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Systematic Review and Cumulative Analysis of Oncologic and Functional Outcomes After Robot-assisted Radical Cystectomy

Bertram Yuh [a,*], Timothy Wilson [a], Bernie Bochner [b], Kevin Chan [a], Joan Palou [c], Arnulf Stenzl [d], Francesco Montorsi [e], George Thalmann [f], Khurshid Guru [g], James W.F. Catto [h], Peter N. Wiklund [i,†], Giacomo Novara [j,†]

[a] City of Hope National Cancer Center, Duarte, CA, USA

[b] Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[c] Fundació Puigvert, Barcelona, Spain

[d] Department of Urology, University of Tübingen, Tübingen, Germany

[e] Department of Urology, University Vita-Salute San Raffaele, Milan, Italy

[f] Department of Urology, University of Bern, Bern, Switzerland

[g] Department of Urology, Roswell Park Cancer Institute, Buffalo, NY, USA

[h] Academic Urology Unit, University of Sheffield, Sheffield, UK

[i] Karolinska University Hospital, Urology, Stockholm, Sweden

[j] Department of Surgery, Oncology, and Gastroenterology - Urology Clinic, University of Padua, Padua, Italy

[†] Contributed equally.

[*] Corresponding author. City of Hope National Cancer Center, Duarte, CA, USA. Tel. +1 626 471 7100; Fax: +1 626 301 8285.

E-mail: byuh@coh.org

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Abstract

Context: Although open radical cystectomy (ORC) is still the standard approach, laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) are increasingly performed.

Objective: To report on a systematic literature review and cumulative analysis of pathologic, oncologic, and functional outcomes of RARC in comparison with ORC and LRC.

Evidence acquisition: Medline, Scopus, and Web of Science databases were searched using a free-text protocol including the terms robot-assisted radical cystectomy or da Vinci radical cystectomy or robot* radical cystectomy. RARC case series and studies comparing RARC with either ORC or LRC were collected. A cumulative analysis was conducted.

Evidence synthesis: The searches retrieved 105 papers, 87 of which reported on pathologic, oncologic, or functional outcomes. Most series were retrospective and had small case numbers, short follow-up, and potential patient selection bias. The lymph node yield during lymph node dissection was 19 (range: 3–55), with half of the series following an extended template (yield range: 11–55). The lymph node–positive rate was 22%. The performance of lymphadenectomy was correlated with surgeon and institutional volume. Cumulative analyses showed no significant difference in lymph node yield between RARC and ORC. Positive surgical margin (PSM) rates were 5.6% (1–1.5% in pT2 disease and 0–31% in pT3 and higher disease). PSM rates did not appear to decrease with sequential case numbers. Cumulative analyses showed no significant difference in rates of surgical margins between RARC and ORC or RARC and LRC. Neoadjuvant chemotherapy use ranged from 0% to 31%, with adjuvant chemotherapy used in 4–22% of patients. Only six series reported a mean follow-up of >36 mo. Three-year disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS) rates were 53–74%,

68–83%, and 72–80%, respectively. The 5-yr DFS, CSS, and OS rates were 53–74%, 66–80%, and 39–66%, respectively. Similar to ORC, disease of higher pathologic stage or evidence of lymph node involvement was associated with worse survival. Very limited data were available with respect to functional outcomes. The 12-mo continence rates with continent diversion were 83–100% in men for daytime continence and 66–76% for nighttime continence. In one series, potency was recovered in 63% of patients who were evaluable at 12 mo.

Conclusions: Oncologic and functional data from RARC remain immature, and longer-term prospective studies are needed. Cumulative analyses demonstrated that lymph node yields and PSM rates were similar between RARC and ORC. Conclusive long-term survival outcomes for RARC were limited, although oncologic outcomes up to 5 yr were similar to those reported for ORC.

Patient summary: Although open radical cystectomy (RC) is still regarded as the standard treatment for muscle-invasive bladder cancer, laparoscopic and robot-assisted RCs are becoming more popular. Templates of lymph node dissection, lymph node yields, and positive surgical margin rates are acceptable with robot-assisted RC. Although definitive comparisons with open RC with respect to oncologic or functional outcomes are lacking, early results appear comparable.

1. Introduction

Radical cystectomy and pelvic lymph node dissection (PLND) is the gold standard treatment for muscle-invasive bladder cancer (MIBC) and high-risk non–muscle-invasive disease [1]. Patients undergoing this operation can experience 66% recurrence-free survival at 10 yr after surgery [2]. The addition of neoadjuvant platinum-based chemotherapy has been shown to improve overall survival (OS) rates by approximately 5% [3]. Robot-assisted radical cystectomy (RARC) was initially described by Menon et al in 2003 [4]. Over time, many international centers have adopted RARC.

Oncologic outcomes from large population-based cohorts of RARC with lengthy follow-up are lacking. Early on in RARC history, surrogates for oncologic control were reported using positive surgical margin (PSM) rates and lymph node yields. More recently, 5-yr survival figures have become available. The majority of these outcomes, however, capture institutions early in their learning curves and incorporate patients potentially selected for the robotic technique, thus avoiding more advanced-stage or technically difficult cases. Data on functional consequences of RARC are even more limited; therefore, the quality of nerve sparing and its effect on potency recovery and continence are inadequately understood.

Because of the expanding evidence available in the field of RARC, and in preparation for the Pasadena international consensus meeting on best practice in RARC and urinary reconstruction, we performed a systematic literature review of perioperative, functional, and oncologic outcomes of RARC in comparison with open radical cystectomy (ORC) and laparoscopic radical cystectomy (LRC).

We report on the systematic review and cumulative analysis of oncologic and functional outcomes of RARC. We systematically examined lymph node yields, PSMs, cancer-specific

survival (CSS), recurrence-free survival, and OS. In addition, functional outcomes after RARC, including urinary continence and erectile function, were systematically examined.

2. Evidence acquisition

A systematic literature search was initially performed in September 2013 using the Medline, Scopus, and Web of Science databases. The searches included only a free-text protocol using the terms robot-assisted radical cystectomy or da Vinci radical cystectomy or robot* radical cystectomy in all the fields of the records for Medline and Scopus searches and in the Title and Topic fields for the Web of Science search. No limits were applied. A full update of the searches was performed on April 28, 2014.

Two authors (G.N. and B.Y.) separately reviewed the records to select RARC case series and studies that compared RARC with ORC and RARC with LRC. Discrepancies were resolved by open discussion. Other significant studies cited in the reference lists of the selected papers were evaluated, as were studies published after the systematic search.

All noncomparative studies reporting the following data on RARC were collected: intraoperative and perioperative data (operative time, blood loss, transfusion rate, in-hospital stay, readmission, complication rates), functional data (urinary continence, erectile function), and oncologic data (PSMs, lymph node yield, disease-free survival [DFS], CSS, OS). The present review included only studies reporting on functional and oncologic data.

Studies reporting on partial cystectomy, prostate-sparing cystectomy, salvage cystectomy, cystectomy for urachal cancer or benign disease, single-case reports, pure laparoscopic (or mixed) series, or laparoendoscopic single-site or natural orifice transluminal endoscopic surgery for radical cystectomy; experimental studies on animal models; congress abstracts; review

papers; editorials; population-based studies; and book chapters were not included in the review. All data retrieved from the selected studies were recorded in an electronic database.

All papers were categorized according to the 2011 levels of evidence (LOEs) for therapy studies: LOE 1, systematic review of randomized trials or n-of-1 trials; LOE 2, randomized trial or observational study with dramatic effect; LOE 3, nonrandomized controlled cohort/follow-up study; LOE 4, case series, case–control study, or historically controlled study; or LOE 5, mechanism-based reasoning [5]. Papers were categorized according to the IDEAL recommendations [6].

2.1. Statistical analysis

Cumulative analysis was conducted using Review Manager v5.2 software designed for composing Cochrane Reviews (Cochrane Collaboration, Oxford, UK). Statistical heterogeneity was tested using the chi-square test. A p value <0.10 was used to indicate heterogeneity. Where there was a lack of heterogeneity, fixed-effects models were used for the cumulative analysis. Random-effects models were used in case of heterogeneity. For continuous outcomes, the results were expressed as weighted mean differences and standard deviations (SDs); for dichotomous variables, results were given as odds ratios (ORs) and 95% confidence intervals (CIs). Because of limitations in the Review Manager v5.2 software, meta-analysis of continuous variables was possible only when rough data were presented as mean and SD. Authors of the papers were contacted to provide missing data, whenever necessary. For all statistical analyses, two-sided $p < 0.05$ was considered statistically significant.

3. Evidence synthesis

3.1. Quality of the studies and level of evidence

Figure 1 shows a flowchart of this systematic review of the literature.

In total, 65 surgical series [4,7–70] and 22 comparative studies [71–92] reported on pathologic, oncologic (n = 18), or functional (n = 9) outcomes of RARC.

Most surgical series were retrospective, single-center studies (LOE 4). Exceptions included prospective studies [8,22,28,35,36,43,52,59,64,66,81,87] and some multi-institutional retrospective collaboration studies [16,23,25,30,45,48,54,61,68]. Only two of the comparative studies were randomized [74,83] (LOE 2b); all other comparative studies were nonrandomized, whether prospective or retrospective (LOE 4).

3.2. Pathologic information

3.2.1. Lymph node yields with robot-assisted radical cystectomy

Table 1 summarizes the number of lymph nodes recovered in published RARC series. The majority of studies (86%) reported extent of lymph node dissection (LND), with more centers performing extended LND (ELND) in recent series. Standard LND typically involved the removal of obturator, internal iliac, external iliac, and some portion of the common iliac lymph nodes bilaterally. ELND templates typically brought the proximal extent up to the aortic bifurcation or inferior mesenteric artery. Approximately half of the analyzed studies reported following an extended template of dissection.

