

Urinary function in female patients after traditional, organ-sparing and nerve-sparing radical cystectomy for bladder cancer: a systematic review and pooled analysis

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Objectives

To determine and summarize the available data on urinary, sexual, and health-related quality-of-life (HRQOL) outcomes after traditional radical cystectomy (RC), reproductive organ-preserving RC (ROPRC) and nerve-sparing RC (NSRC) for bladder cancer (BCa) in female patients.

Methods

The PubMed, SCOPUS and Web of Science databases were searched to identify studies reporting functional outcomes in female patients undergoing RC and urinary diversion for the treatment of BCa. The outcomes of interest were voiding function (for orthotopic neobladder [ONB]), sexual function and HRQOL. The following independent variables were derived and included in the meta-analysis: pooled rate of daytime and nighttime continence/incontinence, and intermittent self-catheterization (ISC) rates. Analyses were performed separately for traditional, organ- and/or nerve-sparing surgical approaches.

Results

Fifty-three studies comprising 2740 female patients (1201 traditional RC and 1539 organ-/nerve-sparing RC, and 264 nerve-sparing-alone RC) were eligible for qualitative synthesis; 44 studies comprising 2418 female patients were included in the

quantitative synthesis. In women with ONB diversion, the pooled rates of daytime continence after traditional RC, ROPRC and NSRC were 75.2%, 79.3% and 71.2%, respectively. The pooled rate of nighttime continence after traditional RC was 59.5%; this rate increased to 70.7% and 71.7% in women who underwent ROPRC and NSRC, respectively. The pooled rate of ISC after traditional RC with ONB diversion in female patients was 27.6% and decreased to 20.6% and 16.8% in patients undergoing ROPRC and NSRC, respectively. The use of different definitions and questionnaires in the assessment of postoperative sexual and HRQOL outcomes did not allow a systematic comparison.

Conclusions

Female organ- and nerve-sparing surgical approaches during RC seem to result in improved voiding function. There is a significant need for well-designed studies exploring sexual and HRQOL outcomes to establish evidence-based management strategies to support a shared decision-making process tailored towards patient expectations and satisfaction. Understanding expected functional, sexual and quality-of-life outcomes is necessary to allow individualized pre- and postoperative counselling and care delivery in female patients planned to undergo RC.

Keywords

radical cystectomy, females, functional, sexual, QoL

Introduction

The surgical technique of radical cystectomy (RC) and the choice of urinary diversion differ between men and women in the management of bladder cancer (BCa). In female patients, the usual anterior pelvic exenteration includes removal of the urethra, urinary bladder and nearby reproductive organs such as the uterus, fallopian tubes, ovaries and anterior vaginal wall (henceforth termed traditional RC). This radical approach severely affects the functionality of the urinary, sexual and reproductive systems. To overcome these limitations of radical surgery, reproductive organ-preserving RC (ROPRC) including pelvic nerve-sparing approaches was developed. The key concept is to balance oncological safety and surgical precision while improving postoperative functional outcomes. Several studies have demonstrated that preservation of the neurovascular bundles and/or reproductive organs in any variation is feasible and oncologically safe in well-selected women [1]. However, to date, due to the lack of high-quality data, ROPRC should not be offered as standard management for BCa according to the recent European Association of Urology guidelines [2].

In a large proportion of existing studies on postoperative functional outcomes after RC, the majority of participants were male, and only a few studies reported on pure female populations [3,4]. Therefore, gender-specific functional, sexual, and health-related quality-of-life (HRQOL) outcomes, as well as data on how nerve-sparing RC (NSRC) and/or ROPRC affect these variables remain unclear. Additionally, there is a lack of awareness among urologists about organ-preserving and adequate peri-operative counselling regarding functional outcomes in women undergoing RC, especially in terms of postoperative sexual dysfunction [3,5,6]. Indeed, even among sexually active women, more than 40% of

physicians do not discuss organ-sparing approaches with their patients [5]. Therefore, systematic comparisons to guide adequate pre- and postoperative counselling and care delivery in female patients planned to undergo RC are needed.

Given the lack of data on functional outcomes in women after RC and urinary diversion, the primary aim of this systematic review and meta-analysis was to determine the urinary, sexual and quality-of-life outcomes after traditional, organ-sparing RC and/or NSRC for BCa in female patients. This may help improve counselling and care delivery in women by creating an evidence-based basis for shared-decision making.

Materials and Methods

Protocol

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7].

Literature Search

The PubMed, SCOPUS and Web of Science databases were searched in March 2022 to identify studies reporting functional outcomes in female patients undergoing RC and urinary diversion. A comprehensive systematic literature search was independently performed by two authors. The following keywords were used in our search strategy: 'radical cystectomy', 'bladder cancer', 'functional outcome', 'sexual function', 'urinary diversion', 'quality of life', and 'women OR female'. The outcomes of interest were voiding function (for orthotopic neobladder [ONB]), sexual function, and HRQOL.

After removing duplicates, two reviewers independently screened the titles and abstracts of articles retrieved.

Subsequently, the full texts of eligible articles were reviewed for final inclusion and data extraction. Any discrepancies during the primary and secondary literature screenings were resolved by referring to the co-authors.

Inclusion and Exclusion Criteria

We included studies if they investigated only female patients (patients) who were treated with RC and any form of urinary diversion (intervention) to assess the differential effects of traditional, and organ- and/or nerve-sparing RC on functional outcomes (outcomes). To be included, comparative and non-comparative studies must have reported on at least one functional outcome such as daytime or nighttime continence/incontinence, intermittent self-catheterization (ISC) rate, sexual function, and/or HRQOL. We excluded reviews, letters, editorials, replies from authors, case reports, and articles not published in English. Cited references of included studies were examined to identify additional studies not retrieved by database searches. Author affiliations were used to help identify studies for which data were reported in more than one publication.

Data Extraction

Data from each study were independently extracted by two reviewers. Extracted data included the following: first author's name; year of publication; study design; recruitment/intervention period; number of patients; age; type of preserving technique; urinary diversion and its type; voiding function report; definition of continence; rates of daytime or nighttime continence/incontinence; ISC; sexual function; HRQOL; and follow-up. All discrepancies regarding data extraction were resolved with co-investigators.

Risk-of-Bias Assessment

The risk of bias was evaluated according to The Risk of bias in non-randomized studies of interventions tool (ROBINS-I). This tool is based on seven domains that include bias due to confounding, participant selection, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result.

Statistical Analyses

If sufficient data were available for evaluation, a meta-analysis of proportions was conducted to calculate the weighted summary overall proportion. These pooled rates represent the average from multiple studies weighted by the inverse of their sampling variances [8]. The proportion of interest was calculated from the relevant numerator (event) and denominator (total cases), if possible. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using Cochrane's Q test and the I^2 statistic. Significant heterogeneity was indicated by a P value < 0.05 in

Cochrane's Q tests and a ratio $>50\%$ in I^2 statistics. We used fixed-effects models for calculation of non-heterogeneous results. Random-effects models were used in cases of heterogeneity. The following independent variables were derived and included in the meta-analysis: pooled rate of daytime or nighttime continence/incontinence, and ISC rate. Analyses were performed separately for traditional, organ-sparing and/or nerve-sparing surgical approaches. An assessment of publication bias using funnel plots was not performed as this has been shown to be problematic in meta-analyses of proportions [9]. All statistical analyses were performed using R 4.0.4.

