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Short term morbidity and mortality following radical cystectomy: a systematic review

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Abstract

Objective: To study short-term (< 90 days) morbidity and mortality following radical cystectomy (RC) for bladder cancer and identify modifiable risk factors associated with these.

Design: Systematic review.

Methods: The systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. PubMed and EMBASE were searched for relevant papers. Studies reporting complications, reoperations, length of stay, and mortality within 90 days were included. Studies were reviewed according to criteria from the Oxford Centre for Evidence-Based Medicine and the quality of evidence was assessed using the New Castle Ottawa Scale.

Results: The search retrieved 1957 articles. Sixty-six articles were included. The quality of evidence was poor to good. Most studies were retrospective, and no randomised clinical trials were identified. Of included studies a median of 6.5 Martin criteria for reporting complications after surgery were fulfilled. The Clavien-Dindo Classification for grading complications was most frequently used. The weighted overall complication rate after RC was 34.9% (range 28.8–68.8) for in house complications, 39.0% (range 27.3–80.0) for 30-day complications, and 58.5% (range 36.1–80.5) for 90-day complications. The most common types of complications reported were gastrointestinal (29.0%) and infectious (26.4%). The weighted mortality rate was 2.4% (range 0.9–4.7) for in house mortality, 2.4% (range 0.3–4.0) for 30-day mortality, and 4.7% (range 0.0–7.0) for 90-day mortality. Age and comorbidity were identified as the best predictors for complications following RC.

Conclusion: Short-term morbidity and mortality is high following RC. Reporting of complications is heterogeneous and the quality of evidence is generally low. There is a continuous need for randomised studies to address any intervention that can reduce the morbidity and mortality following RC.

PROSPERO ID: 104937

Article summary

Strengths and limitations of this study

- This systematic review can provide as a reference paper for future studies and when measuring quality of care.
- This systematic review emphasizes the continuous need to identify and moderate risk factors for complications and optimize postoperative management plans to reduce both morbidity and mortality associated with radical cystectomy.
- This review is limited by heterogeneity in outcome measures of morbidity with lack of clear definitions of surgical complications making direct comparison between studies difficult.

INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection and urinary diversion is the preferred treatment for non-metastatic muscle invasive bladder cancer (BC), and for some cases of high-risk non-muscle invasive BC, in patients fit for major surgery (1). RC is a comprehensive procedure that involves surgery to several organ systems and as a result it is associated with a high postoperative morbidity and mortality. Attempts have been made over the years to reduce postoperative complications such as the introduction of Enhanced Recovery After Surgery (ERAS) programs. However, addressing morbidity and mortality associated with RC across surgical cohorts remains important for preoperative counseling, planning of treatment, identification of modifiable risk factors to reduce morbidity and mortality, future clinical trial design, and for assessment of surgical quality. Several measures of morbidity are clinically important such as complication rate, reoperation rate, length of stay (LOS), readmission rate, and mortality. In this paper we conducted a contemporary systematic review of short-term morbidity and mortality following RC for BC.

METHODS

Search strategy and study selection

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (2). A published protocol (PROSPERO ID: 104937) with pre-specified outcomes, inclusion criteria and search strategy is accessible online.

A systematic literature search in PubMed and EMBASE was conducted on 11th of June 2019 and re-run on 27th of May 2020. A search string was created with the help of an information specialist (Appendix 1).

Articles were screened in a two-stage selection process. In the first stage, two authors (S.L.M. and M.A.R.) reviewed abstracts. All prospective and retrospective studies on short-term (< 90 days) morbidity and mortality after RC were included. Trials with less than 100 participants, indications for cystectomy other than BC, extended procedure (e.g. nephroureterectomy), salvage/palliative cystectomy, organ sparing cystectomy (e.g. partial cystectomy, prostate-sparing cystectomy, vaginal sparing cystectomy, seminal vesicles sparing cystectomy), selected patient group (e.g. certain age groups, women only), feasibility studies, surgical technique-only papers, animal series, and studies not published in English were excluded. Conference papers, case reports, book chapters, review papers, editorials, comments, letters to the editors, and abstracts were also excluded. When in doubt, studies were maintained for further review. In the second stage, full text of all included articles was obtained and read by the same two authors. Agreement was reached through consensus using Covidence Systematic Review software (3). Any disagreement was resolved by discussion and final decision was based on a consensus. In case of duplicate data/study the following criteria were applied in the selection: 1) outcome (studies reporting on complications were prioritized over LOS, mortality), 2) size of the cohort (larger studies were prioritized over smaller studies), 3) methodology (prospective studies were prioritized over retrospective studies and extraction of data from medical/hospital records over record linkage (e.g. ICD-codes in database)), 4) study period (studies with the most recent study period were prioritized).

Data extraction and quality assessment

The following data was extracted from all studies where possible: first author, data source (e.g. single center, multicenter, database), institution/country of origin, study period, year of publication, number of cases, study design, length of follow up, classification system used for grading complications, use of fast track/ERAS protocol, demographics (age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI),

American Society of Anesthesiologists (ASA) score, pT-stage, N-stage, neoadjuvant therapy, previous radiation therapy, prior abdominal/pelvic surgery), outcomes (urinary diversion, number of total complications, complication rate, segregated complications, complication reasons, mortality rate, LOS , reoperations, risk factors for outcomes).

The quality of reporting complications was estimated using the Martin criteria (4). Furthermore, the level of evidence was rated according to criteria from the Oxford Centre for Evidence-Based Medicine (5). The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational comparative studies (6).

Outcome measures

The primary outcome was overall complication rate: number of patients with one or more complication(s) within 90 days after RC regardless of classification system used. Secondary outcomes were the following: rate of graded complications according to severity grade utilized; frequencies of types of complications; LOS, reoperation rate; mortality rate; and risk factors for development of outcomes of morbidity (e.g. complications, death, reoperations).

Statistical analysis

Descriptive statistics were used. A weighted average and range were calculated for all rates. A meta-analysis on risk factors for morbidity was not possible due to high heterogeneity of reporting in the multivariate analysis across studies.

Patient and public involvement

No patients were involved in conducting this review.

RESULTS

The literature search retrieved 1957 articles after removing duplicates. Of these 66 studies met the in- and exclusion criteria (7–72). The process is outlined in Figure 1.

Characteristics of included studies

The characteristics of the included studies are summarized in Table 1. Twenty-nine studies (43.9%) were single-center studies and 37 studies (56.1%) were register or multicenter database studies. Most studies (71.2%) were retrospective, retrospective studies of prospectively maintained databases (12.1%) or combined retrospective and prospective studies (4.5%). Only eight (12.1%) were purely prospective surgical series. Patients were operated in the period 1990–2018. Of included studies only two reported that an ERAS protocol was used for the entire cohort (16,48), and in six studies an ERAS protocol was used in a part of the cohort (33,39,42,67,69,72). In the rest of the included studies an ERAS protocol was not used, or the authors did not report on the perioperative care.

Table 1. Summary of patient characteristics.

		Number of patients with data available (sum of references)	References
Demographics			
Percentage of males (weighted average, % (range))	80.8% (71.1–99.1)	194 769	(7–14,16–23,25,26,28–36,39,41–52,54–72)
Age			
- weighted median (range)	69 years (63–73)	69 076	(7,9–11,13,14,16,17,19–22,26,27,29,30,43,45,47,48,50–52,55–58,60,61,63,65,68–72)
- weighted mean (range)	68.2 years (56.2–72.1)	104 373	(8,12,19,23,29,44,47,48,62,64,70,71)
BMI			
- weighted median (range)	26.1 (22.3–27.8)	10 332	(9,10,14,16,21,22,26,27,30,35,45,47,48,61,63,65,69,71,72)
- weighted mean (range)	27.6 (20.4–29.7)	13 187	(8,12,17–19,28,29,44,47,48,54,59,62,64,67,70,71)
ASA score (weighted average, % (range))			
- I	8.0% (0–35.1)	15 202	(10,11,14,19,26,28–31,33,37,42,45,49,53,55,60,63,65,69–71)
- II	39.0% (1.7–81.9)	15 435	(10,11,14,19,26,28–31,33,37,42,45,46,49,53,55,60,63–65,69–71)
- III	54.0% (7.9–94.0)	13 490	(10,14,19,22,26,28–31,33,42,45,46,49,53,55,59,63–65,70,71)
- IV	4.8% (0–16.3)	12 287	(10,14,19,26,28,29,31,33,42,46,49,53,55,59,64,65,70,71)
CCI (weighted average, % (range))			
- 0	45.6% (6.3–68.1)	114 334	(7,16,20,36,42,50,58,60,70)
- 1	26.7% (4.0–30.6)	85 875	(16,20,34,36,50,58,60,70)
- ≥2	20.9% (2.5–69.4)	88 159	(16,20,22,34,36,48,52,58,60,64,66,70)
Prior abdominal surgery (weighted average, % (range))	41.4% (5.1–55.1)	4 214	(8,12,16,18,21,29,35,45,61,62,71)
Previous radiation (weighted average, % (range))	5.5% (1.3–22.1)	3 910	(8,16,18,21,29,33,51,61,62,71)
Neoadjuvant chemotherapy (weighted average, % (range))	13.2% (0–50.8)	23 678	(8,10,12,14,16–18,22,25,26,33,35,37,41,45,46,49,53,59,60,62,63,65,68–72)
Perioperative details			
Type of diversion (weighted average, % (range))			