The lymph node yield from all series was 19 (range: 3–55). Initial descriptions using a standard template of dissection achieved yields of 18 lymph nodes [59]. Number of lymph nodes recovered with an ELND ranged from 11 to 55. Abaza et al adopted a robotic template similar to the open technique, including external iliac, obturator, hypogastric, common iliac, and presacral up to the aortic bifurcation; the mean lymph node yield was 37.5 (SD: 13.2), demonstrating that lymph node counts could mirror those of open dissection if the same template was followed [88]. In a study of open completion LND after robot-assisted ELND in 11 men, Davis et al removed

only an additional 4 lymph nodes with an open approach after 43 were removed with robot assistance [34]. Time of LND was rarely reported, although it ranged from 44 min in standard LND to 117 min in ELND [8,34]. The lymph node–positive rate was 22%. In series with >20 RARCs, lymph node–positive rates ranged from 6% to 42%. Reports of vascular injuries were rare, and lymphocele rates were 0–9%.

3.2.2. Patient characteristics and surgical aspects influencing lymph node yields with robot-assisted radical cystectomy

Table 2 summarizes the studies assessing the effects of patient characteristics and particular surgical aspects on lymph node yields in RARC series. Cumulative analysis from the International Robotic Cystectomy Consortium (IRCC) with respect to lymphadenectomy in 437 patients found a median of 17 lymph nodes removed, with a 20% node-positivity rate [23]. Patient age and sex did not affect the performance of lymphadenectomy. In a different series, increasing body mass index (BMI) did not appear to negatively affect lymph node yield, with >20 lymph nodes removed in normal, overweight, and obese patients [46].

It is interesting to note that in single-institution series, Richards et al [38], Schumacher et al [39], Guru et al [59], and Pruthi et al [60] did not find higher lymph node yields with increasing sequential case numbers. However, in the IRCC, performance of lymphadenectomy was positively correlated with surgeon and institution volume but was reduced in patients with more advanced disease (pT4 stage), which may reflect operative avoidance of bulky nodal tissue.

3.2.3. Positive surgical margin rates with robot-assisted radical cystectomy

Table 3 summarizes the occurrence of PSMs reported in the RARC series. The reported PSM rates were 5.6% (range: 0–26%). However, in series of >100 patients, margin rates ranged between 4% and 9% [48,53]. PSMs were reported in 1–1.5% of patients with pT2 disease and 0–

31% of patients with pT3 and higher disease. PSM rates from the IRCC in 939 cases were 9% [53].

3.2.4. Patient characteristics and surgical aspects influencing positive surgical margin rates with robot-assisted radical cystectomy

Table 4 summarizes the studies assessing the effects of patient characteristics and particular surgical aspects on PSM rates in RARC series. Notably, Richards et al [38], Schumacher et al [39], and the IRCC [68] did not demonstrate decreasing surgical margin rates with sequential case number. In a study of the role of previous robot-assisted radical prostatectomy (RARP) experience on RARC outcomes, there was a trend toward increased positive margins with increasing RARP volumes, but it did not reach statistical significance ($p = 0.089$) [61]. The authors chiefly attributed this situation to the performance of RARC on patients with higher risk (higher than T3) disease. One study reported that PSMs occurred only in the overweight or obese patients, although pT4 rates were much higher in those patients (26% vs 7%) [65].

3.3. Oncologic information

3.3.1. Chemotherapy use in robot-assisted radical cystectomy

Table 5 summarizes the oncologic outcomes of current RARC publications. Neoadjuvant chemotherapy use was reported in 0–31% of patients. Adjuvant chemotherapy use was reported in 4–22% of patients.

Several studies further analyzed the use of adjuvant chemotherapy after RARC. General indications for selecting patients for adjuvant chemotherapy included pathologic stage pT3–4 or node-positive disease. Pruthi et al described the use of adjuvant chemotherapy in 18 of 100 RARC patients, with mean time to chemotherapy initiation at approximately 7 wk, which was faster than the authors' historical time to chemotherapy in open cystectomy of 10 wk [31]. In a

randomized trial of RARC (n = 21) compared with ORC (n = 20), 7 wk was also the mean time to initiation of chemotherapy after RARC [74]. In one analysis of patients with node-positive disease at the time of RARC, 46% received adjuvant chemotherapy [45].

3.3.2. Survival outcomes after robot-assisted radical cystectomy

Survival represents the gold standard with respect to evaluating effectiveness and risks of treatment; however, RARC reports with 5-yr outcomes have become available only recently. Data remain limited for assessing long-term outcomes, patterns of recurrence, and means for predicting survival. The role of adjuvant treatments after RARC is also poorly defined.

Series detailing cancer control outcomes had a mean follow-up between 6 and 84 mo (Table 5), although only 6 of 18 series (33%) reported a mean follow-up >36 mo. At 1, 2, 3, and 5 yr, DFS was 82–96%, 67–81%, 67–76%, and 53–74%, respectively; CSS was 88–94%, 75–89%, 68–83%, and 66–80%, respectively; and OS was 82–90%, 54–89%, 72–80%, and 39–66%, respectively. In the series with longest follow-up, Khan et al described only 14 patients with ≥5 yr of follow-up, showing DFS of 50%, CSS of 75%, and OS of 64% [66].

Several series reported on adverse oncologic outcomes associated with increased pathologic stage or lymph node involvement [58,93]. In a series of 162 patients with urothelial carcinoma, Yuh et al found that 5-yr survival was worse with higher pathologic stage or lymph node positivity ($p < 0.01$). Patients with a lymph node density of 1–10% (defined as number of positive nodes divided by number of total nodes) had DFS, CSS, and OS of 34%, 49%, and 31%, respectively, whereas patients with lymph node density >10% had further reduced survival of 30%, 38%, and 20%, respectively. Predictors of DFS were lymph node density, pathologic stage, and age-adjusted Charlson comorbidity index, whereas the same measures plus receipt of transfusion were predictive for OS [58]. Similarly, in an analysis of 99 patients with follow-up

>5 yr, pathologic stage and lymph node positivity were independent predictors of DFS, CSS, and OS, whereas positive margin status and Charlson comorbidity index predicted worse OS and CSS [70].

In series with median follow-up of >36 mo, rates of local recurrence without distant disease ranged between 0% (n = 15) and 9% (n = 99) [57,58,66,67,70]. No port-site recurrences occurred in these series. Xylinas et al examined 175 patients with a median follow-up of 37 mo, showing recurrence of disease in 29%. Of these patients, 8 (5%) had local recurrence alone, 11 had local and distant metastases, and 32 had distant metastases alone [57].

In an analysis of patients with positive lymph nodes (n = 50) at the time of PLND, median time to recurrence was 10 mo after RARC [45]. Estimated OS at 36 and 60 mo was 55% and 45%, respectively, with recurrence-free survival at 36 and 60 mo of 43% and 39%, respectively. Similarly, Tyritzis et al reported recurrence-free survival of 34% and OS of 63% after 24 mo in node-positive patients [56].

3.4. Functional information

3.4.1. Continence after urinary diversion and robot-assisted radical cystectomy

Table 6 presents the RARC series reporting on continence outcomes. Although functional outcomes are a major area of study in patients undergoing RARP, a lack of data remains for evaluation after RARC. Worldwide, the number of patients evaluated for continence after orthotopic bladder substitution is <200 from nine reports at the present time. There are also widespread differences in patient selection, methods of data collection, and outcome assessment. Follow-up for continence evaluation varied widely, from 6 to 25 mo. Nerve-sparing procedures were performed in 20–100% of patients. Only three of six series reported using a distinct definition for continence, which was generally no pad or one pad (safety) per day. One of the

earliest RARC series reported an 86% continent rate (seven of eight men) after 3.5 mo [9]. More recent series published 6-mo continence rates of 48–100% for daytime continence and 11–100% for nighttime continence. At 12 mo after RARC, continence rates ranged from 83% to 100% in men and were 67% in women for daytime continence and 66–76% for nighttime continence. Using strict definitions for daytime continence (no or one security pad per day) and nighttime continence (good indicates dry with no protection, fair indicates dry with one awakening), Canda et al examined 23 patients with intracorporeal Studer pouch. After excluding patients who died or were lost to follow-up, 11 of 15 men (73%) and 0 of 2 women were continent during the daytime. Three of these 17 patients (18%) had good nighttime continence, and 4 (24%) had fair continence [33].

Only one series has described continence results in patients undergoing RARC and continent cutaneous diversion. Torrey et al examined 34 patients who had RARC and Indiana pouch continent cutaneous diversion and reported 97% continence at a mean follow-up of 20 mo for both daytime and nighttime. One patient continued to experience daytime and nighttime incontinence requiring the use of pads [41].

3.4.2. Potency recovery after robot-assisted radical cystectomy

Table 7 summarizes the series examining potency outcomes. Similar to continence outcomes, evaluation of erectile function after RARC is not well described. Early reports suggest that erections sufficient for penetration are achievable, although sample sizes were very small and lacked validated objective evaluations. Follow-up was again too short to form definitive conclusions, with only one study reporting outcomes up to 2 yr after RARC. As noted earlier, nerve-sparing procedures were performed in 20–100% of patients. The data recording used

International Index of Erectile Function (IIEF) scores in five of seven series. However, only three series provided a clear definition of potency [12,35,56].

In some early, small series, Mottrie et al [9] and Murphy et al [12] reported sufficient erections in six of seven and three of four men, respectively. Similar to well-described literature on RARP, phosphodiesterase type 5 inhibitors (PDE5-Is) were frequently administered to patients for penile rehabilitation after RARC; however, no comparative data in this setting have demonstrated a benefit.

Several series with intracorporeal neobladder have evaluated erectile function postoperatively, with varying results. In the experience of the Karolinska Institute, 41 of 62 men (66%) underwent nerve-sparing RARC. Of these 41 men, 26 (63%) were potent with or without the use of PDE5-Is after 12 mo [56]. In contrast, Canda et al found IIEF scores >18 in only 1 of 11 preoperatively potent men, although follow-up was shorter (6 mo) [33].

3.5. Cumulative analysis of studies comparing robot-assisted radical cystectomy with open or laparoscopic radical cystectomy

Table 8 summarizes comparative studies evaluating lymph node yield after ORC, LRC, and RARC. In two randomized studies of ORC compared with RARC, lymph node yields were not statistically different [74,83]. Cumulative analyses showed no significant difference in lymph node yield between RARC and ORC (OR: 2.94; 95% CI, −0.28 to 6.15; p = 0.07) (Fig. 2).