Results

Characteristics of the Included Studies

Following abstract screening and full-text review, 53 studies ($n = 2740$) met our inclusion criteria (Fig. S1 [6,10–62]). Among them, 44 studies comprising 2418 female patients were included in the quantitative synthesis (meta-analysis). Table S1 summarizes the characteristics of the included studies. Most of the studies included in this meta-analysis were identified as having a moderate or serious risk of bias according to ROBINS-I.

In the selected studies, a total of 2740 patients underwent traditional ($n = 1201$; 43.8%), organ-sparing (including nerve-sparing; $n = 1539$; 56.2%) or nerve-sparing-alone ($n = 264$; 10%) RC. Overall, 2368 patients underwent ONB diversion. ROPRC refers to variations of the surgical techniques including vaginal-sparing, genitalia-sparing, reproductive organ-sparing RC. The included studies addressed voiding function (47 studies), sexual function (13 studies) and HRQOL (13 studies; Table S2).

Voiding Function in Patients with Orthotopic Neobladder

Among 47 studies reporting on voiding function in female patients with ONB diversion, high heterogeneity was noted for the definitions of continence. In most studies, continence was defined as zero pads or as a maximum of one pad per day (Table S2).

Daytime Continence

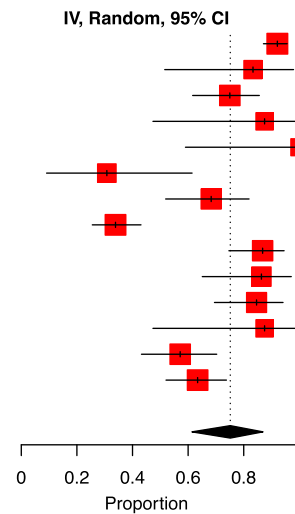
The pooled rate of daytime continence after traditional RC with ONB diversion in female patients was 75.2% (95% CI 61.4–86.9, $I^2 = 92\%$; Fig. 1). In studies reporting on organ-/nerve-sparing surgical approaches, the daytime continence rate increased to 79.3% (95% CI 70.7–86.8, $I^2 = 82\%$) for organ-sparing RC and was 71.2% (95% CI 49.4–89.1, $I^2 = 89\%$) for NSRC.

Fig. 1 Forest plots showing the pooled rates of daytime continence for studies reporting on outcomes in female patients undergoing radical cystectomy (RC) and urinary diversion for treatment of bladder cancer.

(A) Daytime continence: traditional RC

Study	Events	Total	Weight	IV, Random, 95% CI
Ali-El-Dein 2008	163	177	8.2%	0.921 [0.871; 0.956]
Arai 1999	10	12	6.3%	0.833 [0.516; 0.979]
Bartsch 2014	42	56	7.9%	0.750 [0.616; 0.856]
Bayraktar 2001	7	8	5.7%	0.875 [0.473; 0.997]
Cancrini 1995	7	7	5.5%	1.000 [0.590; 1.000]
Hautmann 1996	4	13	6.5%	0.308 [0.091; 0.614]
Jarolim 2000	28	41	7.7%	0.683 [0.519; 0.819]
Jentzmik 2012	41	121	8.1%	0.339 [0.255; 0.430]
Lee 2004	46	53	7.8%	0.868 [0.747; 0.945]
Parra 2004	19	22	7.1%	0.864 [0.651; 0.971]
Pichler 2013	33	39	7.6%	0.846 [0.695; 0.941]
Shimogaki 1999	7	8	5.7%	0.875 [0.473; 0.997]
Yang 2011	32	56	7.9%	0.571 [0.432; 0.703]
Zhou 2021	52	82	8.0%	0.634 [0.520; 0.738]

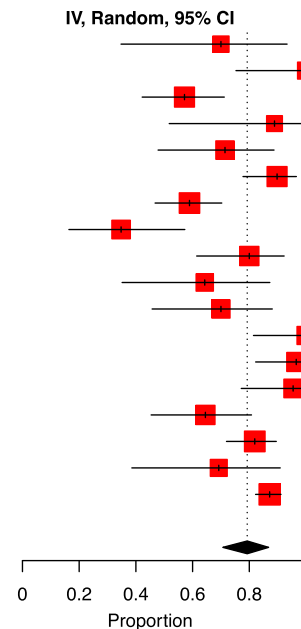
Total (95% CI) 695 100.0% 0.752 [0.614; 0.869]
 Heterogeneity: Tau² = 0.0612; Chi² = 161.56, df = 13 (P < 0.01); I² = 92%



(B) Daytime continence: organ-sparing RC

Study	Events	Total	Weight	IV, Random, 95% CI
Aboseif 1998	7	10	4.2%	0.700 [0.348; 0.933]
Ali-El-Dein 2013	13	13	4.6%	1.000 [0.753; 1.000]
Anderson 2012	28	49	6.4%	0.571 [0.422; 0.712]
Badawy 2011	8	9	4.0%	0.889 [0.518; 0.997]
Chang 2002	15	21	5.4%	0.714 [0.478; 0.887]
Granberg 2008	44	49	6.4%	0.898 [0.778; 0.966]
Gross 2015	43	73	6.7%	0.589 [0.468; 0.703]
Hautmann 1997	8	23	5.5%	0.348 [0.164; 0.573]
Koie 2010	24	30	5.9%	0.800 [0.614; 0.923]
Kulkarni 2008	9	14	4.8%	0.643 [0.351; 0.872]
Lavallée 2022	14	20	5.3%	0.700 [0.457; 0.881]
Moursy 2016	18	18	5.2%	1.000 [0.815; 1.000]
Nesrallah 2005	28	29	5.8%	0.966 [0.822; 0.999]
Roshdy 2016	21	22	5.5%	0.955 [0.772; 0.999]
Rouanne 2014	20	31	5.9%	0.645 [0.454; 0.808]
Stenzl 2001	68	83	6.8%	0.819 [0.720; 0.895]
Wishahi 2015	9	13	4.6%	0.692 [0.386; 0.909]
Zahrn 2017	204	234	7.2%	0.872 [0.822; 0.912]

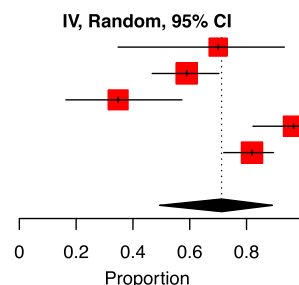
Total (95% CI) 741 100.0% 0.793 [0.707; 0.868]
 Heterogeneity: Tau² = 0.0310; Chi² = 96.97, df = 17 (P < 0.01); I² = 82%



(C) Daytime continence: nerve-sparing RC

Study	Events	Total	Weight	IV, Random, 95% CI
Aboseif 1998	7	10	16.1%	0.700 [0.348; 0.933]
Gross 2015	43	73	22.0%	0.589 [0.468; 0.703]
Hautmann 1997	8	23	19.5%	0.348 [0.164; 0.573]
Nesrallah 2005	28	29	20.2%	0.966 [0.822; 0.999]
Stenzl 2001	68	83	22.2%	0.819 [0.720; 0.895]

Total (95% CI) 218 100.0% 0.712 [0.494; 0.891]
 Heterogeneity: Tau² = 0.0518; Chi² = 36.65, df = 4 (P < 0.01); I² = 89%



Nighttime Continence

The pooled rate of nighttime continence after traditional RC with ONB diversion in female patients was 59.5% (95% CI 43.1–74.9, $I^2 = 94\%$; Fig. 2). In studies reporting on organ-/nerve-sparing surgical approaches, nighttime continence rate increased to 70.7% (95% CI 63.7–77.3, $I^2 = 66\%$) and 71.7% (95% CI 59.1–82.9, $I^2 = 63\%$) in patients who underwent organ-sparing RC and NSRC, respectively.