- ileal conduit	85.0% (31.4–93.8)	80 675	(8,10–14,16–19,21,22,26,29–31,33,35,36,42–51,53–55,60,61,63–72)
- neobladder	10.5% (2.6–62.1)	65 307	(8,10,12–14,16–19,21,22,26,29–31,33,35,36,42–49,51,53–55,60,61,63–67,69–72)
- continent cutaneous diversion	1.25% (0–29.6)	59 853	(8,12–14,16,18,26,29,30,36,43,44,46,48,49,51,54,55,60,61,63,65–67,69,71,72)
- ureterocutaneostomy	1.35% (0–26.7)	58 210	(8,17–19,22,30,31,36,44,47,48,54,60,63,64,66,67,69,72)
- nephrostomy	0.01% (0–0.5)	56 718	(8,18,19,22,31,36,44,49,51,54,60,63,64,66,67,69,72)
Pathological tumor stage (weighted average, % (range))			
- ≤ T1	27.1% (6.4–54.9)	31 317	(10–12,14,15,17–21,25–27,30,31,35,37,42,43,45,46,48,52,54,55,59,60,62–64,71,72)
- T2	29.1% (11.9–56.7)	28 916	(10–12,14,15,17–21,25–27,30,31,35,37,43,45,46,48,49,52,54,55,60,62–64,71)
- T3	28.5% (10.8–42.4)	26 537	(10,12,14,17–21,25–27,30,31,35,43,46–49,52,54,55,60,62–64,71)
- T4	13.2% (2.4–25.9)	26 537	(10,12,14,17–21,25–27,30,31,35,43,46–49,52,54,55,60,62–64,71)
Lymph node positive disease (weighted average, % (%-range))	19.1% (6.3–44.4)	29 615	(10–12,14–16,18–21,25–27,29–31,35,43,45–49,52,54,60,62–64,71,72)
LOS			
- weighted median (%-range))	11 days (4–39)	77 038	(7,10,12–14,16,18,20–22,24,26,28,29,31,33,35,39,40,42,43,45,46,48,50,51,53,55,56,58,59,61–63,65,66,69,71,72)
- weighted mean (%-range)	12.5 days (8.2–27.6)	39 562	(8,19,25,38,39,44,47,48,50,53,54,58,64,67,68,70)

Abbreviations: BMI = Body Mass Index, ASA= American Society of Anesthesiologists, CCI = Charlson Comorbidity Index, LOS= Length of Stay

Complications

Fifty-two studies reported on short term complications as outlined in table 2. The most frequently reported follow-up period was 90 days. Three studies reporting short term complications did not state the exact follow-up period and were therefore excluded from the complication rate analysis (33,40,67). During the primary hospitalization the overall complication rate was 34.9% (28.8–68.8). The complication rate increased with longer follow-up to 39.0% (27.3–80.0) 30 days, and 58.5% (36.1–80.5) 90 days postoperatively. Minor complications accounted for 40.0% (19.9–77.4) and 38.2% (19.0–80.8) of the

complications reported at 30- and 90-days follow-up, respectively. Major complications after RC occurred in 15.5% (4.9–24.8) and 16.9% (13.4–32.0) of patients after 30 and 90 days, respectively. Rates of complications according to the Clavien-Dindo classification and reoperations are further outlined in Table 2.

Table 2. Complications and re-operations.

Outcome	Complication rate, weighted average (%-range)	Number of patients with data available (sum of references)	References
In-hospital complication rate	34.9%*[1] (28.8–68.8)	76171	(19,32,39,50,58,59,61)
30-day complication rate	39.0%*[2] (27.3–80.0)	19160	(9,18,23,28,30,43,44,46,47,51,53,55,60–62,70–72)
- CD grade I	9.2% (6.0–16.1)	1291	(30,35,45,70)
- CD grade II	29.8% (20.6–52.5)	1291	(30,35,45,70)
- CD grade IIIa+b	6.9% (5.6–14.4)	8749	(28,30,35,45,70)
- CD grade IVa+b	7.8% (0.7–11.0)	8749	(28,30,35,45,70)
- CD grade V	1.7% (0.0–2.1)	8982	(28,30,35,45,46,70)
- Minor complication rate*[3](%)	40.0% (19.9–77.4)	2536	(13,18,43,44,51,55,60,62)
- Major complication rate*[4]	15.5% (4.9–24.8)	4499	(13,18,30,43,44,46,51,55,60,62,70,72)
90-day complication rate	58.5*[5]% (36.1–80.5)	10625	(8,10,12,14,16,17,21,22,26,29–31,42,48,49,54,59–61,63–65,69,71,72)
- CD grade I	15.0% (4.0–31.6)	4442	(29,30,54,59,61,64,69)
- CD grade II	38.9% (27.0–67.4)	4442	(29,30,54,59,61,64,69,72)
- CD grade IIIa+b	20.5% (8.5–39,2)	5548	(29–31,54,59,61,64,69,72)
- CD grade IVa+b	3.0% (0.2–8.5)	5548	(29–31,54,59,61,64,69,72)
- CD grade V	3.5% (0.1–3.9)	55440	(29–31,36,48,54,59,61,64,69,72)
- Minor complication rate*[3]	38.2% (19.0–80.8)	56955	(8,12,16,17,21,26,31,36,42,59–61,63,69)
- Major complication rate*[4]	16.9% (13.4–32.0)	59068	(8,12,14,16,17,22,26,29–31,36,42,49,59–61,64,69,72)
Reoperation rate - 30-day - 90-day	 5.8% (3.0–8.7) 12.3% (9.3–18.9)	 11598 1533	 (9,21,27,28,30,44–46,53,62,71) (10,26,30,54,69)

*[1]one study (25) did not report on overall complication rate, *[2]Three studies (13,35,45) did not report on overall complication rate. *[3] minor complications defined as Clavien-Dindo grade I–II, MSKCC grade 1–2 or minor complications. *[4] major complications defined as Clavien-Dindo grade III–V, MSKCC grade 3–5 or major complications. *[5] one study (36) did not report overall complication rate.

Thirty-four studies (8,10,12,14,16,18,19,22,26,28–31,33,35,36,42,45,46,48,49,54,55,59–64,67,69–72) classified complications according to the Clavien-Dindo classification (73), six (9,13,17,43,44,51) studies

classified complications as minor and major complications, three studies (21,27,72) used the Memorial Sloan Kettering Cancer Centre modified Clavien-Dindo classification (61), one study (65) used Common Terminology Criteria for Adverse Events (74), and nine studies (23,25,32,39,40,47,50,53,58) did not use any system for grading complications.

Type of complications

Twenty-one studies reported on types of 90-day complications (Table 3). Gastrointestinal (GI) (29.0%) and infectious (26.4%) complications were the most frequent.

Table 3. Categories and type of 90-day complications.

Category/type	Rate, weighted average (%-range)	Number of patients with data available (sum of references)	References
Gastrointestinal	29.0% (6.7–42.7)	6188	(10,15,16,20,21,24,42,43,48,53,55,63)
- Ileus	16.5% (3.8–33.7)	5073	(6,8,15,16,24,25,36,42,43,48,55,58,59,63)
- Small bowel obstruction	4.6% (1.7–9.0)	3193	(8,15,20,25,42,43,48,55,58,59)
- Constipation	3.3% (0.5–11.4)	2491	(6,8,16,42,43,55)
- Clostridium Difficile colitis	2.3% (0.7–3.8)	2574	(15,43,55,58,63)
- Diarrhea	1.7% (0.6–5.6)	2392	(6,16,42,43,48,55)
- Anastomotic bowel leak	1.1% (0.3–1.9)	3254	(6,15,16,20,55,63)
- Gastrointestinal bleeding	1.0% (0.3–1.3)	2757	(6,15,16,55,63)
Infectious	26.4% (10.9–46.2)	5270	(8,10,15,16,20,21,24,42,43,48,55,63)
- UTI/pyelonephritis	14.1% (1.1–29.7)	4297	(6,15,16,20,36,42,43,48,55,58,59,63)
- Sepsis	4.2% (1.5–8.5)	3812	(15,16,20,36,42,43,48,55,59,63)
- Fever of unknown origin	3.1% (0.6–4.8)	2966	(6,15,16,43,55,63)
- Pelvic/intraabdominal abscess	2.4% (0.1–4.3)	2836	(15,16,42,55,59,63)
Genitourinary	16.0% (6.0–23.5)	5697	(11,15,16,21,24,48,53,55,63)
- Ureter stenosis	3.2% (1.7–7.0)	2539	(6,15,16,20,42,55,59)
- Ureter leakage	3.1% (0.4–5.3)	4282	(6,8,15,16,20,42,43,55,58,59,63)
Wound	13.1% (5.6–27.0)	6424	(6,10,11,15,16,20,21,24,42,53,58,63)
- Dehiscence	4.0% (1.3–4.9)	2722	(20,25,43,55,63)
- Fascial dehiscence	1.6% (0.4–3.5)	2139	(6,15,48,55,59)
- Infection	10.5% (2.4–19.3)	3827	(8,15,20,25,36,43,48,55,63)
Cardiac	6.1% (0.6–16.9)	5366	(6,10,11,15,24,42,43,53,55,58,63)
- Myocardial infarction	1.1% (0.2–3.5)	4170	(6,8,15,20,42,43,48,55,59,63)
- Arrhythmia	4.2% (0.2–14.4)	2923	(6,15,42,43,55,63)
Bleeding	3.5% (0.5–17.8)	2814	(10,24,55,58,63)
- Hematoma	0.9% (0.7–1.2)	1096	(6,8,59)
- Transfusion	23.2% (8.1–45.3)	2606	(6,8,25,42,48,55,58)
Respiratory	5.0% (1.3–11.5)	6845	(6,8,10,11,15,21,24,42,43,48,53,55,63)