Table 9 summarizes PSM rates in RARC, ORC, and LRC. In two randomized trials comparing RARC and ORC, Nix et al and Parekh et al did not show any increase in positive margins with RARC [74,83]. Cumulative analyses showed no significant difference in rates of surgical margins between RARC and ORC (5% and 7%, respectively; OR: 0.71; 95% CI, 0.46–1.1; p = 0.13) (Fig. 3). In two comparative nonrandomized studies between RARC and LRC, no

significant differences in PSM rates were detected (p = 0.86) [87,89].

Table 10 summarizes series that emphasized early oncologic comparisons for RARC, LRC, and ORC, though interpretation should be cautious with small series of shorter follow-up and potential bias of patient selection. A nonrandomized comparison of ORC (n = 52) with RARC (n = 48) with a follow-up of 38 mo showed disease-specific survival of 69% in the ORC group compared with 79% in the RARC group [87]. A series by Nepple et al showed similar estimates in DFS, CSS, and OS, although patients were not matched [82].

3.6. Discussion

Our systematic review sought to identify and report the current state of the literature for RARC with regard to pathologic, oncologic, and functional outcomes. Various oncologic parameters, including pathologic findings and postoperative survival rates, were examined. With regard to nodal dissection, robotic ELND achieves a similar nodal yield to open ELND when performed by experienced surgeons. Nearly all RARC series reported nodal yields >15. With regard to margin rates, most series reported PSM rates of <10%, with rates of approximately 1% in pT2 disease. Although the IRCC (n = 513) reported a very high positive margin rate of 39% in pT4 patients, other authors have reported rates similar to those noted in ORC series.

Although these immediate pathologic variables may act as surrogates for quality of resection, long-term survival outcomes must be analogous to those of ORC for RARC to be a viable surgical option. Currently, oncologic data are immature, and adequate comparative studies of RARC and ORC are nonexistent. In a few analyses measuring CSS and OS at 5 yr postoperatively, results appear similar to those reported in ORC; however, larger numbers and longer follow-up are needed for adequate comparison. At present, data reporting functional analysis of continence and potency recovery after RARC are inadequate to compare RARC

reliably with ORC.

PLND, in conjunction with radical cystectomy, provides a staging benefit as well as a possible advantage for survival in retrospective studies. Stein et al examined 1054 patients treated with radical cystectomy and PLND with a 24% node-positive rate; these patients experienced 5- and 10-yr recurrence-free survival of 35% and 34%, respectively [2]. Although prospective validation is necessary, Leissner et al suggested that ELND improved outcomes in both low-volume node-positive and node-negative patients with greater number of lymph nodes removed [93]. The true survival benefit of ELND must be proven in a prospective fashion to overcome the Will Rogers phenomenon of apparent improved survival that results from stage migration with more thorough dissection.

Early critical concerns of RARC involved whether LND could be performed robotically with the same quality as during ORC. This review suggests that thorough robotic ELND dissection at the time of RARC is possible following a similar template as is performed during ORC. Half of current RARC series describe an extended template dissection, with the average number of lymph nodes removed between 11 and 55. In a small study of open completion LND after robotic LND, only four additional lymph nodes were recovered [34]. Although few series described the time necessary to perform a complete robotic LND, some authors described operative times approaching 2 h for the node dissection alone, suggesting that robotic LND may lengthen operative time. Further study is necessary to determine whether the LND segment of RARC is significantly longer compared with open LND. Complications specific to LND—particularly vascular injuries—were rare, as were lymphoceles, with an incidence <10%. However, complication rates may often be underreported, as reporting guidelines lack standardization.

Assessment of RARC lymph node yields as related to patient characteristics (eg, BMI) or surgeon characteristics (eg, prior RARP experience) has not shown a specific association. Similar to the ORC literature, Bochner et al reported that only extent of LND was associated with lymph node yield when examining variables such as receipt of neoadjuvant chemotherapy, pathologic stage, surgeon, and pathologist [94]. Although performance of LND was associated with higher surgeon volume, analysis of several learning curve evaluations did not find increases in lymph node yield with increasing case number. This result may seem counterintuitive, but it may be that these experienced robotic surgeons were able to translate surgical technique from RARP and PLND and thus reduce the number of cases needed to reach stable lymph node yields. Instead, a reduction in LND time could occur with experience, although it has not been specifically examined. In the IRCC database, patients with pT4 disease had lower nodal yields, possibly related to more difficult dissection or to RARC being performed for palliative intent.

PSM at cystectomy is a measure of disease burden and a predictor of outcome. In a previous study of 1589 patients who underwent radical cystectomy at Memorial Sloan Kettering Cancer Center, the positive margin rate was 4.2%. Risk factors for PSMs were female sex, higher pathologic stage, vascular invasion, mixed histology, and lymph node involvement. Patients with PSMs had a 5-yr CSS of only 32% [95]. In another large multi-institutional analysis of 4400 ORC patients, the incidence of PSMs was 6.3% [96]. A potential challenge of RARC and limitation of current robotic technology is in treating bulkier tumors because of the lack of tactile feedback.

The present systematic review demonstrates that PSMs are uncommon in RARC series and appropriately rare for pT2 disease. No significant difference was found when comparing the surgical margin rate between RARC and ORC. The high variability of positive margins across

studies, between 0% and 26%, suggests significant heterogeneity in cancer characteristics, patient selection, and surgical technique and experience, among other variables. From the systematic review, the weighted average of positive margins in RARC series was 5.6%, which is comparable to the large open series cited earlier. In the aforementioned analysis of 4400 ORC patients, margin-positive rates by stage were 2.3% for pT2, 7.6% for pT3, and 24% for pT4 disease [96]. The effects of the learning curve as institutions adopted this new technology and patient selection toward earlier stage disease likely affected reported margin rates and should be considered when interpreting outcomes. Nonetheless, higher reported rates of positive margins in pT4 disease in some RARC series suggest that caution be taken for higher stage disease, with particular attention paid to the risk of margin involvement.

Several RARC series did not show decreasing margin rates with sequential case volume. A few reasons could explain this observation: (1) The positive margin numbers may be too low to detect a subgroup difference; (2) the learning curve for reducing margins at RARC could be extremely high, with a number not yet reached in smaller learning curve assessments; or (3) over time, more experienced surgeons may be more willing to take on bulky or higher stage tumors. This final hypothesis is supported by a multivariate analysis adjusting for pathologic stage that shows that differences in stage of disease accounted for an increase in margin rates with more experienced robotic surgeons [61].

Chemotherapy use alongside surgery in the treatment of MIBC can be implemented either before or after cystectomy. While neoadjuvant chemotherapy has been shown to confer an OS advantage of 5% in randomized trials [97], the benefit of adjuvant chemotherapy is less proven. In a recent meta-analysis of nine randomized controlled trials comprising 945 patients that investigated the use of adjuvant chemotherapy, benefits to both OS and DFS were appreciated.

Patients receiving adjuvant chemotherapy after cystectomy had 23% relative risk reduction in the risk of death (OS: p = 0.049) and 34% relative decrease in the risk of disease recurrence (DFS: p = 0.014) [98]. For the current systematic review, neoadjuvant chemotherapy use was 0–31%, and adjuvant chemotherapy was delivered to 4–22% of patients. Adjuvant therapy was chiefly administered in patients with advanced-stage pT3 or higher or with positive lymph nodes. Although time to initiation of adjuvant chemotherapy was shorter by 3 wk in the analysis by Pruthi et al, further validation is required [31].

Long-term freedom from disease recurrence and bladder cancer–related death is the primary measure of treatment efficacy with radical cystectomy. Particularly with assessments of survival, gathering data for comparison with the open standard is challenging secondary to the necessity of controlling for cancer characteristics, additional therapies, and the length of follow-up required to detect significant differences. Shorter-interval examinations of survival may not amply capture events such as local recurrence, distant recurrence, or secondary therapies. Only two series in this systematic review compared survival for RARC and ORC. These studies were not randomized and included sequential series of retrospective groups (LOE 4) [82,87]. In a series by Nepple et al, 36 patients who underwent RARC were compared with 29 patients who underwent ORC with a median follow-up of only 12 mo. Estimated 2-yr DFS (67% vs 58%), CSS (75% vs 63%), and OS (68% vs 63%) after RARC and ORC were similar for the two techniques, respectively [82].

Because of limitations of present studies, comparisons must be made to large historical retrospective open series. A long-term analysis of survival in 1100 chemotherapy-naive cystectomy patients by Hautmann et al demonstrated 10-yr CSS and OS rates of 67% and 44%, respectively [99]. For this systematic review, 5-yr estimates for DFS, CSS, and OS were 63–

74%, 66–80%, and 39–66%, respectively. Analogous to stratified outcomes in ORC, survival outcomes were worse in RARC series with increasing pathologic stage and with lymph node metastases. Local control of disease appears to be adequate such that the majority of recurrences after RARC are distant or outside the pelvis. A potential concern for port-site metastases with RARC remains of particular interest. Although no specific published series address this concern and most larger RARC oncologic series did not report any incidents, a few case reports suggest that this concern requires further study.

Since the original description of neurovascular bundle preservation during radical prostatectomy by Walsh et al, techniques to improve functional outcomes through meticulous nerve sparing have been translated to radical cystectomy. Turner et al determined that nerve sparing improved urinary continence after orthotopic urinary diversion [100], and nerve sparing has been shown to assist with recovery of erectile function objectively based on IIEF [101]. Long-term functional evaluations of ileal neobladder continent diversions have demonstrated daytime continence rates of 92% and nighttime continence rates of 80% [102].

To date, very limited data are available regarding functional outcomes of continence or potency after RARC. These analyses have chiefly been limited to only a few centers that exhibit significant heterogeneity. The 12-mo reported continence rates were 88–100% in men and 67% in women for daytime continence and between 66% and 75% for nighttime continence. Potency recovery exhibited even greater variation, with sufficient erection rates between 9% and 81%. Functional outcomes are likely influenced by patient factors and selection, comorbidity, prior treatments, surgeon experience, and technique (eg, the use of cautery vs clips). In addition, methodology of reporting, definitions of continence, measurement tools, rehabilitation programs, and inconsistencies in follow-up can affect the actual measurement of continence and potency.