Day-/Nighttime Incontinence

The pooled rate of day-/nighttime incontinence in female patients after traditional RC with ONB diversion was 11.7% (95% CI 5.1–19.9, $I^2 = 55\%$) and was 19.1% (95% CI 4.7–39.2, $I^2 = 93\%$) in patients who underwent organ-sparing RC (Fig. 3).

Nighttime Incontinence

The pooled rate of nighttime incontinence was 34.6% (95% CI 20.8–49.7, $I^2 = 89\%$) in female patients after traditional RC with ONB diversion (Fig. 4). The nighttime incontinence rate after organ-sparing RC approaches was 22.3% (95% CI 12.4–33.9, $I^2 = 74\%$).

Intermittent Self-Catheterization

The pooled rate of ISC after traditional RC with ONB diversion in female patients was 27.6% (95% CI 20.0–35.8, $I^2 = 80\%$; Fig. 5). In studies reporting on organ-/nerve-sparing surgical approaches, the ISC rate decreased to 20.6% (95% CI 14.5–27.5, $I^2 = 71\%$) and 16.8% (95% CI 6.6–29.9, $I^2 = 61\%$) in patients who underwent organ-sparing RC and NSRC, respectively.

Sexual Function Across All Urinary Diversions

Thirteen studies assessed sexual function in female patients undergoing RC for BCa. Data on this outcome were highly heterogeneous due to a lack of standardized assessments and reporting systems across studies (Table S2). The most commonly used standardized instruments were the Female Sexual Function Index (FSFI) in seven studies and the Index of Female Sexual Function questionnaire in one study. The rest of the studies employed non-standardized sexual function questionnaires, semi-structured interviews with questionnaires or discussions with patients.

Five studies assessed pre- and postoperative sexual function, of which two reported on nerve-sparing surgeries [12,13,21,29,35]. All studies showed a postoperative decline in

mean or median sexual function scores. In a cohort of 11 women undergoing sex-sparing robot-assisted RC, all FSFI domains (arousal, lubrication, orgasm, satisfaction, and pain) significantly improved between 3 and 12 months postoperatively [12]. Comparing the baseline scores to 12-month follow-up scores, there was no statistically significant difference in the arousal and orgasm domains [12]. However, despite improvements, sexual function in lubrication, satisfaction, and pain domains, as well as FSFI global scores, were statistically significantly worse than at baseline [12]. Of note, Volkmer et al. found higher postoperative mean FSFI scores compared to baseline in women with preserved sexual activity following non-nerve-sparing RC and ONB diversion.

Based on a sexual function survey, a recent study reported that 93% of women who underwent ROPRC had at least intermittent thoughts about sex and 87% remained sexually active after surgery [61]. Of these, 38% (5/13 patients) had a high level of sexual satisfaction, and 10 patients engaged in sexual intercourse. Only 1/10 women experienced occasional pain during penetrative intercourse [61]. The median time to resumption of sexual activity was 6 months [61].

Available data show promising results for organ- and nerve-sparing techniques in terms of sexual outcomes. However, there is a lack of data on sexual function and different surgical approaches in women undergoing RC that precludes definitive conclusions regarding the long-term benefit of nerve-sparing and organ-sparing approaches.

Quality of Life Across All Urinary Diversions

Thirteen studies assessed HRQOL in female patients undergoing RC for BCa. Among included studies, there was heterogeneity in terms of data acquisition and used questionnaires (Table S2). Aside from interviews and unvalidated items, the European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire–Cancer 30 (EORTC-QLQ-C30) and Bladder cancer-muscle invasive 30 (BLM30), the medical short-form (SF)-12 and the Functional Assessment of Cancer Therapy – General and Bladder Cancer (FACT-G/-BI) questionnaires were the most commonly used validated tools.

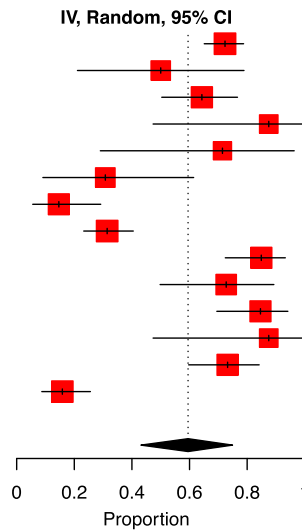
In a small cohort of women undergoing organ-sparing robot-assisted RC ($n = 11$), global health status/quality of life, and physical and emotional functioning items improved significantly over time and were superior compared to baseline at 12 months of follow-up (all $P \leq 0.04$) [12]. In another study only 1/13 patients indicated that ROPRC with ONB reconstruction had a high impact on body image [61]. No study reliably assessed differences in HRQOL outcomes between non-nerve-sparing and nerve-sparing surgical approaches.

Fig. 2 Forest plots showing the pooled rates of nighttime continence for studies reporting on outcomes in female patients undergoing radical cystectomy (RC) and urinary diversion for treatment of bladder cancer.

(A) Nighttime continence: traditional RC

Study	Events	Total	Weight	IV, Random, 95% CI
Ali-El-Dein 2008	128	177	8.0%	0.723 [0.651; 0.788]
Arai 1999	6	12	6.5%	0.500 [0.211; 0.789]
Bartsch 2014	36	56	7.7%	0.643 [0.504; 0.766]
Bayraktar 2001	7	8	5.9%	0.875 [0.473; 0.997]
Cancrini 1995	5	7	5.7%	0.714 [0.290; 0.963]
Hautmann 1996	4	13	6.6%	0.308 [0.091; 0.614]
Jarolim 2000	6	41	7.6%	0.146 [0.056; 0.292]
Jentzmik 2012	38	121	8.0%	0.314 [0.233; 0.405]
Lee 2004	45	53	7.7%	0.849 [0.724; 0.933]
Parra 2004	16	22	7.2%	0.727 [0.498; 0.893]
Pichler 2013	33	39	7.6%	0.846 [0.695; 0.941]
Shimogaki 1999	7	8	5.9%	0.875 [0.473; 0.997]
Yang 2011	41	56	7.7%	0.732 [0.597; 0.842]
Zhou 2021	13	82	7.9%	0.159 [0.087; 0.256]