- Pneumonia	2.8% (0.6–5.9)	3639	(6,15,20,25,36,42,48,55,63)
Thromboembolic	3.6% (0.2–8.1)	4933	(6,8,10,15,20,24,25,42,43,48,55,59,63)
Neurological	2.8% (0.6–7.7)	4557	(6,10,11,15,21,42,43,48,55,63)
Renal failure	2.3% (0.5–6.7)	4070	(6,8,15,16,42,43,55,59,63)
Other - Fistula - Lymphocele	 1.1% (0.6–1.4) 2.1% (1.3–4.7)	 1560 3381	 (6,15,20,42,43,58,59) (6,8,15,20,42,43,48,55,58,59)

UTI: urinary tract infection

Mortality

Fifty-three studies were included in the mortality analysis (Table 4). The weighted average for the in-hospital mortality rate was 2.4% (0.9–4.7), the 30-day mortality rate 2.4% (0.3–4.0) and the 90-day mortality rate 4.7% (0.0–7.0).

Table 4. In-hospital, 30-day, and 90-day mortality.

	Mortality rate, weighted average (%-range)	Number of patients with data available (sum of references)	References
In-hospital mortality	2.4% (0.9–4.7)	87848	(26,35,44,50,52,55,60)
30-day mortality	2.4% (0.3–4.0)	61798	(1–3,7–9,14,18,22,24,27,29,31,32,35,37–40,45,46,51,54–56,63–66)
90-day mortality	4.7% (0.0–7.0)	107702	(1,2,4–6,8,10,11,14–16,18,20,23–25,27,30–32,35,42,43,48,50,53–56,58,59,61–63,65,66)

Quality of studies

Only four of the included studies (12,21,22,61) met 10 of 10 Martin criteria (Appendix 2). The median number of fulfilled Martin criteria was 6.5 (range 2–10). The only criterion fulfilled by all studies was defining the method of accruing data. The level of evidence according to criteria from the Oxford Centre for Evidence-Based Medicine was rated as 3 or 4. The methodological quality across studies was “poor” to “good” assessed using the NOS (Appendix 2).

DISCUSSION

We systematically reviewed the literature to accurately describe short-term morbidity and mortality following RC and identify modifiable risk factors associated with these. The aim was to identify factors that could form the basis for design of future randomised trials on postoperative interventions that can reduce the risk of complications.

RC is an extensive urological procedure and associated with a high risk of short-term minor and major morbidity. Mortality within 90-days of primary surgery is not negligible and occurs in 4.7% according to our review. Our systematic review underlines that complications occur in 1 in 3 patients during hospitalization and that 1 in 5 patients have major complications during the first 30 days after RC. This emphasizes the continuous need to identify and moderate risk factors for complications and optimize postoperative management plans to reduce both morbidity and mortality associated with RC.

Our analysis identified GI and infectious complications as the most frequently reported complications after RC. Overall, GI complications occurred in 29.0% with a postoperative ileus rate of 15.6%. Urinary tract infections (UTI) were the most frequently occurring infectious complications occurring in 14.1% of patients.

Based on the literature reviewed, it was not possible to identify the most important risk factors for GI complications and thus define whether these were potentially modifiable. The risk of ileus, which is often most clinically relevant, seems to be affected by many factors, most importantly increasing age. One study reported increasing age a statistically significant risk factor for ileus with an odds ratio (OR) of 1.30 (95% CI 1.1–1.5) per 10-year increase of age (23). This finding is supported by a large retrospective study of 41 498 patients that found an increased OR of developing ileus with per one year increment in age (OR 1.012, 95% CI 1.009–1.014, $p<0.05$) (75). The study also found that the risk of ileus increased with several chronic conditions such as chronic pulmonary and neurological disease. This underlines that reducing GI complication rates relies primarily on an overall medical assessment and that alternative treatment options should be considered in medically ill patients. Surgeons performing RC must be aware that poor general health status increases the risk of GI complications and entails a poor short-term outcome. Several studies of RC have promoted the implementation of ERAS protocols, which originate from colorectal surgery where ERAS reduces GI complications. However, there is limited evidence for ERAS in an RC setting (76). Only the use of postoperative gum-chewing, the use of Alvimopan (a peripherally acting μ-opioid receptor antagonist currently not available in Europe) and controlled administration of perioperative fluid management (goal directed fluid therapy) to avoid both fluid excess and hypovolemia have been shown to reduce GI complications after RC in randomised clinical trials (RCT) (77–79). Comparative studies indicate that omitting the nasogastric tube and mechanical bowel preparation result in lower GI complications after RC (80,81). ERAS offers good practical guidelines, but the various elements such as early mobilization, omitting pelvic drainage, perioperative body temperature monitoring, and early oral diet are not studied individually but introduced in different modified versions with several components used together. Consequently, it is difficult to derive which factor has the largest impact on reducing GI complications. Meta-analysis of ERAS protocols versus traditional protocols have found a faster return of bowel function and lower overall complication rate in the group managed on an ERAS compared to a standard of care protocol, but the overall level of evidence in RC remains low with regard to ERAS implementation (82,83). A previous study described that only 20% of surgeons that endorse ERAS guidelines actually practiced all interventions recommended by the ERAS society (84).

The anatomical reconstruction of the urinary tract with the use of bowel as urinary diversion following RC will naturally increases the risk of UTI, which can prolong LOS and is leading to re-admittance. Only three of the included studies identified multivariable risk factors that were statistically significant predictors of infectious complications 30 and 90 days after RC (23,28,49). Two studies found that continent reservoirs were associated with a higher risk of UTI compared to ileal conduits. Johnson et al. found that any

continent urinary diversion increased the risk of infectious complications compared to an incontinent urinary diversion (OR 1.68, p<0.001)(28). Nazmy et al. found that an Indiana pouch increased risk of UTI compared to ileal conduit (OR 3.55, 95% CI 1.33–9.44, p=0.01), however an orthotopic bladder substitute did not increase the risk of UTI compared to an ileal conduit (49). Other studies investigating this association have shown conflicting results (85–88). Hollenbeck et al. found preoperative bleeding disorder, poor functional status, preoperative acute renal failure, and a >10% weight loss preoperatively to be associated with an increased risk of UTI (23). In general, the comorbid patient may be at the highest risk for UTI. A large retrospective study of 1133 patients found that a CCI > 2 was associated with a higher 90-day postoperative UTI rate (OR = 1.8, 95% CI 1.1–2.9, p = 0.05) compared to a CCI 0–2 (85). It remains unclear if UTI can be prevented. Pariser et al. demonstrated that a change in prophylactic antibiotic protocol from a narrow to a broader coverage did not reduce the UTI rate, although the 30-day risk of overall infectious complications was reduced following RC from 41% to 30% (p = 0.043) (89). A population-based American study reported a lower infectious event rate when using a combination of antibiotic prophylaxis compared to a single agent antibiotic (OR 0.79, 95% CI 0.70–0.89, p <0.001) (90). The authors also investigated if extended antibiotic treatment > 24 h after RC decreased the risk of infectious complications, but no such association was found. Currently, international guidelines recommend that broad-spectrum antibiotics are used in the prophylactic regimen considering the local microbiological environment (91,92). However, RCTs addressing antibiotic prophylaxis regarding type, timing and duration for the risk of UTI are lacking and warranted.

Infectious and GI complications also account for the largest share of major complications (10,61,69). A recent study on reoperations in a cohort of 10 848 patients found that 60% of reoperations occurring within 30 days after RC were of gastrointestinal origin (93). The study also demonstrated that a reoperation within 30 days increased the short-term mortality (6.6% vs. 1.6%, p<0.01) compared to no reoperation. In several studies patient related factors, age and comorbidity, were identified as the most important factors for mortality at index hospitalization, as well as 30- and 90 days following surgery (11,17,24,27,32,38,41,52,66,68).