Specific functional concerns of RARC related to patient selection are that many patients may be older or have poor baseline erectile function. Moreover, technical concerns for a possible PSM, which portends a dismal outcome, may affect the performance of nerve sparing. The lack of conclusive data regarding functional recovery after RARC is a necessary area for future study. There is no evidence to date that the results from a recent systematic review on RARP finding slight advantages to continence and potency recovery compared with open radical prostatectomy or laparoscopic radical prostatectomy extrapolate to RARC [103]. Precise definitions of continence and potency are necessary so that future data acquisition can be carried out in a standardized, stringent, and uniform fashion for both ORC and RARC.

From a methodological perspective, the most relevant limitations of this systematic review are the quality of the available studies, the small number of patients in and the retrospective nature of most series, the shorter-term follow-up of these studies, and the lack of standardized definitions. The papers included in the present review included only two small randomized controlled trials; the remaining series are LOE 3 or 4. Comparisons made in these single-institution studies inevitably carry the risk of selection bias. Even in randomized controlled studies, there were unlikely to have been equally experienced open and robotic surgeons operating on comparable patients. Heterogeneity in lymph node templates, sampling methods, specimen handling, and pathologic review may affect lymph node yields. Most cumulative outcomes were weighted by the results of experienced surgeons, which may make conclusions difficult to generalize. The inability to account for surgeon factors or specific technique modifications is another limitation. Most series failed to provide specific information concerning relevant aspects of the reconstructive portions of the operation.

4. Conclusions

Sufficient lymph node yields are achievable through robotic PLND if an extended template is followed. PSM rates appear similar with RARC and ORC. Conclusive long-term survival outcomes for RARC are limited, although oncologic outcomes of ≤5 yr are similar to those reported for ORC. Initial functional outcomes appear favorable; however, additional research on continence and potency after RARC is needed.

Author contributions: Bertram Yuh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yuh, Wilson, Bochner, Montorsi, Chan, Thalmann, Palou, Stenzl, Guru, Catto, Novara, Wiklund.
Acquisition of data: Yuh, Wilson, Bochner, Montorsi, Chan, Thalmann, Palou, Stenzl, Guru, Catto, Novara, Wiklund.
Analysis and interpretation of data: Yuh, Novara.
Drafting of the manuscript: Yuh, Wilson, Bochner, Montorsi, Chan, Thalmann, Palou, Stenzl, Guru, Catto, Novara, Wiklund.
Critical revision of the manuscript for important intellectual content: Yuh, Wilson, Bochner, Montorsi, Chan, Thalmann, Palou, Stenzl, Guru, Catto, Novara, Wiklund.
Statistical analysis: Yuh, Novara.
Obtaining funding: Wilson.
Administrative, technical, or material support: Yuh, Wilson, Bochner, Montorsi, Chan, Thalmann, Palou, Stenzl, Guru, Catto, Novara, Wiklund.
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Figure legends

Fig. 1 – Flowchart of the systematic review.

Fig. 2 – Comparison of lymph node yields following robot-assisted or open radical cystectomy.

CI = confidence interval; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation.

Fig. 3 – Comparison of positive surgical margin rates following robot-assisted or open radical cystectomy.

CI = confidence interval; M-H = Mantel-Haenszel; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

Table

Table 1 – Lymph node yields in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases, no.	Study design	Extension of LND	Operative time, min	Retrieved nodes, no.	pN+, %	Metastatic nodes, median, no.	Complications due to LND
Menon et al, 2003 [4]	Henry Ford Hospital	1	17	Retrospective	Standard	–	–	6	–	–
Menon et al, 2004 [7]	Henry Ford Hospital	1	3 female	Retrospective	Standard	–	12	0	–	–
Guru et al, 2007 [8]	Roswell Park Cancer Institute	1	20	Prospective	Standard	44	13	15	1	–
Mottrie et al, 2007 [9]	O.L.V.–Clinic	2a	27	Retrospective	Extended	–	23	9	–	–
Pruthi et al, 2008 [71]	UNC	2a	20	Retrospective	Standard	–	19	10	–	–
Hemal et al, 2008 [10]	All India Institute of Medical Sciences	1	6	Retrospective	Standard	–	12	17	–	–
Lowentritt et al, 2008 [11]	Tulane University	2a	4	Retrospective	Standard	–	12	25	–	–
Murphy et al, 2008 [12]	Guy's Hospital	2a	23	Retrospective	Standard	–	16	9	–	–
Park et al, 2008 [13]	Yonsei	2a	4	Retrospective	Standard	–	17	0	–	–
Pruthi et al, 2008 [14]	UNC	2a	12 female	Retrospective	Standard, then extended	–	19	17	–	–
Pruthi et al, 2008 [15]	UNC	2b	50	Retrospective	Standard	–	19	20	–	–
Wang et al, 2008 [72]	Cornell	2b	33	Retrospective	Standard	–	17	19	–	–
Woods et al, 2008 [16]	Mayo Arizona Tulane University	2b	27	Multi-institutional	Extended	–	12.3	33	3.1	0
Yuh et al, 2008 [17]	Roswell Park Cancer Institute	2a	54	Retrospective	Extended	–	17	–	–	–
Gamboa et al , 2009 [18]	University of California, Irvine	2a	41	Retrospective	Standard	–	23	14	4	–
Pruthi et al, 2009 [19]	UNC	2b	50 10 female 40 male	Retrospective	Standard, then extended	–	19 19 18	16	–	–

Palou Redorta et al, 2009 [20]	Barcelona Autonomous University	2a	9	Retrospective	Extended	60	10	0	–	–
Yuh et al, 2009 [21]	Roswell Park Cancer Institute	2b	73	Retrospective	Extended	–	19	–	–	–
Guru et al, 2010 [22]	Roswell Park Cancer Institute	2a	26	Prospective	Extended	–	21	29	1	Internal iliac artery injury: 1
Hellenthal et al, 2011 [23]	IRCC	2b	437	Multi-institutional	–	–	17	20	–	–
Josephson et al, 2010 [24]	City of Hope Cancer Center	2b	58	Retrospective	Extended	–	27	24	–	–
Kang et al, 2010 [25]	Multicenter	2b	71 standard LND	Retrospective	Standard	–	15.7	10	–	–
			33 extended LND		Extended		24.7			
Kasraeian et al, 2010 [26]	Montsouris Institute	2a	9	Retrospective	Extended	–	11	22	–	0
Kauffman et al, 2011 [27]	Cornell	2b	85	Retrospective	Extended	–	19	15	–	–
Kwon et al, 2010 [28]	Kyungpook National University	2a	17	Prospective	Standard	–	6	6	1	0
Lavery et al, 2011 [29]	Ohio State University	2a	15	Retrospective	Extended	107	41.8	20	–	0
Martin et al, 2010 [30]	Mayo Arizona	2b	59	Multi-institutional	Extended	–	–	34	–	–
	Tulane University									
Ng et al, 2010 [73]	Cornell	2b	83	Retrospective	Standard	–	16	16	–	–
Nix et al, 2010 [74]	UNC	3	21	RCT	Standard	–	19	19	–	–
Pruthi et al, 2010 [31]	UNC	2b	100	Retrospective	Standard, then extended	–	19	20	–	–
Richards et al, 2010 [75]	Wake Forest University	2b	35	Retrospective	Extended	–	16	29	–	–
Akbulut et al, 2011 [32]	Ankara Ataturk Training and Research Hospital	2a	12	Not reported	Extended	–	21.3	42	–	8
Canda et al, 2012 [33]	Ankara Ataturk Training and Research Hospital	2a	27	Not reported	Extended	–	24.8	22	–	–
Davis et al, 2011 [34]	University of Texas M.D. Anderson Cancer Center	2a	11	Retrospective	Extended	117	43	9	1	–
Jonsson et al, 2011 [35]	Karolinska Institute	2b	45	Prospective	Standard	–	19	20	–	–
			36		Extended		19	17		

			neobladder							
			9 ileal conduit				27	33		
Khan et al, 2011 [36]	Guy's Hospital	2a	50	Prospective	–	–	17	–	–	–
Manoharan et al, 2011 [37]	University of Miami	2a	14	Retrospective	Standard	–	12	–	–	–
Martin et al, 2011 [76]	Mayo Arizona	2b	19	Retrospective	–	–	16	–	–	–
Richards et al, 2011 [38]	Wake Forest University	2b	60	Retrospective	Extended	–	17	30	–	Lymphocele: 1
Schumacher et al, 2011 [39]	Karolinska Institute	2b	45	Retrospective	Standard 49%, extended 31%	–	22.5	–	1.5	Lymphocele: 2
Shah et al, 2011 [40]	Ohio State University	2b	30	Retrospective	Extended	–	–	30	–	–
Torrey et al, 2011 [41]	City of Hope Cancer Center	2b	34	Retrospective	Extended	–	28.9	–	–	–
Cho et al, 2012 [42]	Hallym University College of Medicine	2b	35	Retrospective	Standard	–	–	6	–	–
Goh et al, 2012 [43]	Keck School of Medicine, University of Southern California, Los Angeles	2a	15	Prospective	Superextended	–	55	26	–	–
Lau et al, 2012 [44]	City of Hope Cancer Center	2b	23 (aged >80 yr)	Retrospective	Extended	–	20.4	22	–	–
Mmeje et al, 2013 [45]	Mayo Arizona UNC	2b	50	Multi-institutional	Extended	–	18	100	3	–
Poch et al, 2012 [46]	Roswell Park Cancer Institute	2b	56	Retrospective	–	–	25	16	–	–
Richards et al, 2012 [77]	Wake Forest University	2b	20 (aged >75 yr)	Retrospective	Extended	–	17	35	–	–
Saar et al, 2013 [47]	Saarland University	2b	62	Retrospective	–	–	14.2	21	–	–
Smith et al, 2012 [48]	Mayo Arizona UNC, Tulane University	2b	227	Multi-institutional	–	–	18	20	–	–
Styn et al, 2012 [78]	University of Michigan	2b	50	Retrospective	–	–	14.3	12	–	–
Sung et al, 2012 [79]	Samsung Medical Center	2b	35	Retrospective	Standard	–	19.1	26	–	Lymphocele: 1
Treiyer et al, 2012 [49]	Saarland University	2b	91	Retrospective	Standard	–	14.5	14	–	–