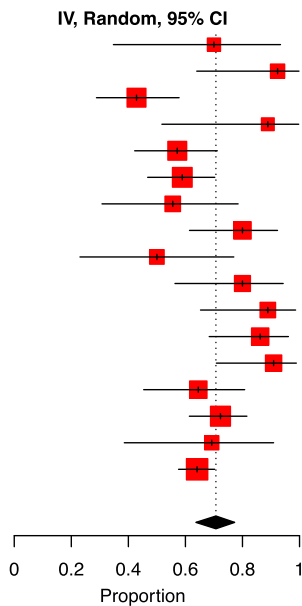
Total (95% CI) 695 100.0% 0.595 [0.431; 0.749]
 Heterogeneity: Tau² = 0.0780; Chi² = 202.31, df = 13 (P < 0.01); I² = 94%



(B) Nighttime continence: organ-sparing RC

Study	Events	Total	Weight	IV, Random, 95% CI
Aboseif 1998	7	10	3.6%	0.700 [0.348; 0.933]
Ali-El-Dein 2013	12	13	4.2%	0.923 [0.640; 0.998]
Anderson 2012	21	49	7.4%	0.429 [0.288; 0.578]
Badawy 2011	8	9	3.4%	0.889 [0.518; 0.997]
Granberg 2008	28	49	7.4%	0.571 [0.422; 0.712]
Gross 2015	43	73	8.1%	0.589 [0.468; 0.703]
Hautmann 2000	10	18	5.0%	0.556 [0.308; 0.785]
Koie 2010	24	30	6.3%	0.800 [0.614; 0.923]
Kulkarni 2008	7	14	4.4%	0.500 [0.230; 0.770]
Lavallée 2022	16	20	5.3%	0.800 [0.563; 0.943]
Moursy 2016	16	18	5.0%	0.889 [0.653; 0.986]
Nesrallah 2005	25	29	6.2%	0.862 [0.683; 0.961]
Roshdy 2016	20	22	5.5%	0.909 [0.708; 0.989]
Rouanne 2014	20	31	6.3%	0.645 [0.454; 0.808]
Stenzl 2001	60	83	8.3%	0.723 [0.614; 0.816]
Wishahi 2015	9	13	4.2%	0.692 [0.386; 0.909]
Zahran 2017	150	234	9.5%	0.641 [0.576; 0.702]

Total (95% CI) 715 100.0% 0.707 [0.637; 0.773]
 Heterogeneity: Tau² = 0.0127; Chi² = 47.40, df = 16 (P < 0.01); I² = 66%



(C) Nighttime continence: nerve-sparing RC

Study	Events	Total	Weight	IV, Random, 95% CI
Aboseif 1998	7	10	12.5%	0.700 [0.348; 0.933]
Gross 2015	43	73	31.7%	0.589 [0.468; 0.703]
Nesrallah 2005	25	29	23.0%	0.862 [0.683; 0.961]
Stenzl 2001	60	83	32.7%	0.723 [0.614; 0.816]

Total (95% CI) 195 100.0% 0.717 [0.591; 0.829]
 Heterogeneity: Tau² = 0.0099; Chi² = 8.12, df = 3 (P = 0.04); I² = 63%

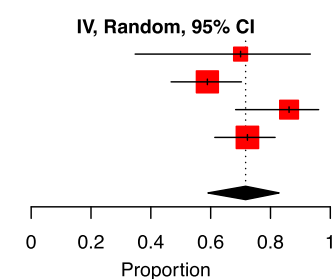
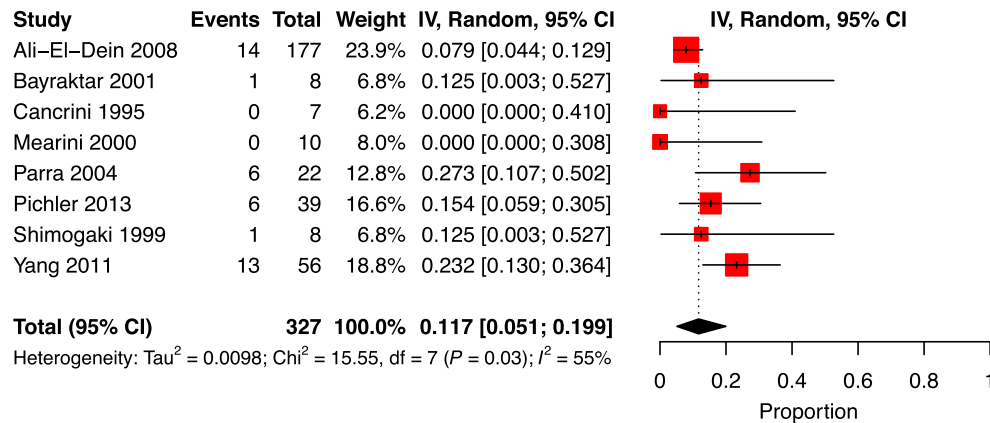
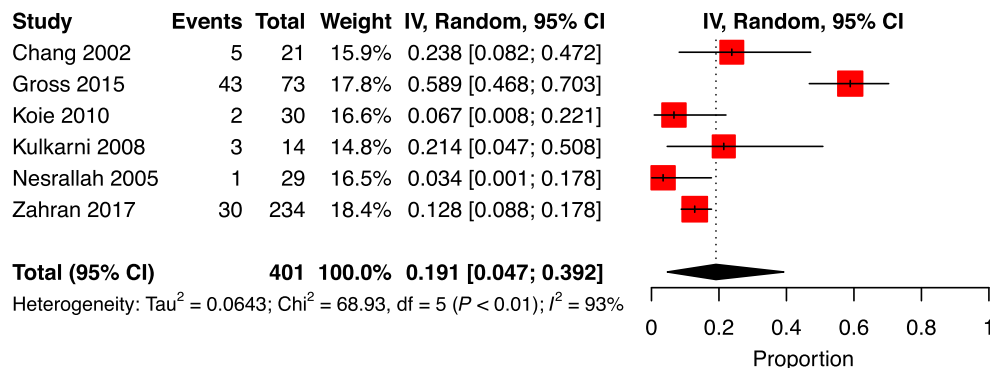


Fig. 3 Forest plots showing the pooled rates of day-/nighttime incontinence for studies reporting on outcomes in female patients undergoing radical cystectomy (RC) and urinary diversion for treatment of bladder cancer.

(A) Day-/nighttime incontinence: traditional RC



(B) Day-/nighttime incontinence: organ-sparing RC



Most studies reported on postoperative HRQOL between women undergoing RC with ONB reconstruction, ileal conduit (IC) or different types of continent urinary diversion and did not find a statistical difference [19,30,46]. However, if in women with ONB reconstruction continence was preserved postoperatively, ONB diversion was associated with better global health, physical, emotional and cognitive functioning, and fatigue on the EORTC-QLQ-C30 scale compared to IC diversion [19]. In a French study, 77% of women with ONB considered their postoperative health as good, very good, or excellent [62]. Comparing women undergoing RC with ONB reconstruction to age-matched population-based controls, one study found no significant differences in postoperative HRQOL with the exception of significantly lower scores for the 'role limitations because of emotional problems' item of the SF-36 [50]. Women who underwent ONB reconstruction were significantly more affected by financial difficulties compared to women with IC diversion in the study by Siracusano et al. [59]. Regarding other types of urinary

diversion, patients who underwent a ureterocutaneostomy showed a trend towards worse 'appetite loss' and 'fatigue' scores as well worse 'physical well-being' and 'emotional well-being' compared to those who had IC or ONB [36].