In addition to patient-related factors, the impact of hospital volume, surgical experience, and surgical technique has been addressed. A meta-analysis of seven studies found that the risk of postoperative mortality after RC was decreased by 45% when performed at a high-volume center compared to a low volume center (pooled estimated effect OR 0.55 (95% CI 0.44–0.69)) (94). Two studies found a significant decreased post-operative mortality when performed by high-volume surgeons (OR 0.55, 95% CI 0.41–0.73 and OR 0.64, 95% CI 0.44–0.91). Studies also show that complications are reduced with both increasing hospital and surgeon volume (32,36,95,96). Unfortunately, the distinction between low- vs high-volume is not well-defined and thus not clearly comparable between studies. The European Association of Urology (EAU) Muscle-invasive and Metastatic Bladder Cancer Guideline Panel recommends RC to be performed at centers with at least 10 RC/year and preferably >20 RC/year (97). The surgical technique has been investigated in 12 of the included studies in this review (18,20,29,31,33,35,45,48,62,64). Open RC was compared to robotic-assisted RC in ten of these non-randomised papers. In seven of these publications, a significantly reduced complication rate was found. However, four RCTs comparing open and robotic surgery (not included in the review) did not find a difference in complication rates (98–102). All RCTs have been conducted with extracorporeal urinary diversion performed and it is speculated that robot-assisted RC with

intracorporeal urinary diversion may have a lower complication rate compared to open RC. The question in hand is currently being studied in the ongoing iROC trial (103).

There are limitations of this review that must be addressed. Most of the included studies were retrospective which limits the clinical utility. It is important to notice that we excluded studies with less than 100 patients and studies investigating subgroups of patients such as certain age groups, types of urinary diversion or T-stages of BC. Since most RCTs on RC have less than 100 participants and often exclude patients with certain characteristics they were not included in this review.

The difficulties of comparing RC studies are manifold. Firstly, selection bias between cohorts must be expected. This is reflected by the wide range for the estimates of the weighted averages for ASA score and CCI (Table 1). The selection of patients fit for RC is known to be associated with great variation among centers (104). Secondly, there was no standardized reporting of complications. Most used different classification systems for severity grade of complications with the Clavien-Dindo classification being the most frequent. Thirdly, even when using a grading system as Clavien-Dindo with certain criteria, the scale can be interpreted differently or modified in some way. For example, some studies do not calculate blood transfusions as a complication even though it could be argued to be a grade II complication. Fourthly, measures of morbidity can be defined differently across studies. For example, ileus is reported in up to 20% of patients undergoing RC. However, the reporting of ileus may be questioned as a previous systematic review found that ileus was defined differently across studies, and in the majority of included studies it was not defined at all (105). There is an increased focus on more uniform reporting of morbidity following RC and the EAU have proposed authors to use quality criteria originally proposed by Martin et al. (4,106). In the present review only four studies fulfilled all the Martin criteria. A previous non-systematic review from 2007 found no study reporting on complications after RC fulfilling all the Martin criteria. Lastly, publication bias must be emphasized as an important limitation.

We refrained from a meta-analysis of predictors of morbidity and mortality in this review as the number of studies investigating the same risk variable and outcome were too small for an analysis. Identifying clinical predictors may aid to the prevention of postoperative morbidity and mortality. Currently there is no risk-assessment tool to predict postoperative outcomes after RC, and little correlation is found between the most frequently used risk-scoring systems (e.g. CCI and ASA score) and postoperative outcomes (70). Nevertheless, in the included studies of this review, comorbidity was in multivariate logistic regression analysis consistently associated with a significantly increased OR of both complications (12,17,22,23,32,49,51,58,60,61,72) and mortality (11,17,24,32,41,52,66). Surprisingly, there is a paucity of prospective studies studying the subjects of the most common complications after RC in order to identify clinical predictors of these. Furthermore, prospective randomised studies comparing different interventions/regimens are lacking.

CONCLUSION

This review shows that RC is associated with high risk of morbidity and mortality. However, with thorough patient selection, experienced surgeons, treatment at a high-volume hospital and the implementation of an

ERAS protocol morbidity and mortality can likely be reduced. Trials addressing medical or surgical interventions to reduce short-term complication are needed.

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COMPETING INTERESTS

None declared.

AUTHORS CONTRIBUTIONS

All authors contributed to the research idea and the question. S.L.M., U.N.J., and M.A.R. wrote the protocol. S.L.M. and M.A.R. screened all abstracts and full texts for inclusion. S.L.M. did all the data extraction and the statistics. S.L.M. drafted the manuscript and all authors contributed to the editing of the manuscript and approved the final manuscript.

REFERENCES

1. Alfred Witjes J, Lebret T, Compérat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. *Eur Urol*. 2017 Mar;71(3):462–75.

2. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015 Jan 1;4(1):1.

3. Covidence Systematic Review Software [Internet]. Veritas Health Innovation Ltd, Melbourne, Australia. Available from: www.covidence.org

4. Martin RCG, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg*. 2002 Jun;235(6):803–13.

5. Howick J, Chalmers I, Glasziou P, et al. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. [Internet]. Available from: http://www.cebm.net/index.aspx?o=5653

6. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. [cited 2020 May 6]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

7. Afshar M, Goodfellow H, Jackson-Spence F, et al. Centralisation of radical cystectomies for bladder cancer in England, a decade on from the "Improving Outcomes Guidance": the case for super centralisation. *BJU Int*. 2018 Feb;121(2):217–24.

8. Al-Daghmin A, Kauffman EC, Shi Y, et al. Efficacy of robot-assisted radical cystectomy (RARC) in advanced bladder cancer: results from the International Radical Cystectomy Consortium (IRCC). *BJU Int*. 2014 Jul;114(1):98–103.

9. Arora K, Hanson KT, Habermann EB, et al. Early Complications and Mortality following Radical Cystectomy: Associations with Malnutrition and Obesity. *Bl cancer* (Amsterdam, Netherlands). 2018 Oct;4(4):377–88.

10. Björnsson O, Gudmundsson EO, Marteinsson VT, et al. Radical cystectomy in the treatment of bladder cancer in Iceland: A population-based study. *Scand J Urol*. 2016 Jan 2;50(1):65–70.

11. Boorjian SA, Kim SP, Tollefson MK, et al. Comparative performance of comorbidity indices for estimating perioperative and 5-year all cause mortality following radical cystectomy for bladder cancer. *J Urol*. 2013 Jul;190(1):55–60.

12. Cantiello F, Cicione A, Autorino R, et al. Metabolic Syndrome, Obesity, and Radical Cystectomy Complications: A Clavien Classification System-Based Analysis. *Clin Genitourin Cancer*. 2014 Oct;12(5):384–93.

13. Chang SS, Cookson MS, Baumgartner RG, et al. Analysis of early complications after radical cystectomy: results of a collaborative care pathway. *J Urol*. 2002 May;167(5):2012–6.

14. De Nunzio C, Cindolo L, Leonardo C, et al. Analysis of radical cystectomy and urinary diversion complications with the Clavien classification system in an Italian real life cohort. *Eur J Surg Oncol*. 2013 Jul;39(7):792–8.

15. de Vries RR, Visser O, Nieuwenhuijzen JA, et al. Outcome of treatment of bladder cancer: a comparison between low-volume hospitals and an oncology centre. *World J Urol*. 2010 Aug;28(4):431–7.

16. Djaladat H, Katebian B, Bazargani ST, et al. 90-Day complication rate in patients undergoing radical cystectomy with enhanced recovery protocol: a prospective cohort study. *World J Urol*. 2017 Jun 12;35(6):907–11.

17. Fairey A, Chetner M, Metcalfe J, et al. Associations Among Age, Comorbidity and Clinical Outcomes After Radical Cystectomy: Results From the Alberta Urology Institute Radical Cystectomy Database. *J Urol*. 2008 Jul;180(1):128–34.

18. Flamiatos JF, Chen Y, Lambert WE, et al. Open versus robot-assisted radical cystectomy: 30-day perioperative comparison and predictors for cost-to-patient, complication, and readmission. *J Robot Surg*. 2019 Feb;13(1):129–40.

19. Gschliesser T, Eredics K, Berger I, et al. The Impact of Gender on Tumour Stage in In-House Complications and Choice of Urinary Diversion: Results of the Austrian Cystectomy Registry. *Urol Int*. 2017;99(4):429–35.

20. Hanna N, Leow JJ, Sun M, et al. Comparative effectiveness of robot-assisted vs. open radical cystectomy. *Urol Oncol*. 2018 Mar;36(3):88.e1-88.e9.

21. Hayn MH, Hellenthal NJ, Hussain A, et al. Defining Morbidity of Robot-Assisted Radical Cystectomy Using a Standardized Reporting Methodology. *Eur Urol*. 2011 Feb;59(2):213–8.

22. Hirobe M, Tanaka T, Shindo T, et al. Complications within 90 days after radical cystectomy for bladder cancer: results of a multicenter prospective study in Japan. *Int J Clin Oncol*. 2018 Aug 13;23(4):734–41.