Tsui et al, 2012 [50]	Chang Gung Memorial Taiwan	2a	8	Retrospective	Standard	–	3	12.50	–	–
Yuh et al, 2012 [51]	City of Hope Cancer Center	2b	196	Retrospective	Extended	–	28	22	–	Lymphocele: 3
Collins et al, 2013 [52]	Karolinska Institute	2b	113	Prospective	Extended 56%, standard 34%, limited 5%, none 5%	–	21	20	–	Lymphocele: 5
Johar et al, 2013 [53]	IRCC	2b	939	Multi-institutional	–	–	18.1	26	–	–
Maes et al, 2013 [80]	Metro Health Hospital	2b	14	Retrospective	Extended	–	11.9	7	–	–
Marshall et al, 2013 [54]	IRCC	2b	765	Multi-institutional	Extended 58%, standard 40%, no LND 2%	–	18	27	–	–
Musch et al, 2014 [81]	Klinikin Essen–Mitte	2b	100	Prospective	–	–	26.5	20	–	Lymphocele: 4
Nazmy et al, 2014 [55]	City of Hope Cancer Center	2b	209	Retrospective	Extended	–	–	22	–	Lymphocele: 3
Nepple et al, 2013 [82]	Washington University	2b	36	Retrospective	Standard	–	17	22	–	–
Parekh et al, 2013 [83]	University of Texas Health Sciences Center at San Antonio	3	20	RCT	Standard	–	11	20	–	–
Tyritzis et al, 2013 [56]	Karolinska Institute	2b	70	Retrospective	Standard 43% Extended 48%	–	21	14	–	Lymphocele: 6 Lymphedema: 1
Xylinas et al, 2013 [57]	Cornell	2b	175	Retrospective	Standard	–	19	17	–	Lymphocele: 2
Phillips et al, 2014 [69]	Seward St. Elizabeth Medical Center	2b	23 (>80 yr)	Retrospective	Extended	–	19	–	–	
Raza et al, in press [70]	Roswell Park Cancer Institute	2b	99	Retrospective	–	–	20.7	36	–	–
Yuh et al, 2014 [58]	City of Hope Cancer Center	2b	162	Retrospective	Extended	–	28	23	–	–
Total							19.3	23		

IRCC = International Robotic Cystectomy Consortium; LND = lymph node dissection; RCT = randomized controlled trial; UNC = University of North Carolina.

Table

Table 2 – Impact of patient characteristics and surgical aspects on lymph node yield in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases	Study design	Extension of LND	Operative time, min	Retrieved nodes, no.	pN+, %
Patient BMI								
Poch et al, 2012 [46]	Roswell Park Cancer Institute	2b	56	Retrospective	–	–	25	16
			BMI <25: 14				22	7
			BMI 25 to <30: 21				23	14
			BMI ≥30: 21				20	24
Case volume								
Guru et al, 2008 [59]	Roswell Park Cancer Institute	2a	1–12	Prospective	Extended	46	33% >13	8
			13–24			44	66% >13	33
			25–36			41	83% >13	25
			37–47			43	72% >13	64
			48–58			56	91% >13	18
Pruthi et al, 2008 [60]	University of North Carolina	2b	50	Retrospective	Standard	–	19	–
			1–10				21	
			11–20				19	
			21–30				20	
			31–40				17	
			41–50				20	
Richards et al, 2011 [38]	Wake Forest University	2b	60	Retrospective	Extended	–	17	30
			1–20				17	
			21–40				19.1	
			41–60				14.4	
Schumacher et al, 2011 [39]	Karolinska Institute	2b	45	Retrospective	Standard 49% Extended 31%	–	22.5	–
			1–15		Standard 40% Extended 7%			
			16–30		Standard 47% Extended 53%			

			31–45		Standard 60% Extended 33%			
Prior RARP experience								
Hayn et al, 2010 [61]	IRCC	2b	496	Retrospective	–	–	17.8	–
			≤50 previous RARP: 83				13.7	
			51–100 previous RARP: 187				19.8	
			101–150 previous RARP: 176				19.6	
			>150 previous RARP: 50				11.8*	

BMI = body mass index; RCC = International Robotic Cystectomy Consortium; LND = lymph node dissection; RARP = robot-assisted radical prostatectomy.

* Statistically significant.

Table

Table 3 – Positive surgical margins in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases, no.	Study design	Pathologic stage, %		Overall PSM rate, %	PSM location	PSM rate, %	
					≤pT2	≥pT3			≤pT2	≥pT3
Menon et al, 2003 [4]	Henry Ford Hospital	1	17	Retrospective	–	–	0	–	0	0
Yohannes et al, 2003 [62]	Creighton University	1	2	Retrospective	0	100	0	–	0	0
Menon et al, 2004 [7]	Henry Ford Hospital	1	3 female	Retrospective	66	33	0	–	0	0
Rhee et al, 2006 [84]	University of Virginia	1	7	Retrospective	43	57	0	–	0	0
Guru, et al, 2007 [8]	Roswell Park Cancer Institute	1	20	Prospective	40	60	15	Prostate: 1 Ureter: 1 Vagina: 1	0	25
Mottrie et al, 2007 [9]	O.L.V.–Clinic	2a	27	Retrospective	78	22	4	Ureter: 1	–	–
Pruthi et al, 2008 [71]	UNC	2a	20	Retrospective	70	20	0	–	0	0
Hemal et al, 2008 [10]	All India Institute of Medical Sciences	1	6	Retrospective	67	33	0	–	0	0
Lowentritt et al, 2008 [11]	Tulane University	2a	4	Retrospective	25	75	0	–	0	0
Murphy et al, 2008 [12]	Guy's Hospital	2a	23	Retrospective	74	17	0	–	0	0
Park et al, 2008 [13]	Yonsei	2a	4	Retrospective	50	50	0	–	0	0
Pruthi et al, 2008 [14]	UNC	2a	12 female	Retrospective	58	25	0	–	0	0
Pruthi et al, 2008 [15]	UNC	2b	50	Retrospective	66	14	0	–	0	0
Pruthi et al, 2009 [19]	UNC	2b	50	Retrospective	66	18	0	–	0	0
			10 female		50	30				
			40 male		70	15				
Wang et al, 2008 [72]	Cornell	2b	33	Retrospective	72	28	6	Perivesical fat: 2	0	22
Woods et al, 2008	Mayo Arizona	2b	27	Multi-institutional	–	–	7	–	0	–

[16]	Tulane University									
Yuh et al, 2008 [17]	Roswell Park Cancer Institute	2a	54	Retrospective	44	56	13	–	0	23
Gamboa et al, 2009 [18]	University of California, Irvine	2a	41	Retrospective	–	–	5	–	0	–
Palou Redorta et al, 2009 [20]	Barcelona Autonomous University	2a	9	Retrospective	66	33	11	–	–	–
Yuh et al, 2009 [21]	Roswell Park Cancer Institute	2b	73	Retrospective	45	55	10	–	0	18
Guru et al, 2010 [22]	Roswell Park Cancer Institute	2a	20	Prospective	62	38	4	–	0	9
Hayn et al, 2010 [61]	IRCC	2b	482	Multi-institutional	64	36	7	–	–	–
Hellenthal et al, 2010 [68]	IRCC	2b	513	Multi-institutional	64	36	7	–	1.50	17
Kang et al, 2010 [25]	Multicenter	2b	104	Multi-institutional	70	30	5	–	–	–
Kasraeian et al, 2010 [26]	Montsouris Institute	2a	9	Retrospective	44	66	0	–	–	–
Kauffman et al, 2011 [27]	Cornell	2b	85	Retrospective	64	36	6	–	0	16
Kwon et al, 2010 [28]	Kyungpook National University	2a	17	Prospective	59	41	0	–	0	0
Martin et al, 2010 [30]	Mayo Arizona Tulane University	2b	59	Multi-institutional	47	53	–	–	–	–
Ng et al, 2010 [73]	Cornell	2b	83	Retrospective	61	39	7	–	0	19
Nix et al, 2010 [74]	UNC	3	21	RCT	67	14	0	–	0	0
Pruthi et al, 2010 [31]	UNC	2b	100	Retrospective	67	13	0	–	0	0
Richards et al, 2010 [75]	Wake Forest University	2b	35	Retrospective	60	40	3	–	–	–
Akbulut et al, 2011 [32]	Ankara Ataturk Training and Research Hospital	2a	12	Not reported	58	42	0	–	0	0

Canda et al, 2012 [33]	Ankara Ataturk Rraining and Research Hospital	2a	27	Not reported	56	44	4	–	0	4
Davis et al, 2011 [34]	University of Texas M.D. Anderson Cancer Center	2a	11	Retrospective	92	8	0	–	–	–
Jonsson et al, 2011 [35]	Karolinska Institute	2b	45	Prospective	78	22	2	–	0	10
Khan et al, 2011 [36]	Guy's Hospital	2a	50	Prospective	72	28	2	–	0	7
Manoharan et al, 2011 [37]	University of Miami	2a	14	Retrospective	–	–	0	–	0	0
Martin et al, 2011 [76]	Mayo Arizona	2b	19	Retrospective	42	58	–	–	–	–
Richards et al, 2011 [38]	Wake Forest University	2b	60	Retrospective	63	37	10	–	–	–
Schumacher et al, 2011 [39]	Karolinska Institute	2b	45	Retrospective	78	22	2	Ureter: 1	0	10
Shah et al, 2011 [40]	Ohio State University	2b	30	Retrospective	65	35	7	–	0	22
Cho et al, 2012 [42]	Hallym University College of Medicine	2b	35	Retrospective	86	14	3	–	–	–
Goh et al, 2012 [43]	Keck School of Medicine, University of Southern California, Los Angeles	2a	15	Prospective	67	33	0	–	–	–
Lau et al, 2012 [44]	City of Hope Cancer Center	2b	23 (aged >80 yr)	Retrospective	61	39	13	Ureter: 1	–	–
Mmeje et al, 2013 [45]	Mayo Arizona UNC	2b	50	Multi-institutional	34	66	2	–	–	–
Poch et al, 2012 [46]	Roswell Park Cancer Institute	2b	56	Retrospective	55	45	–	–	–	–
Richards et al, 2012 [77]	Wake Forest University	2b	20 (aged >75 yr)	Retrospective	60	40	5	–	–	–

