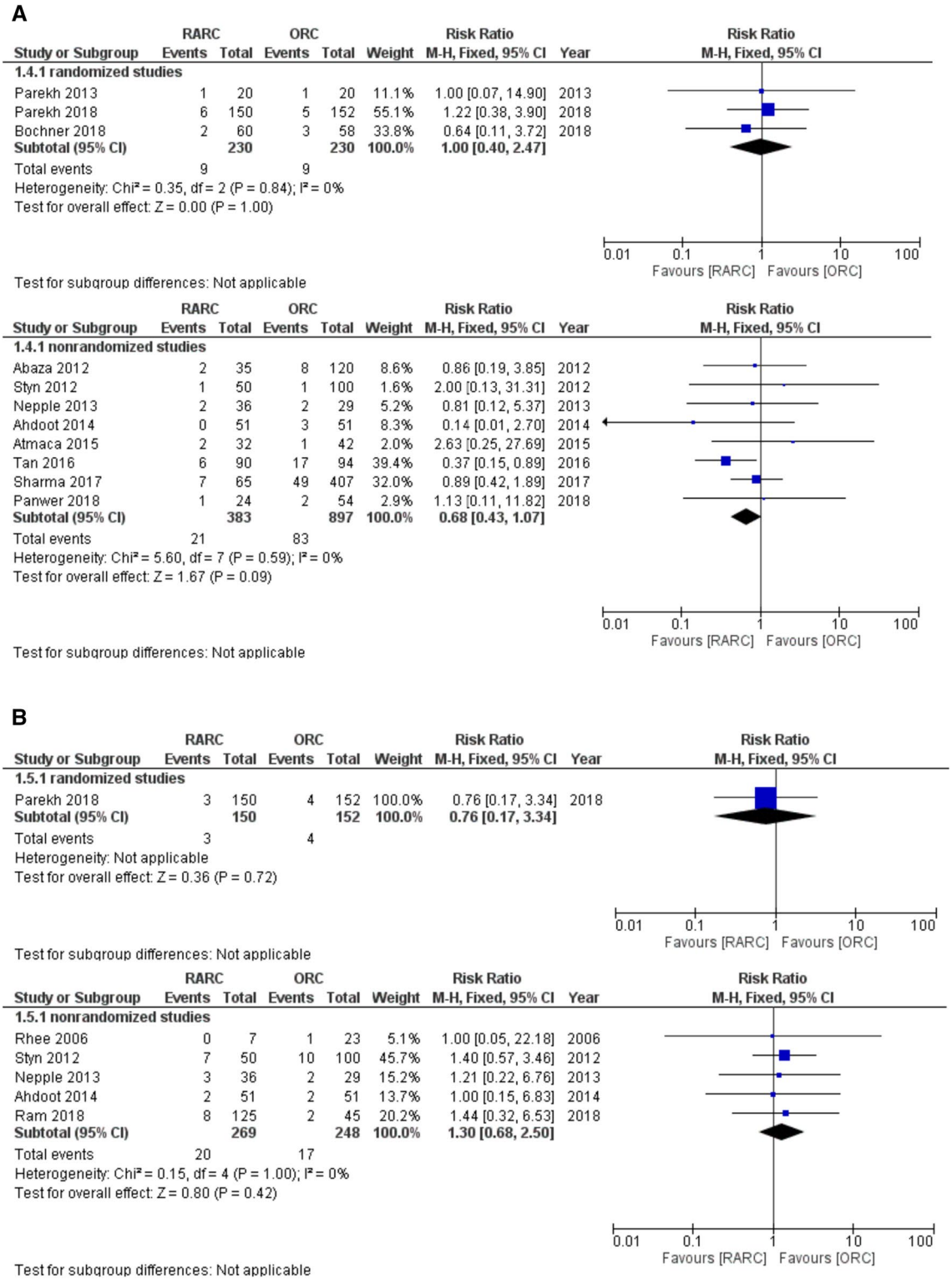


**Fig. 3** Forest plots showing the comparison of (**a**) soft tissue positive surgical margin and (**b**) ureteral/urethral positive surgical margin between RARC and ORC. *CI* confidence interval, *M–H* Mantel–Haenszel test, *ORC* open radical cystectomy, *RARC* robot-assisted radical cystectomy, *SD* standard deviation

surgical margin (STSM) is associated with an almost unanimous locoregional recurrence, distant metastasis and eventual death within 24 months after surgery [48, 49, 52].