23. Hollenbeck BK, Miller DC, Taub D, et al. Identifying risk factors for potentially avoidable

complications following radical cystectomy. *J Urol*. 2005 Oct;174(4 Pt 1):1231–7.

24. Hollenbeck BK, Miller DC, Taub DA, et al. The Effects of Adjusting for Case Mix on Mortality and Length of Stay Following Radical Cystectomy. *J Urol*. 2006 Oct;176(4):1363–8.

25. Hu JC, Chughtai B, O'Malley P, et al. Perioperative Outcomes, Health Care Costs, and Survival After Robotic-assisted Versus Open Radical Cystectomy: A National Comparative Effectiveness Study. *Eur Urol*. 2016 Jul;70(1):195–202.

26. Jerlström T, Gårdmark T, Carringer M, et al. Urinary bladder cancer treated with radical cystectomy: Perioperative parameters and early complications prospectively registered in a national population-based database. *Scand J Urol*. 2014 Aug 21;48(4):334–40.

27. Johar RS, Hayn MH, Stegemann AP, et al. Complications After Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *Eur Urol*. 2013 Jul;64(1):52–7.

28. Johnson SC, Smith ZL, Golan S, et al. Temporal trends in perioperative morbidity for radical cystectomy using the National Surgical Quality Improvement Program database. *Urol Oncol Semin Orig Investig*. 2017 Nov;35(11):659.e13-659.e19.

29. Kader AK, Richards KA, et al. Robot-assisted laparoscopic vs open radical cystectomy: comparison of complications and perioperative oncological outcomes in 200 patients. *BJU Int*. 2013 Aug;112(4):E290–4.

30. Kanno T, Ito K, Sawada A, et al. Complications and reoperations after laparoscopic radical cystectomy in a Japanese multicenter cohort. *Int J Urol*. 2019 Apr;26(4):493–8.

31. Khan MS, Challacombe B, Elhage O, et al. A dual-centre, cohort comparison of open, laparoscopic and robotic-assisted radical cystectomy. *Int J Clin Pract*. 2012 Jul;66(7):656–62.

32. Kim SP, Boorjian SA, Shah ND, et al. Contemporary trends of in-hospital complications and mortality for radical cystectomy. *BJU Int*. 2012 Oct;110(8):1163–8.

33. Koupparis A, Villeda-Sandoval C, Weale N, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion: impact on an established enhanced recovery protocol. *BJU Int*. 2015 Dec;116(6):924–31.

34. Kulkarni GS, Urbach DR, Austin PC, et al. Impact of provider volume on operative mortality after radical cystectomy in a publicly funded healthcare system. *Can Urol Assoc J*. 2013;7(11–12):425–9.

35. Lenfant L, Campi R, Parra J, et al. Robotic versus open radical cystectomy throughout the learning phase: insights from a real-life multicenter study. *World J Urol*. 2019 Nov;

36. Leow JJ, Reese S, Trinh Q-D, et al. Impact of surgeon volume on the morbidity and costs of radical cystectomy in the USA: a contemporary population-based analysis. *BJU Int*. 2015 May;115(5):713–21.

37. Liedberg F, Holmberg E, Holmäng S, et al. Long-term follow-up after radical cystectomy with emphasis on complications and reoperations: A Swedish population-based survey. *Scand J Urol* Nephrol. 2012 Feb 19;46(1):14–8.

38. Lin W-Y, Wu C-T, Chen M-F, et al. Cystectomy for bladder cancer in elderly patients is not associated with increased 30- and 90-day mortality or readmission, length of stay, and cost: propensity score

matching using a population database. *Cancer Manag Res*. 2018;10:1413–8.

39. Liu B, Domes T, Jana K. Evaluation of an enhanced recovery protocol on patients having radical cystectomy for bladder cancer. *Can Urol Assoc J*. 2018 Jul;12(12):421–6.

40. Llorente C, Lopez B, Hernandez V, et al. Variability in complications and operative mortality after radical cystectomy in Spain. *Actas Urol Esp*. 2017 Jan;41(1):32–8.

41. Llorente C, Guijarro A, Hernandez V, et al. Effect of hospital volume on 90-day mortality after radical cystectomy for bladder cancer in Spain. *World J Urol*. 2020 May;38(5):1221–8.

42. Llorente C, Guijarro A, Hernández V, et al. Outcomes of an enhanced recovery after radical cystectomy program in a prospective multicenter study: compliance and key components for success. *World J Urol*. 2020 Mar;

43. Lowrance WT, Rumohr JA, Chang SS, et al. Contemporary open radical cystectomy: analysis of perioperative outcomes. *J Urol*. 2008 Apr;179(4):1313–8.

44. Malavaud B, Vaessen C, Mouzin M, et al. Complications for radical cystectomy. Impact of the American Society of Anesthesiologists score. *Eur Urol*. 2001 Jan;39(1):79–84.

45. Mazzone E, D'Hondt F, Beato S, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion decreases postoperative complications only in highly comorbid patients: findings that rely on a standardized methodology recommended by the European Association of Urology Guidelines. *World J Urol*. 2020 May;

46. Monn MF, Kaimakliotis HZ, Cary KC, et al. Short-term morbidity and mortality of Indiana pouch, ileal conduit, and neobladder urinary diversion following radical cystectomy. *Urol Oncol Semin Orig Investig*. 2014 Nov;32(8):1151–7.

47. Moschini M, Gandaglia G, Dell'Oglio P, et al. Incidence and Predictors of 30-Day Readmission in Patients Treated With Radical Cystectomy: A Single Center European Experience. *Clin Genitourin Cancer*. 2016 Aug;14(4):e341-6.

48. Musch M, Janowski M, Steves A, et al. Comparison of early postoperative morbidity after robot-assisted and open radical cystectomy: results of a prospective observational study. *BJU Int*. 2014 Mar;113(3):458–67.

49. Nazmy M, Yuh B, Kawachi M, et al. Early and Late Complications of Robot-Assisted Radical Cystectomy: A Standardized Analysis by Urinary Diversion Type. *J Urol*. 2014 Mar;191(3):681–7.

50. Nazzani S, Mazzone E, Preisser F, et al. Comparison of Perioperative Outcomes Between Open and Robotic Radical Cystectomy: A Population-Based Analysis. *J Endourol*. 2018 Aug;32(8):701–9.

51. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary Diversions after Cystectomy: The Association of Clinical Factors, Complications and Functional Results of Four Different Diversions. *Eur Urol*. 2008 Apr;53(4):834–44.

52. Novotny V, Froehner M, Koch R, et al. Age, American Society of Anesthesiologists physical status classification and Charlson score are independent predictors of 90-day mortality after radical cystectomy. *World J Urol*. 2016 Aug;34(8):1123–9.

53. Novotny V, Hakenberg OW, Wiessner D, et al. Perioperative Complications of Radical Cystectomy in

a Contemporary Series. *Eur Urol*. 2007 Feb;51(2):397–402.

54. Patidar N, Yadav P, Sureka SK, et al. An audit of early complications of radical cystectomy using Clavien-Dindo classification. *Indian J Urol*. 2016;32(4):282–7.

55. Peyton CC, Reich RR, Tang D, et al. Identifying and Codifying Complications after Radical Cystectomy: Comparison of Administrative Diagnostic and Procedure Codes, and Clinical Chart Review. *J Urol*. 2019 Nov;202(5):913–9.

56. Porter MP, Gore JL, Wright JL. Hospital volume and 90-day mortality risk after radical cystectomy: a population-based cohort study. *World J Urol*. 2011 Feb;29(1):73–7.

57. Quek ML, Stein JP, Daneshmand S, et al. A Critical Analysis of Perioperative Mortality From Radical Cystectomy. *J Urol*. 2006 Mar;175(3):886–90.

58. Roghmann F, Sukumar S, Ravi P, T et al. Radical Cystectomy in the Elderly: National Trends and Disparities in Perioperative Outcomes and Quality of Care. *Urol Int*. 2014;92(1):27–34.

59. Salminen AP, Koskinen I, Perez IM, et al. Neoadjuvant Chemotherapy Does Not Increase the Morbidity of Radical Cystectomy: A 10-year Retrospective Nationwide Study. *Eur Urol* Oncol. 2018 Dec;1(6):525–30.

60. Schmid M, Rink M, Traumann M, et al. Evidence from the "PROspective MulticEnTer RadIcal Cystectomy Series 2011 (PROMETRICS 2011)" Study: How are Preoperative Patient Characteristics Associated with Urinary Diversion Type After Radical Cystectomy for Bladder Cancer? *Ann Surg Oncol*. 2015 Mar 28;22(3):1032–42.

61. Shabsigh A, Korets R, Vora KC, et al. Defining Early Morbidity of Radical Cystectomy for Patients with Bladder Cancer Using a Standardized Reporting Methodology. *Eur Urol*. 2009 Jan;55(1):164–76.