Saar et al, 2013 [47]	Saarland University	2b	62	Retrospective	64	36	2	–	–	–
Smith et al, 2012 [48]	Mayo Arizona UNC, Tulane University	2b	227	Multi-institutional	–	–	2	–	–	–
Styn et al, 2012 [78]	University of Michigan	2b	50	Retrospective	60	40	2	–	–	–
Sung et al, 2012 [79]	Samsung Medical Center	2b	35	Retrospective	43	57	–	–	–	–
Treiyer et al, 2012 [49]	Saarland University	2b	91	Retrospective	67	33	2	Urethra: 1 Prostate: 1	–	–
Tsui et al, 2012 [50]	Chang Gung Memorial	2a	8	Retrospective	75	25	0	–	0	0
Yuh et al, 2012 [51]	City of Hope Cancer Center	2b	196	Retrospective	64	36	4	–	–	–
Azzouni et al, 2013 [63]	Roswell Park Cancer Institute	2b	100	Retrospective	35	65	4	–	–	–
Collins et al, 2013 [52]	Karolinska Institute	2b	113	Prospective	75	25	5	Ureter: 1	1	18
Johar et al, 2013 [53]	Multicenter	2b	939	Retrospective	49	51	9	–	–	–
Maes et al, 2013 [80]	Metro Health Hospital	2b	14	Retrospective	43	57	21	–	–	–
Marshall et al, 2013 [54]	IRCC	2b	765	Multi-institutional	59	41	–	–	–	–
Musch et al, 2014 [81]	Klinikin Essen–Mitte	2b	100	Prospective	61	39	2	–	–	–
Nazmy et al, 2014 [55]	City of Hope Cancer Center	2b	209	Retrospective	65	35	3	–	–	–
Nepple et al, 2013 [82]	Washington University	2b	36	Retrospective	53	47	6	–	0	12
Parekh et al, 2013 [83]	University of Texas Health Sciences Center at San Antonio	3	20	RCT	50	50	5	–	0	10
Tyritzis et al, 2013 [56]	Karolinska Institute	2b	70	Retrospective	86	14	1.5	Ureter: 1	0	10
Xylinas et al, 2013 [57]	Cornell	2b	175	Retrospective	65	35	5	–	–	–
Phillips et al, 2014 [69]	Seward St. Elizabeth Medical	2b	23 (aged >80 yr)	Retrospective	30	70	26	–	–	–

	Center									
Raza et al, in press [70]	Roswell Park Cancer Institute	2b	99	Retrospective	48	52	8	–	–	
Yuh et al, 2014 [58]	City of Hope Cancer Center	2b	162	Retrospective	67	33	4	–	–	–
Total					60	40	5.6			

IRCC = International Robotic Cystectomy Consortium; PSM = positive surgical margin; RCT = randomized controlled trial; UNC = University of North Carolina.

Table

Table 4 – Predictors of positive surgical margins in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases	Study design	Pathologic stage,%		Overall PSM rate, %	PSM rate, %	
					≤pT2	≥pT3		≤pT2	≥pT3
Case volume									
Guru et al, 2008 [59]	Roswell Park Cancer Institute	2a	1–12	Prospective	33	66	17	–	–
			13–24		58	42	25		
			25–36		50	50	0		
			37–47		46	54	9		
			48–58		64	36	0		
Hayn et al, 2011 [64]	Roswell Park Cancer Institute	2a	1–50	Prospective	51	49	8	–	–
			51–100				12		
			101–164				6		
Richards et al, 2011 [38]	Wake Forest University	2b	60	Retrospective	63	37	10	–	–
			1–20		55	45	5		
			21–40		70	30	5		
			41–60		65	35	20		
Schumacher et al, 2011 [39]	Karolinska Institute	2b	45	Retrospective	78	22	2	0	10
			1–15		87	13	0		
			16–30		67	33	7		
			31–45		80	20	0		
Azzouni et al, 2013 [63]	Roswell Park Cancer Institute	2b	100	Retrospective	35	65	4	–	–
			1–25		36	64	4		
			26–50		40	60	4		
			51–75		44	56	4		
			76–100		20	80	4		
Previous RARP experience									
Hayn et al, 2010 [61]	IRCC	2b	482	Retrospective	64	36	7	–	–
			≤50 previous RARP: 83		68	32	4		
			51–100 previous RARP:		76	24	5		

			173						
			101–150 previous RARP: 168		54	46	9.5		
			>150 previous RARP: 48		42	58	12.5		
Patient BMI									
Butt et al, 2008 [65]	Roswell Park Cancer Institute	2a	BMI <25: 14	Retrospective	64	36	0	0	–
			BMI 25–29: 18		28	72	28		
			BMI ≥30: 17		42	58	6		
Poch et al, 2012 [46]	Roswell Park Cancer Institute	2b	56	Retrospective	55	45	–	–	–
			BMI <25: 14		50	50			
			BMI 25 to <30: 21		57	43			
			BMI ≥30: 21		52	48			
Intracorporeal vs extracorporeal diversion									
Kang et al, 2012 [85]	Korea University School of Medicine	2a	38 extracorporeal diversion	Retrospective	76	24	2.5	–	–
			4 intracorporeal diversion		100	0	0		

BMI = body mass index; IRCC = International Robotic Cystectomy Consortium; PSM = positive surgical margin; RARP = robot-assisted radical prostatectomy.

Table

Table 5 – Survival outcomes in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases, no.	Study design	Follow-up, mo	Neoadjuvant chemotherapy, %	Adjuvant chemotherapy, %	DFS estimates, %			CSS estimates, %			OS estimates, %		
								1 yr	3 yr	5 yr	1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Pruthi et al, 2008 [15]	UNC	2b	50	Retrospective	13.2	0	22	–	–	–	94 (13 mo)	–	–	90 (13 mo)	–	–
Murphy et al, 2008 [12]	Guy's Hospital	2a	23	Retrospective	17	29	–	91 (17 mo)	–	–	–	–	–	–	–	–
Josephson et al, 2010 [24]	City of Hope Cancer Center	2b	58	Retrospective	12	22	–	–	76 (2 yr)	–	–	76 (2 yr)	–	–	54 (2 yr)	–
Kang et al, 2010 [25]	Multicenter	2b	104	Retrospective	12	–	–	96	–	–	–	–	–	–	–	–
Kauffman et al, 2011 [27]	Cornell	2b	85	Retrospective	18	20	12	79	73 (2 yr)		88	85 (2 yr)		83	79 (2 yr)	
Martin et al, 2010 [30]	Mayo Arizona Tulane University	2b	59	Multi-institutional	21	17	–	82	71	–	–	–	–	82	72	–
Pruthi et al, 2010 [31]	UNC	2b	100	Retrospective	21.2	5	18	–	–	–	94 (21 mo)	–	–	91 (21 mo)	–	–
Canda et al, 2012 [33]	Ankara Ataturk Training and Research Hospital	2a	27	Not reported	6	–	4	85 (6 mo)	–	–	89 (6 mo)	–	–	72 (6 mo)	–	–
Mmeje et al, 2013 [45]	Mayo Arizona UNC	2b	50	Multi-institutional	41.5	12	46	–	43	39	–	–	–	–	55	45
Treiyer et al, 2012 [49]	Saarland University	2b	91	Retrospective	15	0	–	–	–	–	94 (15 mo)	–	–	93 (15 mo)	–	–
Collins et al, 2013 [52]	Karolinska Institute	2b	113	Prospective	25	31	–	–	–	–	–	81	67	–	80	66
Khan et al, 2013 [66]	Guy's & St. Thomas Hospital	1	14	Prospective	84	28	14	50			75			64		
Nepple et	Washington	2b	36	Retrospective	12	6	–	–	67	–	–	75	–	–	68	–

al, 2013 [82]	University								(2 yr)			(2 yr)			(2 yr)	
Snow-Lisy et al, 2014 [67]	Cleveland Clinic	2b	17	Retrospective	67	–	–	–	–	–	–	–	69	–	–	39
Tyritzis et al, 2013 [56]	Karolinska Institute	2b	70	Retrospective	30.3	24	–	–	81 (2 yr)	–	–	89 (2 yr)	–	–	89 (2 yr)	–
Xylinas et al, 2013 [57]	Cornell	2b	175	Retrospective	37		19	–	67	63	–	68	66	–	–	–
Raza et al, in press [70]	Roswell Park Cancer Institute	2b	99	Retrospective	73.9	6	29	–	–	53	–	–	68	–	–	42
Yuh et al, 2014 [58]	City of Hope Cancer Center	2b	162	Retrospective	52	23	–	–	76	74	–	83	80	–	61	54

CSS = cancer-specific survival; DFS = disease-free survival; OS = overall survival; UNC = University of North Carolina.