We found no difference in STSM rates between RARC and ORC in both RCTs and NRCTs. The pooled rates of STSM in NRCTs were 3.6% for RARC and 8.3% for ORC, which is comparable to historic rates of STSM in expert centers [48, 49]. In our meta-analysis of STSM, all included studies were performed in experienced centers with ≥ 10RCs/year. In RCTs, there was also no difference in STSM rates (3.6% vs 3.6%). Therefore, one could conclude that RARC does not lead to higher rates of STSM compared to ORC performed at experienced centers. Such experience is what patients, regulators and insurances require more and more through centralization of complex surgery such as RC [53].

We found no difference in lymph node yields between RARC and ORC in both RCTs and NRCTs. The extent of LND is a quality criteria for RC. There has been discussion on the optimal LND and whether it is a surrogate for the quality of surgery and care delivered in a complex disease such as MIBC [52]. The EAU guidelines do not establish the extent of LND and number of lymph nodes needed to be removed [1]. Bochner et al. [54]. found that if lymph nodes are given to the pathologist in packets rather than en bloc, the number of lymph nodes removed will be higher. While the number of lymph nodes and template of LND are critical for RC, RFS and eventually CSS and OS are the more important endpoints for the patients and their caretakers.

We found no difference in RFS, CSS and OS between RARC and ORC in both RCTs and NRCTs. However, the median follow-up duration for most studies is too short to allow a conclusive statement. Indeed, most recurrences happen in patients treated with RC within the first 2 years [55]. In the current study, there were only three NRCTs with follow-up duration of more than 2 years [15, 28, 38]. These studies demonstrated that RARC was associated with a higher RFS compared to ORC without significant difference. The explanations of these results might be that the RARC arm has a shorter follow-up duration and includes lower stage patients. Indeed, in RCTs, there is no difference in RFS between RARC and ORC. Nguyen et al. [40]. reported that RARC had higher extrapelvic and peritoneal carcinomatosis compared to ORC. The issue of potential peritoneal tumor spread as a result of the effect of pneumoperitoneum warrants further research.

The major limitation of this meta-analysis is the quality of included studies; All NRCTs were observational and retrospective studies with high risks of bias and confounding. In particular, selection bias may have affected oncologic outcomes. Additionally, heterogeneity in definition of PSM, lymph node template, pathologic review may affect oncologic outcomes. For example, some articles reported PSM as soft tissue status, other articles defined PSM as soft tissue and ureteral/urethral status or did not report. This discrepancy is an ascertainment bias which is related to selection bias. Additionally, the lack of longer follow-up RCTs limit to allow a conclusive statement regarding the long-term oncologic outcomes. In addition, neoadjuvant chemotherapy has been shown an 8% improvement in 5-year survival outcomes in muscle-invasive bladder cancer [56]. In this systematic reviews, pooled NAC rates were 21.9% (2.0–100%) in RARC and 19.1% (0–100%) in ORC. Given the impact of NAC on oncologic outcomes, this might limit the generalizability of our results. Taken together, we highlight that ORC is still the gold standard treatment for MIBC and very high risk NMIBC; RARC might be an alternative by an experienced surgeon. A further long-term follow-up studies are necessary to evaluate further survival outcomes and to differentially assess the quality of life and complications.

## Conclusions

Based on the current evidence, there is no difference in the rate of PSMs, lymph node yield, location of recurrence and survival outcomes between RARC and ORC in RCTs. In NRCTs, only PSM rates were better for RARC compared to ORC, but this discrepancy could be likely due to biases in selection and reporting. Furthermore, well-designed studies regarding survival outcomes with long-term data between RARC and ORC are needed to evaluate the oncologic outcomes of these two surgical approaches and to differentially assess the quality of life and complications.

**Acknowledgements** The authors gratefully acknowledge the contributions of all study participants and staff.

**Author contributions** TI: Project development, Data collection, Data analysis, Manuscript writing. SK: Project development, Data collection, Data analysis, Manuscript writing. BF: Project development, Data collection, Data analysis. NF: Manuscript writing (Performed writing discussion section). AB: Manuscript writing (Performed editing introduction and discussion section). PIK: Manuscript writing (Performed critical editing result section). KMG: Manuscript writing (Performed writing result section and editing discussion section). SE: Manuscript writing (Performed writing discussion section). YN: Manuscript writing (Performed critical editing discussion section). MA: Project development, Data collection, Data analysis, Manuscript writing. SFS: Project development, Manuscript writing. All authors read and approved the final manuscript.

**Funding** None declared.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The authors have no ethical conflicts to disclose.

**Informed consent** The ethical approval was unnecessary because this study based on summary and analysis of the results of previous studies.

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