62. Styn NR, Montgomery JS, Wood DP, et al. Matched Comparison of Robotic-assisted and Open Radical Cystectomy. *Urology*. 2012 Jun;79(6):1303–9.

63. Su S, Gu L, Ma X, et al. Comparison of Laparoscopic and Robot-assisted Radical Cystectomy for Bladder Cancer: Perioperative and Oncologic Outcomes. *Clin Genitourin Cancer*. 2019 Oct;17(5):e1048–53.

64. Sung HH, Ahn J-S, Seo S Il, et al. A Comparison of Early Complications Between Open and Robot-Assisted Radical Cystectomy. *J Endourol*. 2012 Jun;26(6):670–5.

65. Svatek RS, Fisher MB, Matin SF, et al. Risk Factor Analysis in a Contemporary Cystectomy Cohort Using Standardized Reporting Methodology and Adverse Event Criteria. *J Urol*. 2010 Mar;183(3):929–34.

66. Udovicich C, Perera M, Huq M, et al. Hospital volume and perioperative outcomes for radical cystectomy: a population study. *BJU Int*. 2017 May;119 Suppl:26–32.

67. Wei C, Wan F, Zhao H, et al. Application of enhanced recovery after surgery in patients undergoing radical cystectomy. *J Int Med Res*. 2018 Dec;46(12):5011–8.

68. Wissing MD, Santos F, Zakaria AS, et al. Short- and long-term survival has improved after radical cystectomy for bladder cancer in Québec during the years 2000-2015. *J Surg Oncol*. 2019 Jun;119(8):1135–44.

69. Takada N, Abe T, Shinohara N, et al. Peri-operative morbidity and mortality related to radical cystectomy: a multi-institutional retrospective study in Japan. *BJU Int*. 2012 Dec;110(11b):E756–64.

70. Woldu SL, Sanli O, Clinton TN, et al. Validating the predictors of outcomes after radical cystectomy for bladder cancer. *Cancer*. 2019 Jan 15;125(2):223–31.

71. Xylinas E, Green DA, Otto B, et al. Robotic-assisted Radical Cystectomy With Extracorporeal Urinary Diversion for Urothelial Carcinoma of the Bladder: Analysis of Complications and Oncologic Outcomes in 175 Patients With a Median Follow-up of 3 Years. *Urology*. 2013 Dec;82(6):1323–9.

72. Zhang JH, Ericson KJ, Thomas LJ, et al. Large Single Institution Comparison of Perioperative Outcomes and Complications of Open Radical Cystectomy, Intracorporeal Robot-Assisted Radical Cystectomy and Robotic Extracorporeal Approach. *J Urol*. 2020 Mar;203(3):512–21.

73. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo Classification of Surgical Complications. *Ann Surg*. 2009 Aug;250(2):187–96.

74. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003;13(3):176–81.

75. Nutt M, Scaief S, Dynda D, et al. Ileus and small bowel obstruction after radical cystectomy for bladder cancer: Analysis from the Nationwide Inpatient Sample. *Surg Oncol*. 2018 Sep;27(3):341–5.

76. Cerantola Y, Valerio M, Persson B, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) society recommendations. *Clin Nutr*. 2013 Dec;32(6):879–87.

77. Pillai P, McEleavy I, Gaughan M, et al. A Double-Blind Randomized Controlled Clinical Trial to Assess the Effect of Doppler Optimized Intraoperative Fluid Management on Outcome Following Radical Cystectomy. *J Urol*. 2011 Dec;186(6):2201–6.

78. Choi H, Kang SHSG, Yoon DK, et al. Chewing Gum Has a Stimulatory Effect on Bowel Motility in Patients After Open or Robotic Radical Cystectomy for Bladder Cancer: A Prospective Randomized Comparative Study. *Urology*. 2011 Apr;77(4):884–90.

79. Lee CT, Chang SS, Kamat AM, et al. Alvimopan Accelerates Gastrointestinal Recovery After Radical Cystectomy: A Multicenter Randomized Placebo-Controlled Trial. *Eur Urol*. 2014 Aug;66(2):265–72.

80. Inman BA, Harel F, Tiguert R, et al. Routine Nasogastric Tubes Are Not Required Following Cystectomy With Urinary Diversion: A Comparative Analysis of 430 Patients. *J Urol*. 2003 Nov;170(5):1888–91.

81. Shafii M, Murphy DM, Donovan MG, et al. Is mechanical bowel preparation necessary in patients undergoing cystectomy and urinary diversion? *BJU Int*. 2002 May 12;89(9):879–81.

82. Wessels F, Lenhart M, Kowalewski KF, et al. Early recovery after surgery for radical cystectomy: comprehensive assessment and meta-analysis of existing protocols. *World J Urol*. 2020 Mar 2;

83. Williams SB, Cumberbatch MGK, Kamat AM, et al. Reporting Radical Cystectomy Outcomes Following Implementation of Enhanced Recovery After Surgery Protocols: A Systematic Review and Individual Patient Data Meta-analysis. *Eur Urol* [Internet]. 2020;1–12. Available from: https://doi.org/10.1016/j.eururo.2020.06.039

84. Baack Kukreja JE, Messing EM, Shah JB. Are we doing "better"? The discrepancy between perception and practice of enhanced recovery after cystectomy principles among urologic oncologists. *Urol Oncol*. 2016 Mar;34(3):120.e17-21.

85. Clifford TG, Katebian B, Van Horn CM, et al. Urinary tract infections following radical cystectomy and urinary diversion: a review of 1133 patients. *World J Urol*. 2018 May 25;36(5):775–81.

86. van Hemelrijck M, Thorstenson A, Smith P, et al. Risk of in-hospital complications after radical cystectomy for urinary bladder carcinoma: population-based follow-up study of 7608 patients. *BJU Int*. 2013 Dec;112(8):1113–20.

87. Kolwijck E, Seegers AEM, Tops SCM, et al. Incidence and microbiology of postoperative infections after radical cystectomy and ureteral stent removal; a retrospective cohort study. *BMC Infect Dis*. 2019;19(1):303.

88. Parker WP, Tollefson MK, Heins CN, et al. Characterization of perioperative infection risk among patients undergoing radical cystectomy: Results from the national surgical quality improvement program. *Urol Oncol*. 2016 Dec;34(12):532.e13-532.e19.

89. Pariser JJ, Anderson BB, Pearce SM, et al. The effect of broader, directed antimicrobial prophylaxis including fungal coverage on perioperative infectious complications after radical cystectomy. *Urol Oncol Semin Orig Investig.* 2016;34(3):121.e9-121.e14.

90. Krasnow RE, Mossanen M, Koo S, et al. Prophylactic Antibiotics and Postoperative Complications of Radical Cystectomy: A Population Based Analysis in the United States. *J Urol*. 2017;198(2):297–304.

91. European Association of Urology. Guideline on urological infections [Internet]. [cited 2020 Apr 20]. Available from: https://uroweb.org/guideline/urological-infections/#3

92. American Urological Association. Urologic Procedures and Antimicrobial Prophylaxis (2019) [Internet]. [cited 2020 May 11]. Available from: https://www.auanet.org/guidelines/urologic-procedures-and-antimicrobial-prophylaxis-(2019)

93. Reese SW, Ji E, Paciotti M, et al. Risk factors and reasons for reoperation after radical cystectomy. *Urol Oncol Semin Orig Investig*. 2020 Apr;38(4):269–77.

94. Goossens-Laan CA, Gooiker GA, van Gijn W, et al. A systematic review and meta-analysis of the relationship between hospital/surgeon volume and outcome for radical cystectomy: an update for the ongoing debate. *Eur Urol*. 2011 May;59(5):775–83.

95. Konety BR, Allareddy V, Herr H. Complications after radical cystectomy: analysis of population-based data. *Urology*. 2006 Jul;68(1):58–64.

96. Vetterlein MW, Meyer CP, Leyh-Bannurah S-R, et al. Effect of Hospital and Surgeon Case Volume on Perioperative Quality of Care and Short-term Outcomes After Radical Cystectomy for Muscle-invasive Bladder Cancer: Results From a European Tertiary Care Center Cohort. *Clin Genitourin Cancer*. 2017 Oct;15(5):e809–17.

97. Bruins HM, Veskimäe E, Hernández V, et al. The Importance of Hospital and Surgeon Volume as Major Determinants of Morbidity and Mortality After Radical Cystectomy for Bladder Cancer: A Systematic Review and Recommendations by the European Association of Urology Muscle-invasive and Metastatic Bladd. *Eur Urol Oncol*. 2019 Dec 19;

98. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label , randomised , phase 3 , non-inferiority trial. *Lancet*. 2018 Jun;391(10139):2525–36.

99. Nix J, Smith A, Kurpad R, et al. Prospective Randomized Controlled Trial of Robotic versus Open Radical Cystectomy for Bladder Cancer: Perioperative and Pathologic Results. *Eur Urol*. 2010 Feb;57(2):196–201.

100. Bochner BH, Dalbagni G, Sjoberg DD, et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. *Eur Urol*. 2015 Jun;67(6):1042–50.