Table

Table 6 – Urinary continence rates in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases, no.	Study design	Nerve-sparing surgery, %	Intracorporeal diversion, %	Follow-up, mo	Method of data collection	*Continence* definition	Continence rate, %		
										3 mo	6 mo	12 mo
Mottrie et al, 2007 [9]	O.L.V.–Clinic	2a	27	Retrospective	29	0	10.2	–	–	86	–	–
Murphy et al, 2008 [12]	Guy's Hospital	2a	23	Retrospective	20	0	17	–	–	–	–	100 D 75 N (17 mo)
Palou Redorta et al, 2009 [20]	Barcelona Autonomous University	2a	9	Retrospective	100	0	7	–	–		100 D and N (7 mo)	
Canda et al, 2012 [33]	Ankara Ataturk Training and Research Hospital	2a	27	Not reported	89	100	6	–	D: 0–1 safety pads	–	48	–
									N: dry with no protection		11	
Jonsson et al, 2011 [35]	Karolinska Institute	2b	36	Prospective	55	100	25	–	0–1 pads	–	–	83 D 66 N
Manoharan et al, 2011 [37]	University of Miami	2a	14	Retrospective	–	0	–	–	–	93 D 71 N		
Torrey et al, 2012 [41]	City of Hope Cancer Center	2b	34	Retrospective	0	0 (all Indiana pouch)	12.1	Physician charting	–	–	–	97
Goh et al, 2012 [43]	Keck School of Medicine, University of Southern California, Los Angeles	2a	15	Prospective	–	100	3	–	–	75		
Tyritzis et al, 2013 [56]	Karolinska Institute	2b	70	Retrospective	58 BNS 8 UNS	100	12	Internally validated questionnaire	0–1 pads	–	D: 77 men, 40 women	D: 88 men, 67 women

											N: 54 men, 40 women	N: 76 men, 76 women

BNS = bilateral nerve sparing; D = daytime; N = nocturnal; UNS = unilateral nerve sparing.

Table

Table 7 – Erectile function in robot-assisted radical cystectomy series

Reference	Institution	IDEAL stage	Cases, no.	Nerve-sparing surgery, %	Study design	Follow-up, mo	Method of data collection	*Potency* definition	Potency rate at follow-up
Mottrie et al, 2007 [9]	O.L.V.–Clinic	2a	27	29	Retrospective	10.2	–	–	86%
Murphy et al, 2008 [12]	Guy's Hospital	2a	23	20	Retrospective	17	IIEF	IIEF >21 with or without PDE5-I	75%
Palou Redorta et al, 2009 [20]	Barcelona Autonomous University	2a	9	100	Retrospective	7	–	–	100%
Akbulut et al, 2011 [32]	Ankara Ataturk Training and Research Hospital	2a	12	82 bilateral 9 unilateral	Not reported	7.1	IIEF	None provided	A single patient with IIEF >18
Canda et al, 2012 [33]	Ankara Ataturk Training and Research Hospital	2a	27	89	Not reported	6	IIEF	None provided	A single patient with IIEF >18
Jonsson et al, 2011 [35]	Karolinska Institute	2b	36	55	Prospective	25	IIEF	Adequate for penetration with or without PDE5-I	41% at 12 mo 75% of patients having nerve sparing
Tyritzis et al, 2013 [56]	Karolinska Institute	2b	70	58 bilateral 8 unilateral	Retrospective	12	IIEF	Adequate for penetration with or without PDE5-I	81% at 12 mo

IIEF = International Index of Erectile Function; PDE5-I = phosphodiesterase type 5 inhibitor.

Table

Table 8 – Comparative studies evaluating lymph node yield after open, laparoscopic, and robot-assisted radical cystectomy

Comparison	Level of evidence	Reference	Cases, no.	Study design	Extension of LND	Retrieved nodes, no.	pN+, no. (%)	Metastatic nodes, no., median
ORC vs RARC	2							
		Nix et al, 2010 [74]	21 RARC 20 ORC	RCT	Standard	19 18	4 (19) 7 (35)	–
		Parekh et al, 2013 [83]	20 RARC 20 ORC	RCT	Standard	17.2 ± 13 24.2 ± 16.4	4 (20) 4 (20)	–
	3							
		Pruthi et al, 2008 [71]	20 RARC 24 ORC	Gender matched Retrospective	Standard	19 16	2 (10) 5 (21)	–
		Wang et al, 2008 [72]	33 RARC 21 ORC	Nonmatched	Standard	17 20	19 34*	–
		Ng et al, 2010 [73]	83 RARC 104 ORC	Nonmatched	Standard	17.9 ± 10.4 15.7 ± 13.2	13 (16) 24 (23)*	–
		Richards et al, 2010 [75]	35 RARC 35 ORC	Nonmatched	Extended	16 15	10 (29) 10 (29)	–
		Martin et al, 2011 [76]	19 RARC 14 ORC	Nonmatched	–	16 13	–	–
		Gondo et al, 2012 [92]	11 RARC 15 ORC	Nonmatched	Extended	20.7 ± 8.2 13.8 ± 6.6*	9 13	–
		Khan et al, 2012 [87]	48 RARC 52 ORC	Prospective	Extended	16 11	5 15	–
		Richards et al, 2012 [77]	20 RARC 20 ORC (>75 yr)	Nonmatched	Extended	17 15	7 (35) 3 (15)	–
		Styn et al, 2012 [78]	50 RARC 100 ORC	1:2 by age, sex, clinical stage, diversion	–	14.3 ± 9.1 15.2 ± 9.5	6 (12) 19 (19)	–
		Sung et al, 2012 [79]	35 RARC 104 ORC	Nonmatched	Standard	19.1 ± 8.2 12.9 ± 9.0 *	9 (26) 27 (26)	–

		Knox et al, 2013 [86]	58 RARC 84 ORC	Nonmatched	Extended	21 17	1 3	–
		Maes et al, 2013 [80]	14 RARC 14 ORC	Nonmatched	Extended	11.9 9.5	1 (7) 5 (35)	–
		Musch et al, 2014 [81]	100 RARC 42 ORC	Nonmatched	–	27.5 ± 11.0 19.6 ± 8.8*	20 (20) 9 (21)	–
		Nepple et al, 2013 [82]	36 RARC 29 ORC	Nonmatched	Standard	17 14	8 (22) 7 (24)	–
	4	Abaza et al, 2012 [88]	35 RARC 120 ORC	Nonmatched	Extended	37.5 ± 13.2 36.9 ± 14.8	12 (34) 36 (30)	1.5 2
LRC vs RARC								
	3	Khan et al, 2012 [87]	48 RARC 58 LRC	Prospective	Extended	16 10	5 10	–
	4	Abraham et al, 2007 [89]	14 RARC 20 LRC	Nonmatched	10 extended 16 extended	22.3 16.5	2 (10) 2 (12.5)	

LND = lymph node dissection; LRC = laparoscopic radical cystectomy: ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; RCT = randomized controlled trial.

* Statistically significant.

Table

Table 9 – Comparative studies evaluating positive surgical margins after open, laparoscopic, and robot-assisted radical cystectomy

Comparison	Level of evidence	Reference	Cases, no.	Pathologic stage, %		Overall PSM, no. (%)	PSM in pT2 cancer
				pT2	pT3		
ORC vs RARC	2b						
		Nix et al, 2010 [74]	21 RARC	67	14	0	0
			20 ORC	40	25	0	0
		Parekh et al, 2013 [83]	20 RARC	50	50	1 (5)	0
			20 ORC	65	35	1 (5)	0
	3						
		Rhee et al, 2006 [84]	7 RARC	86	14	0	0
			23 ORC	43	57	0	0
		Galich et al, 2006 [90]	13 RARC	54	46	0	–
			24 ORC	37	63	3 (12)	
		Pruthi et al, 2007 [71]	20 RARC	78	22	0	0
			24 ORC	63	37	0	
		Wang et al, 2008 [72]	33 RARC	72	28	2 (6)	–
			21 ORC	43	57	3 (14)	
		Ng et al, 2010 [73]	83 RARC	61	39	6 (7)	0
			104 ORC	58	42	9 (9)	0
		Richards et al, 2010 [75]	35 RARC	60	40	1 (3)	–
			35 ORC	57	43	3 (9)	
		Martin et al, 2011 [76]	19 RARC	42	58	–	–
			14 ORC	93	7		
		Gondo et al, 2012 [92]	11 RARC	91	9	1 (9)	–
			15 ORC	53	47	2 (13)	
		Khan et al, 2012 [87]	48 RARC	75	25	0	–
			52 ORC	50	50	6 (10)	
		Richards et al, 2012 [77]	20 RARC	60	40	1 (5)	–
			20 ORC (>75 yr)	50	50	2 (10)	
		Styn et al,	50 RARC	60	40	1 (2)	–

		2012 [78]	100 ORC	72	28	1 (1)	
		Sung et al, 2012 [79]	35 RARC 104 ORC	43 38	57 62	–	–
		Kader et al, 2013 [91]	100 RARC 100 ORC	58 53	42 47	12 (12) 11 (11)	–
		Knox et al, 2013 [86]	58 RARC 84 ORC	66 43	34 57	4 (7) 7 (8)	–
		Maes et al, 2013 [80]	14 RARC 14 ORC	43 57	57 43	3 (21) 2 (14)	–
		Musch et al, 2013 [81]	100 RARC 42 ORC	61 57	39 43	2 (2) 1 (2)	–
		Nepple et al, 2013 [82]	36 RARC 29 ORC	53 58	47 42	2 (6) 2 (7)	0 0
	4	Abaza et al, 2012 [88]	35 RARC 120 ORC	60 45	23 42	2 (6) 8 (7)	0 0
LRC vs RARC							
	3	Khan et al, 2012 [87]	48 RARC 58 LRC	75 57	25 43	0 2 (4)	–
	4	Abraham et al, 2007 [89]	14 RARC 20 LRC	–	–	1 (7) 0	0 –

LRC = laparoscopic radical cystectomy; ORC = open radical cystectomy; PSM = positive surgical margin; RARC = robot-assisted radical cystectomy.

Table

Table 10 – Comparative studies evaluating recurrence-free, cancer-specific, and overall survival estimates after open, laparoscopic, and robot-assisted radical cystectomy

Comparison	Level of evidence	Reference	Cases, no.	Study design	Follow–up, mo	Neoadjuvant chemotherapy, %	DFS estimates, %	CSS estimates, %	OS estimates, %
ORC vs RARC	3								
		Khan et al, 2012 [87]	48 RARC 52 ORC	Prospective	38	–	–	79 69	–
		Nepple et al, 2013 [82]	36 RARC 29 ORC	Nonmatched	12	6 14	67 (2 yr) 58 (2 yr)	75 (2 yr) 63 (2 yr)	68 (2 yr) 63 (2 yr)
LRC vs RARC	3								
		Khan et al, 2012 [87]	48 RARC 58 LRC	Prospective	38	–	–	79 93	–

CSS = cancer-specific survival; DFS = disease-free survival; LRC = laparoscopic radical cystectomy; ORC = open radical cystectomy; OS = overall survival; RARC = robot-assisted radical cystectomy.