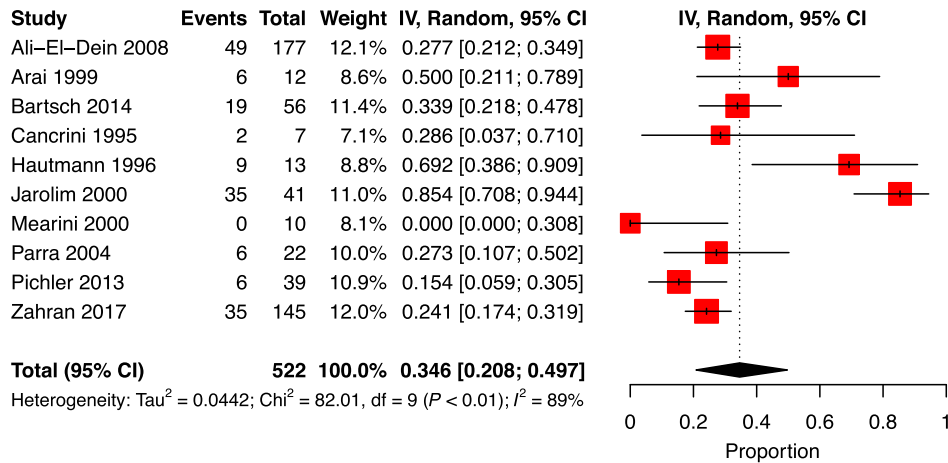
The use of different definitions and questionnaires in the assessment of postoperative HRQOL outcomes limits comparability between studies. High-quality evidence HRQOL data after RC in female patients are too scarce to make reliable and accurate conclusions.

Discussion

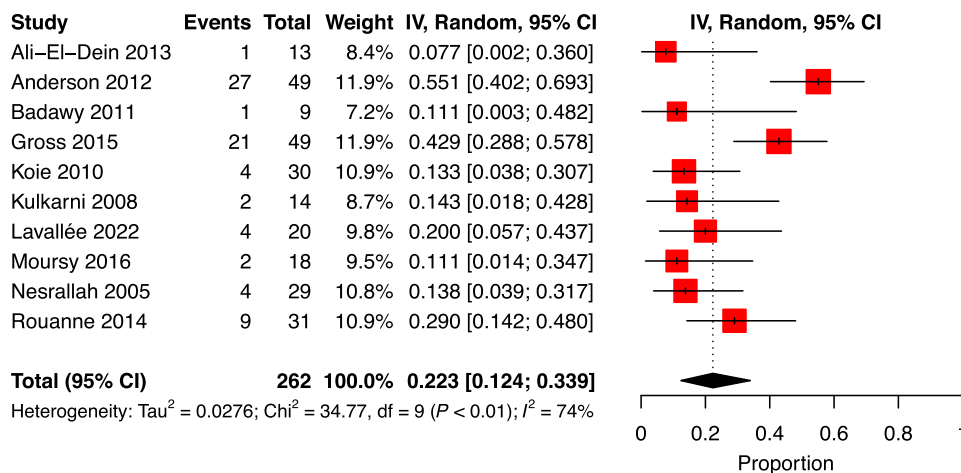
To improve clinicians' awareness regarding female patients' needs and to help guide the shared decision-making process prior to RC, we performed a systematic review and meta-analysis of functional outcomes in female patients undergoing RC and urinary diversion for the treatment of BCa. There is an overall need for well-designed studies, exploring postoperative functional outcomes in female

Fig. 4 Forest plots showing the pooled rates of nighttime incontinence for studies reporting on outcomes in female patients undergoing radical cystectomy (RC) and urinary diversion for treatment of bladder cancer.

(A) Nighttime incontinence: traditional RC



(B) Nighttime incontinence: organ-sparing RC



patients. Our analyses indicated superior functional outcomes of organ- and nerve-sparing surgical approaches in women compared to the traditional RC approach.

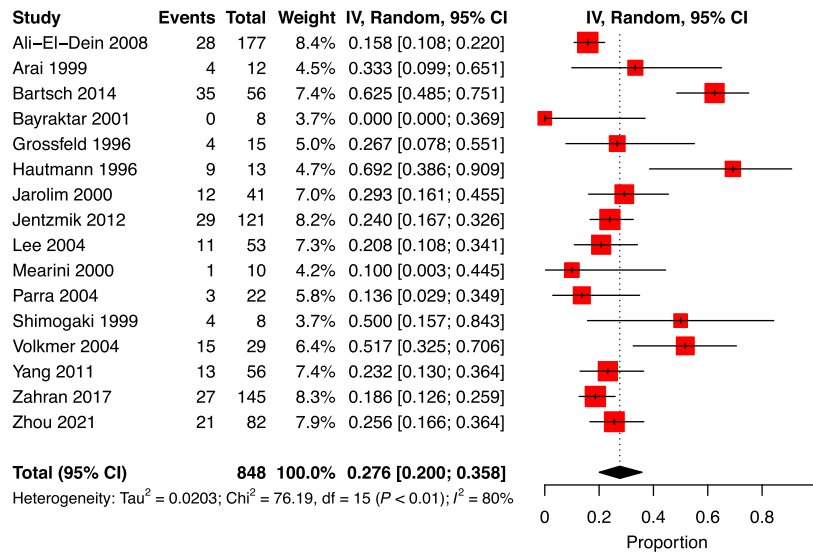
Despite the better outcomes achieved with organ-sparing surgical approaches, these results should be interpreted with caution due to the relatively poor quality of available evidence. To date, there is no single prospective trial targeted towards rigorous assessment of women's peri-operative needs. Moreover, based on available data, systematic comparisons between different surgical approaches are difficult, and existing patient-reported outcomes are limited by the lack of standardized assessment. The included retrospective studies were mainly based on small heterogeneous cohorts with

inconsistent definitions of outcomes and high variability in questionnaires used.

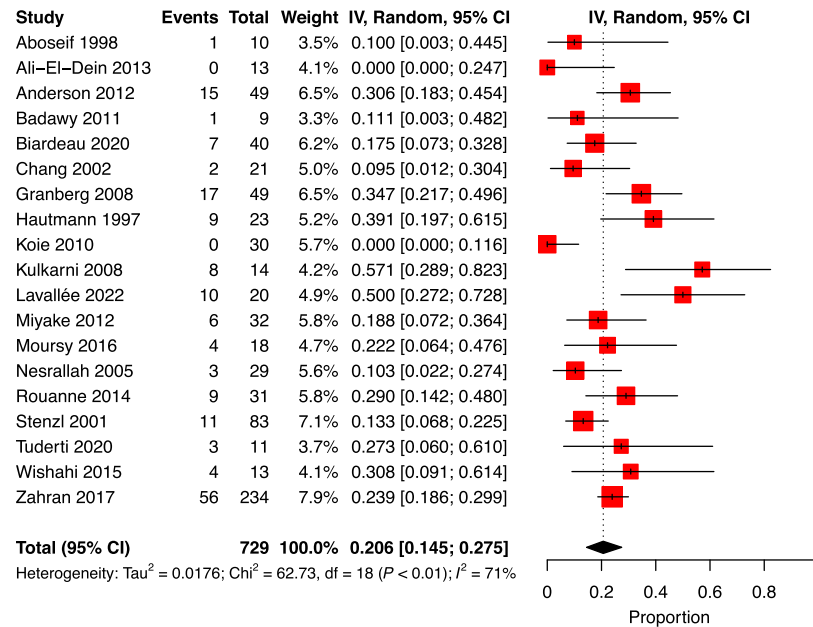
Regarding postoperative HRQOL outcomes, given the paucity of high-quality data, only trends may be delineated. Indeed, no study compared HRQOL between non-nerve-sparing and nerve-sparing surgical approaches. Overall, there was no difference in HRQOL outcomes between ONB and IC patients after RC. Moreover, patients may experience a postoperative improvement in HRQOL. A comparable trend was observed for both sexes in a recent study that systematically assessed postoperative HRQOL for 24 months in a mixed cohort of men and women undergoing RC [4]. In brief, global quality-of-life domain scores remained similar to