101. Parekh DJ, Messer J, Fitzgerald J, et al. Perioperative Outcomes and Oncologic Efficacy from a Pilot Prospective Randomized Clinical Trial of Open Versus Robotic Assisted Radical Cystectomy. *J Urol*. 2013 Feb;189(2):474–9.

102. Khan MS, Gan C, Ahmed K, et al. A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). *Eur Urol*. 2016 Apr;69(4):613–21.

103. Catto JWF, Khetrapal P, Ambler G, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy (iROC): Protocol for a randomised controlled trial with internal feasibility study. *BMJ Open*. 2018;8(8):1–10.

104. Williams SB, Huo J, Chamie K, et al. Underutilization of Radical Cystectomy Among Patients Diagnosed with Clinical Stage T2 Muscle-invasive Bladder Cancer. *Eur Urol Focus*. 2017 Apr;3(2–3):258–64.

105. Ramirez JA, McIntosh AG, Strehlow R, et al. Definition, incidence, risk factors, and prevention of paralytic ileus following radical cystectomy: a systematic review. *Eur Urol*. 2013 Oct;64(4):588–97.

106. Mitropoulos D, Artibani W, Graefen M, et al. Reporting and Grading of Complications After Urologic Surgical Procedures: An ad hoc EAU Guidelines Panel Assessment and Recommendations. *Eur Urol*. 2012 Feb;61(2):341–9.

Legend for Figure 1: Figure 1. PRISMA flowchart

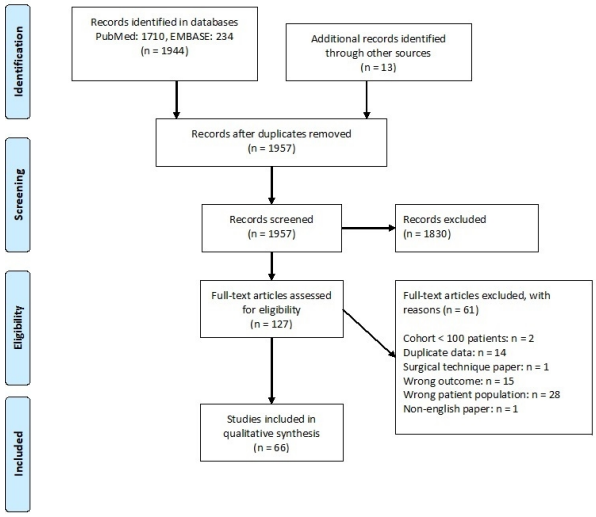

Figure 1. PRISMA flowchart

333x187mm (96 x 96 DPI)

Appendix 1

Database	Search string
PubMed/MEDLINE	**#1**: “urinary bladder neoplasms” [MeSH Terms] OR "urothelial carcinoma"[Title/Abstract]) OR "invasive urothelial bladder carcinomas"[Title/Abstract]) OR "bladder cancer"[Title/Abstract] **#2**: "cystectomy"[Text Word] OR "cystoprostatectomy"[Title/Abstract] **#3**: “postoperative complications”[Text Word] OR “length of stay”[Text Word] OR “complication*”[Title/Abstract] OR “clavien*”[Title/Abstract] OR “reoperation*”[Title/Abstract] OR “mortality”[Title/Abstract] **#4**: #1 AND #2 AND #3 **#5**: #4 NOT (“review” [Publication Type] OR “letter”[Publication Type] OR “comment”[Publication Type]) Filter: English, humans, publication date 1990-
EMBASE	**#1**: exp bladder cancer/ OR bladder carcinoma.mp/ OR muscle invasive bladder cancer.mp OR bladder cancer.mp OR invasive urothelial cancer.mp OR urothelial carcinoma.mp **#2**: exp cystectomy/ OR cystectomy.mp OR cystoprostatectomy.mp **#3**: exp postoperative complication/ OR exp length of stay/ OR complication/ OR exp reoperation/ OR clavien*.mp OR complication*.mp OR reoperation*.mp OR length of stay.mp OR mortality.mp **#4**: #1 AND #2 AND #3 Limits: human, English language, exclude Medline journals

Appendix 2

Reference	Number of Martin criteria fulfilled	New Castle-Ottawa Scale score		
		Selection	Comparability	Outcome
Afshar et al.	NA	****	**	**
Al-Daghmin et al.	5	****	*	***
Arora et al.	5	****	**	***
Björnsson et al.	7	****	0	***
Boorjian et al.	NA	***	**	***
Cantiello et al.	10	****	0	***
Chang et al.	6	****	*	***
De Nunzio et al.	7	****	**	**
de Vries et al.	NA	****	**	***
Djaladat et al.	9	****	**	**
Fairey et al.	5	****	**	***
Flamiatos et al.	6	****	*	***
Gschliesser et al.	5*	****	**	***
Hanna et al.	NA	****	**	**
Hayn et al.	10	****	**	***
Hirobe et al.	10	****	**	***
Hollenbeck et al. (2005)	5	****	*	***
Hollenbeck et al. (2006)	NA	****	**	***
Hu et al.	4*	****	**	***
Jerlström et al.	7	****	*	***
Johar et al.	8	****	**	***
Johnson et al.	6	****	**	***

Kader et al.	5	****	0	***
Kanno et al.	7	****	0	***
Khan et al.	8	****	**	***
Kim et al.	6*	****	*	***
Koupparis et al.	5	****	0	***
Kulkarni et al.	NA	****	**	***
Lenfant et al.	6	****	0	***
Leow et al.	3	****	**	***
Liedberg et al.	NA	****	0	***
Lin et al.	NA	****	**	***
Liu et al.	5*	****	0	***
Llorente et al. (2017)	2	****	*	***
Llorente et al. (2020)	7	****	**	***
Llorente et al. (2020)	NA	****	**	***
Lowrance et al.	7	****	0	***
Malavaud et al.	6	****	0	***
Mazzone et al.	9	****	**	***
Monn et al.	9	****	**	***
Moschini et al.	2	****	*	***
Musch et al.	7	****	0	***
Nazmy et al.	8	****	**	***
Nazzani et al.	4*	****	**	***
Nieuwenhuijzen et al.	8	****	*	***
Novotny et al. (2007)	NA	****	0	***
Novotny et al. (2016)	5	****	**	***

Patidar et al.	7	****	0	***
Peyton et al.	5	****	0	***
Porter et al.	NA	****	**	***
Quek et al.	NA	****	0	***
Roghmann et al.	5	****	**	***
Salminen et al.	7	****	**	***
Schmid et al.	4	****	*	***
Shabsigh et al.	10	****	**	***
Styn et al.	6	****	**	***
Su et al.	5	****	0	***
Sung et al.	9	****	*	***
Svatek et al.	9	****	*	***
Takada et al.	9	****	*	***
Udovicuch et al.	NA	****	0	***
Wei et al.	3	****	0	*
Wissing et al.	NA	****	**	***
Woldu et al.	4	****	**	***
Xylinas et al.	7	****	0	***
Zhang et al.	7	****	**	***

NA: Not applicable (study not reporting complications). *Studies have been scored as fulfilling the criteria of "outpatient information included" as this criterium does not apply to the studies with an outcome period including in-house complications only.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Surgery
Keywords:	Bladder disorders < UROLOGY, SURGERY, Urological tumours < UROLOGY

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Short-term morbidity and mortality following radical cystectomy: a systematic review

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Abstract

Objective: To study short-term (< 90 days) morbidity and mortality following radical cystectomy (RC) for bladder cancer and identify modifiable risk factors associated with these.

Design: Systematic review.

Methods: The systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. PubMed and EMBASE were searched for relevant papers on 11th of June 2019 and re-run on the 27th of May 2020. Studies reporting complications, reoperations, length of stay, and mortality within 90 days were included. Studies were reviewed according to criteria from the Oxford Centre for Evidence-Based Medicine and the quality of evidence was assessed using the New Castle Ottawa Scale.

Results: The search retrieved 1957 articles. Sixty-six articles were included. The quality of evidence was poor to good. Most studies were retrospective, and no randomised clinical trials were identified. Of included studies a median of 6 Martin criteria for reporting complications after surgery were fulfilled. The Clavien-Dindo Classification for grading complications was most frequently used. The weighted overall complication rate after RC was 34.9% (range 28.8–68.8) for in house complications, 39.0% (range 27.3–80.0) for 30-day complications, and 58.5% (range 36.1–80.5) for 90-day complications. The most common types of complications reported were gastrointestinal (29.0%) and infectious (26.4%). The weighted mortality rate was 2.4% (range 0.9–4.7) for in house mortality, 2.1% (0.0–3.7) for 30-day mortality, and 4.7% (range 0.0–7.0) for 90-day mortality. Age and comorbidity were identified as the best predictors for complications following RC.

Conclusion: Short-term morbidity and mortality is high following RC. Reporting of complications is heterogeneous and the quality of evidence is generally low. There is a continuous need for randomised studies to address any intervention that can reduce morbidity and mortality following RC.