Illustration

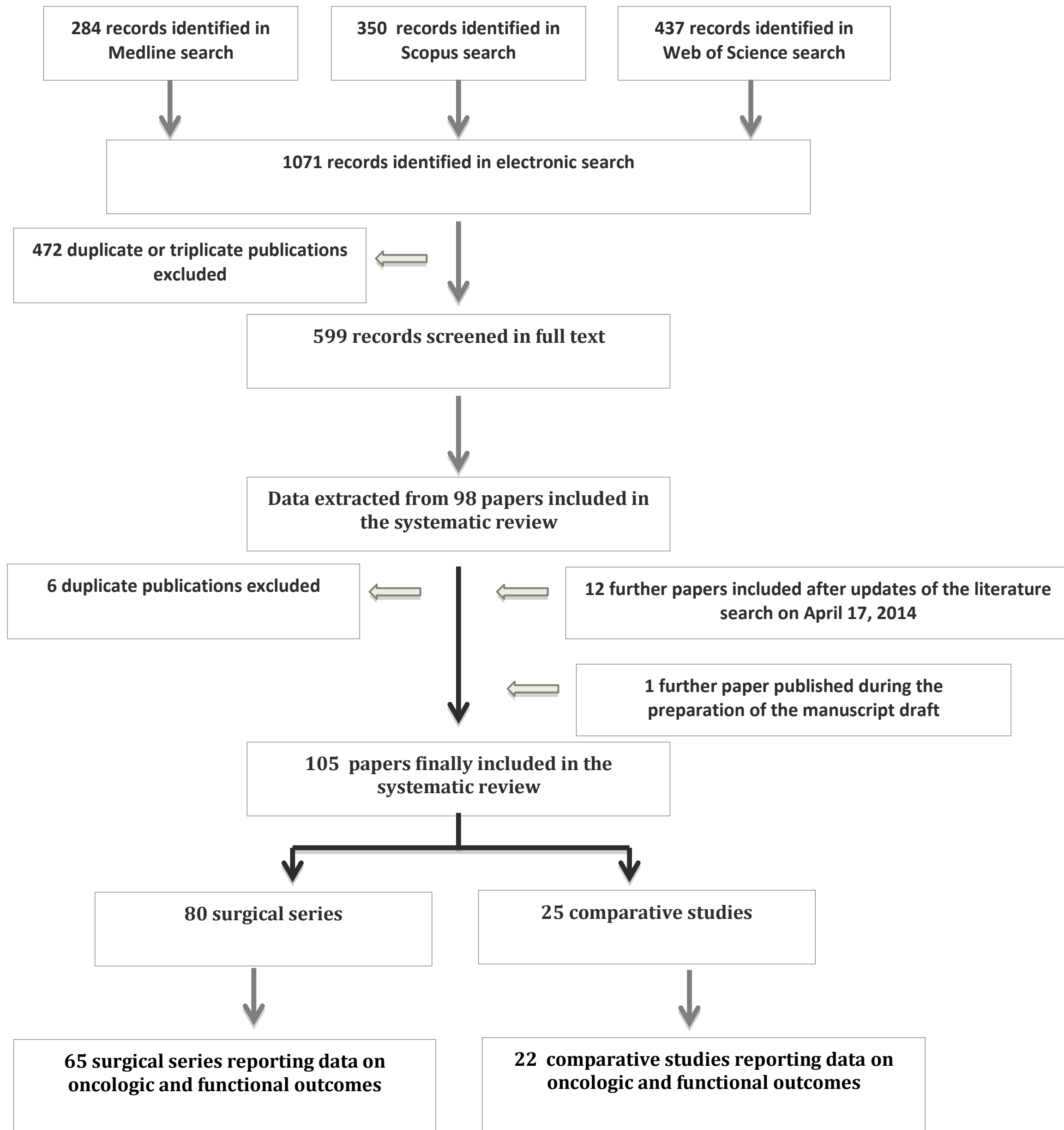


Figure 2

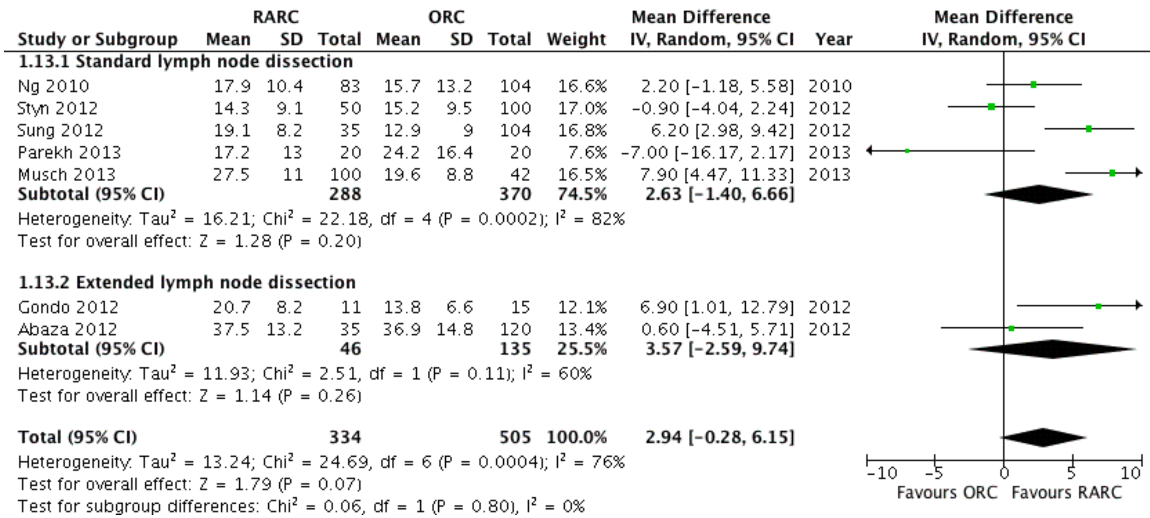
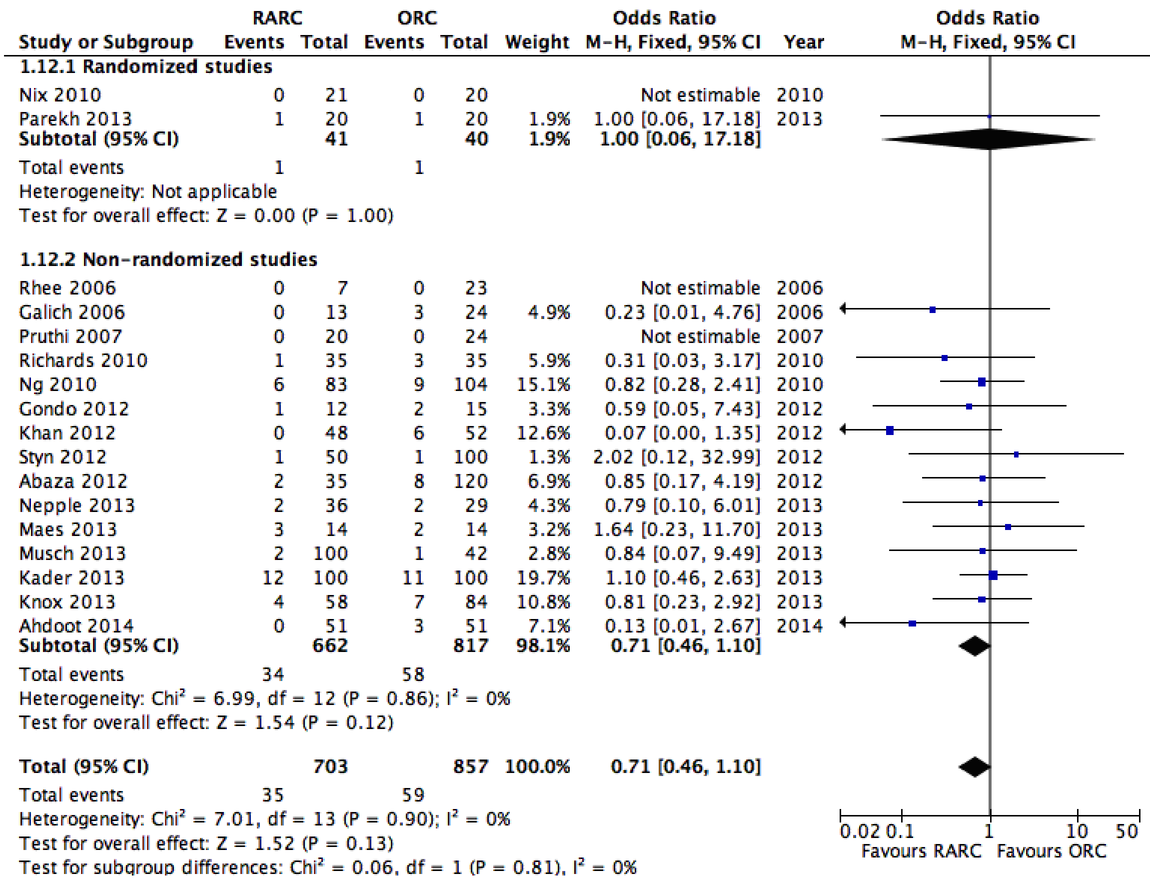


Figure 3



Instructions to typesetter re EURUROL-D-14-01774

Figure 2:
--Change Favours to: Favors
-- Change Tau^2 to: τ^2
--Change Chi^2 to: χ^2
--Format p values as: $p < 0.00001$, $p = 0.002$

Figure 3:
--Change Favours to: Favors
--Delete hyphen: Nonrandomized
--Format p values as: $p < 0.00001$, $p = 0.002$
--Change Chi^2 to: χ^2