Fig. 5 Forest plots showing the pooled rates of intermittent self-catheterization for studies reporting on outcomes in female patients undergoing radical cystectomy (RC) and urinary diversion for treatment of bladder cancer.

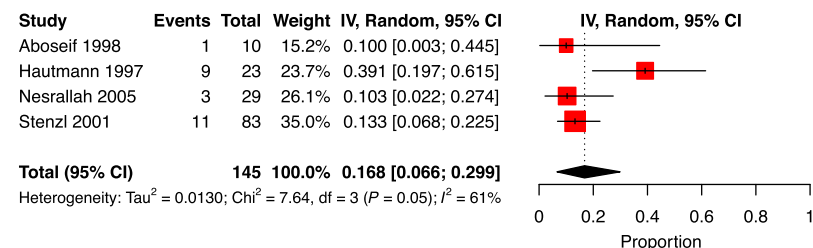
(A) Intermittent self-catheterization rate: traditional RC



(B) Intermittent self-catheterization rate: organ-sparing RC



(C) Intermittent self-catheterization rate: nerve-sparing RC



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the baseline score at 3 months postoperatively and gradually improved afterwards for both ONB and IC [4]. We believe that postoperative HRQOL after RC should be one of the key measures of BCa management to guide the preoperative shared decision-making process between patients and their surgeons. Individuals' perceptions of disease-related HRQOL are strongly influenced by postoperative urinary and sexual dysfunction.

Organ- and nerve-sparing surgical approaches appear to improve voiding function in women with ONB reconstruction, but criteria favouring the procedure choice may depend on the patient's preoperative comorbidities, continence status, and desired outcomes. Regarding ONB reconstruction, the risks of postoperative incontinence and hypercontinence are important [63]. Functional evaluation in ONB diversion has been objectively performed mostly in male patients, with reported urinary continence rates of up to 96% at 12 months [64,65]. In our systematic review and meta-analysis, the pooled rate of nighttime incontinence rate was 34.6% after traditional RC, compared to 22.3% after an organ-sparing approach. It has been suggested that, by preservation of the urethral innervation, nerve-sparing surgical techniques may prevent atrophy of the proximal urethra, thereby improving postoperative outcomes [66]. Furthermore, a longer functional urethra length as well as higher pre- and postoperative urethral closing pressure at rest has been shown to be associated with improved postoperative urinary function [38].

The pooled rate of ISC after traditional RC with ONB diversion was 27.6% compared to 20.6% and 16.8% in females who underwent organ- and nerve-sparing RC, respectively. Despite refinements in surgical technique, preoperative counselling should encompass the non-negligible risk of need for postoperative ISC [40,42]. Furthermore, surgical alterations to the ONB that can reduce the risk of requiring ISC, such as round ligament suspension and uterus preservation, as well as other treatment options, such as cutaneous continent diversions, should be part of the preoperative counselling [20].

The vast majority of the included studies did not systematically assess baseline and postoperative sexual function [67]. According to current data, it is not possible to estimate the true impact of RC on sexual function and its postoperative recovery in women. First, in most studies, baseline sexual function prior to RC has been insufficiently or not at all analysed. Second, assessment of postoperative sexual function was not performed at homogenous time points or with adequate follow-up. Third, the most commonly used FSFI scale does not capture sexual dysfunction in sexually inactive women [68]. Almost all studies that analysed baseline sexual function found a postoperative decline in FSFI scores, suggesting that

postoperative recovery will never be as good as baseline function regardless, despite nerve-sparing approaches in some studies [12,21,29]. Our systematic review highlights the urgent need for well-designed studies assessing female sexual function prior to and post RC as a separate outcome measure. Moreover, reproductive organ preservation strategies should be developed regardless of the type of urinary diversion, as the extent of surgery is the major determinant of postoperative sexual functionality. Particular effort should be directed towards understanding long-term sexual recovery.

By summarizing the existing evidence, we believe that the present study may help raise awareness among physicians and improve preoperative counselling and expectation setting for female patients. The main strength of the present systematic review and meta-analysis is that it is the first to assess and compare the pooled rates of continence/ incontinence and ISC in women undergoing traditional, organ- and nerve-sparing RC and ONB reconstruction for the treatment of BCa. Nevertheless, the study also has some limitations. First, the vast majority of the included studies were limited by their single-institutional retrospective design, small sample sizes, and immature follow-up. Second, there was heterogeneity in the definition of interventions and outcome evaluation across included studies, which can lead to potential confounding and bias. To overcome the inconsistencies in surgical approaches, we performed separate analyses for traditional, organ- and/or nerve-sparing approaches. Third, discrepancy across the included studies in the definition of continence (the majority of included studies did not report results using validated questionnaires), as well as in the questionnaires used for sexual function and HRQOL assessment, might contribute to heterogeneity among the studies. This heterogeneity highlights the need for a standardized preoperative assessment and patient counselling. It is clear that well-designed prospective comparative trials are required to further improve outcomes in female patients undergoing RC for BCa.

In conclusion, adequate pre- and postoperative counselling regarding functional outcomes is an unmet need in female patients undergoing RC for BCa. Our analysis indicates the superior functional benefit of organ- and nerve-sparing surgical approaches in terms of voiding function after ONB reconstruction. However, sexual and quality-of-life outcomes in women undergoing RC remains an understudied field. There is a significant need for studies exploring functional outcomes in women after RC to establish and improve standardized patient-centred counselling and care delivery.

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References

- Veskimäe E, Neuzillet Y, Rouanne M et al. Systematic review of the oncological and functional outcomes of pelvic organ-preserving radical cystectomy (RC) compared with standard RC in women who undergo curative surgery and orthotopic neobladder substitution for bladder cancer. *BJU Int* 2017; 120: 12–24
- Witjes JA, Bruins HM, Carrión A et al. EAU Guidelines on muscle-invasive and metastatic bladder cancer, in EAU Guidelines. 2022.
- Westerman ME, Kokorovic A, Wang XS et al. Radical cystectomy and perioperative sexual function: a cross-sectional analysis. *J Sex Med* 2020; 17: 1995–2004
- Clements MB, Atkinson TM, Dalbagni GM et al. Health-related quality of life for patients undergoing radical cystectomy: results of a Large prospective cohort. *Eur Urol* 2021; 81: 294–304
- Gupta N, Kucirka LM, Semerjian A et al. Comparing provider-led sexual health counseling of male and female patients undergoing radical cystectomy. *J Sex Med* 2020; 17: 949–56
- Gupta N, Rasmussen SEVP, Haney N et al. Understanding psychosocial and sexual health concerns among women with bladder cancer undergoing radical cystectomy. *Urology* 2021; 151: 145–53
- Hutton B, Salanti G, Caldwell DM et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162: 777–84
- Wang N. *How to Conduct a Meta-Analysis of Proportions in R: A Comprehensive Tutorial*. New York: John Jay College of Criminal Justice, 2016: 1–63
- Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; 67: 897–903
- Stenzl A, Colleselli K, Bartsch G. Update of urethra-sparing approaches in cystectomy in women. *World J Urol* 1997; 15: 134–8
- Stenzl A, Jarolim L, Coloby P et al. Urethra-sparing cystectomy and orthotopic urinary diversion in women with malignant pelvic tumors. *Cancer* 2001; 92: 1864–71
- Tuderti G, Mastroianni R, Flammia S et al. Sex-sparing robot-assisted radical cystectomy with intracorporeal Padua ileal neobladder in female: surgical technique, perioperative, oncologic and functional outcomes. *J Clin Med* 2020; 9: 1–10
- Volkmer BG, Gschwend JE, Herkommer K, Simon J, Küfer R, Hautmann RE. Cystectomy and orthotopic ileal neobladder: the impact on female sexuality. *J Urol* 2004; 172: 2353–7
- Wishahi M, Elganzoury H. Survival up to 5–15 years in young women following genital sparing radical cystectomy and neobladder: oncological outcome and quality of life. Single–surgeon and single–institution experience. *Cent Eur J Urol* 2015; 68: 141–5
- Wishahi M, Ismail MA, Elganzoury H et al. Genital-sparing cystectomy versus standard urethral-sparing cystectomy followed with orthotopic neobladder in women with bladder cancer: incidence and causes of hypercontinence with an ultrastructure study of urethral smooth muscles. *Open Access Maced J Med Sci* 2019; 7: 978–81
- Yang G, Whitson JM, Breyer BN, Konety BR, Carroll PR. Oncological and functional outcomes of radical cystectomy and orthotopic bladder replacement in women. *Urology* 2011; 77: 878–83
- Zahrán MH, El-Hefnawy AS, Zidan EM, El-Bilsha MA, Taha DE, Ali-El-Dein B. Health-related quality of life after radical cystectomy and neobladder reconstruction in women: impact of voiding and continence status. *Int J Urol* 2014; 21: 887–92
- Zahrán MH, Eldemerdash Y, Taha DE, Sheir K, Shaaban AA, Ali-El-Dein B. Chronic urinary retention after radical cystectomy and orthotopic neobladder in women: risk factors and relation to time. *Urol Oncol Semin Orig Investig* 2017; 35: 671.e11–671.e16
- Zahrán MH, Taha DE, Harráz AM et al. Health related quality of life after radical cystectomy in women: orthotopic neobladder versus ileal loop conduit and impact of incontinence. *Minerva Urol Nefrol* 2017; 69: 262–70
- Zhou X, He P, Ji H et al. Round ligament suspending treatment in orthotopic ileal-neobladder after radical cystectomy in women: a single-centre prospective randomised trial. *BJU Int* 2021; 128: 187–95
- Zippe CD, Raina R, Shah AD et al. Female sexual dysfunction after radical cystectomy: a new outcome measure. *Urology* 2004; 63: 1153–7
- Abosief SR, Borirakchanyavat S, Lue TF, Carroll PR. Continence mechanism of the ileal neobladder in women: a urodynamics study. *World J Urol* 1998; 16: 400–4
- Ali-El-Dein B, Mosbah A, Osman Y et al. Preservation of the internal genital organs during radical cystectomy in selected women with bladder cancer: a report on 15 cases with long term follow-up. *Eur J Surg Oncol* 2013; 39: 358–64
- Ali-El-Dein B, Gomha M, Ghoneim MA. Critical evaluation of the problem of chronic urinary retention after orthotopic bladder substitution in women. *J Urol* 2002; 168: 587–92
- Anderson CB, Cookson MS, Chang SS, Clark PE, Smith JA, Kaufman MR. Voiding function in women with orthotopic neobladder urinary diversion. *J Urol* 2012; 188: 200–4
- Arai Yoichi AYO, Okubo K, Konami T et al. Voiding function of orthotopic ileal neobladder in women. *Urology* 1999; 54: 44–9
- Bartsch G, Daneshmand S, Skinner EC, Syan S, Skinner DG, Penson DF. Urinary functional outcomes in female neobladder patients. *World J Urol* 2014; 32: 221–8
- Bayraktar Z, Sevin G, Gurbuz G, Taşci AI. Ileal orthotopic neobladder in women: the first experiences from Turkey and our modifications. *Int Urol Nephrol* 2001; 32: 371–5
- Bhatt A, Nandipati K, Dhar N et al. Neurovascular preservation in orthotopic cystectomy: impact on female sexual function. *Urology* 2006; 67: 742–5
- Biardeau X, Lamande N, Tondut L et al. Quality of life associated with orthotopic neobladder and ileal conduit in women: a multicentric cross-sectional study. *Prog En Urol* 2020; 30: 80–8
- Booth BB, Rasmussen A, Jensen JB. Evaluating sexual function in women after radical cystectomy as treatment for bladder cancer. *Scand J Urol* 2015; 49: 463–7
- Cancrini A, De Carli P, Fattahi H, Pompeo V, Cantiani R, Von Heland M. Orthotopic ileal neobladder in female patients after radical cystectomy: 2-year experience. *J Urol* 1995; 153(3 Pt 2): 956–8
- Chang SS, Cole E, Cookson MS, Peterson M, Smith JA. Preservation of the anterior vaginal wall during female radical cystectomy with orthotopic urinary diversion: technique and results. *J Urol* 2002; 168: 1442–5
- Denewer A. Re: gynecologic-tract spring extra peritoneal retrograde radical cystectomy with neobladder. *Int Braz J Urol* 2008; 34: 369–70
- El-Bahnasawy MS, Osman Y, El-Hefnawy A et al. Radical cystectomy and urinary diversion in women: impact on sexual function. *Scand J Urol Nephrol* 2011; 45: 332–8

- 36 Gacci M, Saleh O, Cai T et al. Quality of life in women undergoing urinary diversion for bladder cancer: results of a multicenter study among long-term disease-free survivors. *Health Qual Life Outcomes* 2013; 11: 2–7
- 37 Granberg CF, Boorjian SA, Crispen PL et al. Functional and oncological outcomes after orthotopic neobladder reconstruction in women. *BJU Int* 2008; 102: 1551–5
- 38 Gross T, Meierhans Ruf SD, Meissner C, Ochsner K, Studer UE. Orthotopic ileal bladder substitution in women: factors influencing urinary incontinence and hypercontinence. *Eur Urol* 2015; 68: 664–71
- 39 Grossfeld GD, Stein JP, Bennett CJ et al. Lower urinary tract reconstruction in the female using the Kock ileal reservoir with bilateral ureteroileal urethrostomy: update of continence results and fluorourodynamic findings. *Urology* 1996; 48: 383–8
- 40 Hautmann RE. The ileal neobladder to the female urethra. *Urol Clin North Am* 1997; 24: 827–35
- 41 Hautmann RE, de Petriconi R, Kleinschmidt K, Gottfried HW, Gschwend JE. Orthotopic ileal neobladder in females: impact of the urethral resection line on functional results. *Int Urogynecol J* 2000; 11: 224–30
- 42 Hautmann RE, Paiss T, De Petriconi R. The ileal neobladder in women: 9 years of experience with 18 patients. *J Urol* 1996; 155: 76–81
- 43 Jarolím L, Babjuk M, Pecher SM et al. Causes and treatment of residual urine volume after orthotopic bladder replacement in women. *Eur Urol* 2000; 38: 748–52
- 44 Jentzmik F, Schrader AJ, de Petriconi R et al. The ileal neobladder in female patients with bladder cancer: long-term clinical, functional, and oncological outcome. *World J Urol* 2012; 30: 733–9
- 45 Koie T, Hatakeyama S, Yoneyama T, Hashimoto Y, Kamimura N, Ohyama C. Uterus-, fallopian tube-, ovary-, and vagina-sparing cystectomy followed by U-shaped ileal neobladder construction for female bladder cancer patients: oncological and functional outcomes. *Urology* 2010; 75: 1499–503
- 46 Large MC, Katz MH, Shikanov S, Eggener SE, Steinberg GD. Orthotopic neobladder versus Indiana pouch in women: a comparison of health related quality of life outcomes. *J Urol* 2010; 183: 201–6
- 47 Lee CT, Hafez KS, Sheffield JH, Joshi DP, Montie JE. Orthotopic bladder substitution in women: nontraditional applications. *J Urol* 2004; 171: 1585–8
- 48 Lin TX, Huang J, Xu KW et al. Laparoscopic radical cystectomy with orthotopic ileal neobladder: report of 108 cases. *Natl Med J China* 2008; 88: 2437–40
- 49 Mearini E, Mearini L, Zucchi A, Costantini E, Goracci G, Porena M. Detubularized rectosigmoid neobladder in women after cystectomy for bladder cancer. *J Surg Oncol* 2000; 74: 49–52
- 50 Miyake H, Furukawa J, Muramaki M, Takenaka A, Fujisawa M. Orthotopic bladder substitution following radical cystectomy in women: comparative study between sigmoid and ileal neobladders. *Urol Oncol Semin Orig Investig* 2012; 30: 38–43
- 51 Moursy EES, Eldahshoursy MZ, Gamal WM, Badawy AA. Orthotopic genital sparing radical cystectomy in pre-menopausal women with muscle-invasive bladder carcinoma: a prospective study. *Indian J Urol* 2016; 32: 65–70
- 52 Nesrallah LJ, Almeida FG, Dall'Oglio MF, Nesrallah AJ, Srougi M. Experience with the orthotopic ileal neobladder in women: a mid-term follow-up. *BJU Int* 2005; 95: 1045–7
- 53 Parra R, Berni K, Cummings J. Orthotopic bladder substitution in women with an ileocolonic pouch: functional and oncological outcome. *Arch Esp Urol* 2004; 57: 769–74
- 54 Pichler R, Zangerl F, Leonhartsberger N, Stöhr B, Horninger W, Steiner H. Orthotopic bladder replacement in women: focus on functional results of a retrospective, single-centre study. *Scand J Urol* 2013; 47: 295–301
- 55 Puppo P, Introini C, Calvi P, Naselli A. Prevention of chronic urinary retention in orthotopic bladder replacement in the female. *Eur Urol* 2005; 47: 674–8
- 56 Roshdy S, Senbel A, Khater A et al. Genital sparing cystectomy for female bladder cancer and its functional outcome; a seven years' experience with 24 cases. *Indian J Surg Oncol* 2016; 7: 307–11
- 57 Schover LR, Van Eschenbach AC. Sexual function and female radical cystectomy: a case series. *J Urol* 1985; 134: 465–8
- 58 Shimogaki H, Okada H, Fujisawa M et al. Long-term experience with orthotopic reconstruction of the lower urinary tract in women. *J Urol* 1999; 161: 573–7
- 59 Siracusano S, D'Elia C, Cerruto MA et al. Quality of life following urinary diversion: orthotopic ileal neobladder versus ileal conduit. A multicentre study among long-term, female bladder cancer survivors. *Eur J Surg Oncol* 2019; 45: 477–81
- 60 Badawy AA, Abolyosr A, Mohamed ER, Abuzeid AM. Orthotopic diversion after cystectomy in women: a single-centre experience with a 10-year follow-up. *Arab J Urol* 2011; 9: 267–71
- 61 Lavallée E, Dovey Z, Pathak P et al. Functional and oncological outcomes of female pelvic organ-preserving robot-assisted radical cystectomy. *Eur Urol Open Sci* 2022; 36: 34–40
- 62 Rouanne M, Legrand G, Neuzillet Y et al. Long-term women-reported quality of life after radical cystectomy and orthotopic ileal neobladder reconstruction. *Ann Surg Oncol* 2014; 21: 1398–404
- 63 Gakis G, Stenzl A. Considerations for orthotopic diversions in women. *Curr Opin Urol* 2015; 25: 550–4
- 64 Martini A, Falagario UG, Russo A et al. Robot-assisted radical cystectomy with orthotopic neobladder reconstruction: techniques and functional outcomes in males. *Eur Urol* 2023; S0302-2838(23)02728-8 <https://doi.org/10.1016/j.eururo.2023.04.009>
- 65 Ferriero M, Simone G, Rocchegiani A et al. Early and late urodynamic assessment of Padua ileal bladder. *Urology* 2009; 73: 1357–62
- 66 Kessler TM, Studer UE, Burkhard FC. Increased proximal urethral sensory threshold after radical pelvic surgery in women. *Neurourol Urodyn* 2007; 26: 208–12
- 67 von Deimling M, Laukhtina E, Pradere B et al. Radical cystectomy and urinary diversion in women: techniques, outcomes, and challenges—a narrative review. *Transl Androl Urol* 2022; 11: 1598–610
- 68 Rosen R, Brown C, Heiman J et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; 26: 191–205

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Abbreviations: BCa, bladder cancer; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire–Cancer 30; FSFI, Female Sexual Function Index; HRQOL, health-related quality of life; IC, ileal conduit; ISC, intermittent self-catheterization; NSRC, nerve-sparing radical cystectomy; ONB, orthotopic neobladder; RC, radical cystectomy; ROBINS-I, Risk of bias in non-randomized studies of interventions tool; ROPRC, reproductive organ-preserving radical cystectomy; SF, short-form.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Flow diagram of the study selection procedure for the systematic review and meta-analysis.

Table S1 Characteristics of included studies reporting on functional outcomes in female patients undergoing radical cystectomy and urinary diversion for treatment of bladder cancer.

Table S2 Functional outcomes report in female patients undergoing radical cystectomy and urinary diversion for treatment of bladder cancer.