PROSPERO ID: 104937

Article summary

Strengths and limitations of this study

- This systematic review can provide as a reference paper for future studies and when measuring quality of care.
- This systematic review emphasizes the continuous need to identify and moderate risk factors for complications and optimize postoperative management plans to reduce both morbidity and mortality associated with radical cystectomy.
- This review is limited by heterogeneity in outcome measures of morbidity with a lack of clear definitions of surgical complications making a direct comparison between studies difficult.

INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection and urinary diversion is the preferred treatment for non-metastatic muscle-invasive bladder cancer (BC), and for some cases of high-risk non-muscle-invasive BC, in patients fit for major surgery (1). RC is a comprehensive procedure that involves surgery to several organ systems and as a result it is associated with high postoperative morbidity and mortality. Attempts have been made over the years to reduce postoperative complications such as the introduction of Enhanced Recovery After Surgery (ERAS) programs. However, addressing morbidity and mortality associated with RC across surgical cohorts remains important for preoperative counselling, planning of treatment, identification of modifiable risk factors to reduce morbidity and mortality, future clinical trial design, and for assessment of surgical quality. Several measures of morbidity are clinically important such as complication rate, reoperation rate, length of stay (LOS), readmission rate, and mortality. In this paper, we conducted a contemporary systematic review of the prevalence of short-term (< 90 days) morbidity and mortality following RC for BC.

METHODS

Search strategy and study selection

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (2). A published protocol (PROSPERO ID: 104937) with pre-specified outcomes, inclusion criteria and search strategy is accessible online.

A systematic literature search in PubMed and EMBASE was conducted on 11th of June 2019 and re-run on the 27th of May 2020. A search string was created with the help of an information specialist (Appendix 1).

Articles were screened in a two-stage selection process. In the first stage, two authors (S.L.M. and M.A.R.) reviewed abstracts. All prospective and retrospective studies on short-term (< 90 days) morbidity and mortality after RC were included. Trials with less than 100 participants, indications for cystectomy other than BC, extended procedure (e.g. nephroureterectomy), salvage/palliative cystectomy, organ sparing cystectomy (e.g. partial cystectomy, prostate-sparing cystectomy, vaginal sparing cystectomy, seminal vesicles sparing cystectomy), selected patient group (e.g. certain age groups, women only), feasibility studies, surgical technique-only papers, animal series, and studies not published in English were excluded. Conference papers, case reports, book chapters, review papers, editorials, comments, letters to the editors, and abstracts were also excluded. When in doubt, studies were maintained for further review. In the second stage, the full text of all included articles was obtained and read by the same two authors. An agreement was reached through consensus using Covidence Systematic Review software (3). Any disagreement was resolved by discussion and the final decision was based on a consensus. In case of duplicate data/study the following criteria were applied in the selection: 1) outcome (studies reporting on complications were prioritized over LOS, mortality), 2) size of the cohort (larger studies were prioritized over smaller studies), 3) methodology (prospective studies were prioritized over retrospective studies and extraction of data from medical/hospital records over record linkage (e.g. ICD-codes in a database)), 4) study period (studies with the most recent study period were prioritized).

Data extraction and quality assessment

The following data was extracted from all studies where possible: first author, data source (e.g. single-centre, multicenter, database), institution/country of origin, study period, year of publication, number of cases, study design, length of follow up, the classification system used for grading complications, use of fast track/ERAS protocol, demographics (age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI),

American Society of Anesthesiologists (ASA) score, pT-stage, N-stage, neoadjuvant therapy, previous radiation therapy, prior abdominal/pelvic surgery), outcomes (urinary diversion, number of total complications, complication rate, segregated complications, complication reasons, mortality rate, LOS, reoperations, risk factors for outcomes).

The quality of reporting complications was estimated using the Martin criteria providing a score from 0–10 (4). Furthermore, the level of evidence was rated according to criteria from the Oxford Centre for Evidence-Based Medicine (5). The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational comparative studies (6).

Outcome measures

The primary outcome was the overall complication rate: the number of patients with one or more complication(s) within 90 days after RC regardless of the classification system used. Secondary outcomes were the following: rate of graded complications according to severity grade utilized; frequencies of types of complications; LOS, reoperation rate; mortality rate; and risk factors for the development of outcomes of morbidity (e.g. complications, death, reoperations).

Statistical analysis

Descriptive statistics were used. A weighted average and range were calculated for all rates. A meta-analysis on risk factors for morbidity was not possible due to the high heterogeneity of reporting in the multivariate analysis across studies.

Patient and public involvement

No patients were involved in conducting this review.

RESULTS

The literature search retrieved 1957 articles after removing duplicates. Of these 66 studies met the in- and exclusion criteria (7–72). The process is outlined in Figure 1.

Characteristics of included studies

The characteristics of the included studies are summarized in Table 1. Twenty-nine studies (43.9%) were single-centre studies and 37 studies (56.1%) were register or multicenter database studies. Most studies (71.2%) were retrospective, retrospective studies of prospectively maintained databases (12.1%) or combined retrospective and prospective studies (4.5%). Only eight (12.1%) were purely prospective surgical series. Patients were operated in the period 1990–2018. Of included studies, only two reported that an ERAS protocol was used for the entire cohort (16,48), and in six studies an ERAS protocol was used in a part of the cohort (33,39,42,67,69,72). In the rest of the included studies, an ERAS protocol was not used, or the authors did not report on perioperative care.

Table 1. Summary of patient characteristics.

		Number of patients with data available (sum of references)	References
Demographics			
Percentage of males (weighted average, % (range))	80.8% (71.1–99.1)	194 769	(7–14,16–23,25,26,28–36,39,41–52,54–72)
Age			
- weighted median (range)	69 years (63–73)	69 076	(7,9–11,13,14,16,17,19–22,26,27,29,30,43,45,47,48,50–52,55–58,60,61,63,65,68–72)
- weighted mean (range)	68.2 years (56.2–72.1)	104 373	(8,12,19,23,29,44,47,48,62,64,70,71)
BMI			
- weighted median (range)	26.1 (22.3–27.8)	10 332	(9,10,14,16,21,22,26,27,30,35,45,47,48,61,63,65,69,71,72)
- weighted mean (range)	27.6 (20.4–29.7)	13 187	(8,12,17–19,28,29,44,47,48,54,59,62,64,67,70,71)
ASA score (weighted average, % (range))			
- I	8.0% (0–35.1)	15 202	(10,11,14,19,26,28–31,33,37,42,45,49,53,55,60,63,65,69–71)
- II	39.0% (1.7–81.9)	15 435	(10,11,14,19,26,28–31,33,37,42,45,46,49,53,55,60,63–65,69–71)
- III	54.0% (7.9–94.0)	13 490	(10,14,19,22,26,28–31,33,42,45,46,49,53,55,59,63–65,70,71)
- IV	4.8% (0–16.3)	12 287	(10,14,19,26,28,29,31,33,42,46,49,53,55,59,64,65,70,71)
CCI (weighted average, % (range))			
- 0	45.6% (6.3–68.1)	114 334	(7,16,20,36,42,50,58,60,70)
- 1	26.7% (4.0–30.6)	85 875	(16,20,34,36,50,58,60,70)
- ≥2	20.9% (2.5–69.4)	88 159	(16,20,22,34,36,48,52,58,60,64,66,70)
Prior abdominal surgery (weighted average, % (range))	41.4% (5.1–55.1)	4 214	(8,12,16,18,21,29,35,45,61,62,71)
Previous pelvic radiation* (weighted average, % (range))	5.5% (1.3–22.1)	3 910	(8,16,18,21,29,33,51,61,62,71)
Neoadjuvant chemotherapy (weighted average, % (range))	13.2% (0–50.8)	23 678	(8,10,12,14,16–18,22,25,26,33,35,37,41,45,46,49,53,59,60,62,63,65,68–72)
Perioperative details			
Surgical approach (weighted average, % (range))		107 822	(8,11,13,16–22,25–31,33,35,36,39,41,43,45,47–51,53,54,60,62–64,70–72)
- open	86.5% (0–100)		
- laparoscopic	1.8% (0–100)		

- robot-assisted laparoscopic	10.9% (0–100)		
Type of diversion (weighted average, % (range))			
- ileal conduit	85.0% (31.4–93.8)	80 675	(8,10–14,16–19,21,22,26,29–31,33,35,36,42–51,53–55,60,61,63–72)
- neobladder	10.5% (2.6–62.1)	65 307	(8,10,12–14,16–19,21,22,26,29–31,33,35,36,42–49,51,53–55,60,61,63–67,69–72)
- continent cutaneous diversion	1.25% (0–29.6)	59 853	(8,12–14,16,18,26,29,30,36,43,44,46,48,49,51,54,55,60,61,63,65–67,69,71,72)
- ureterocutaneostomy	1.35% (0–26.7)	58 210	(8,17–19,22,30,31,36,44,47,48,54,60,63,64,66,67,69,72)
- nephrostomy	0.01% (0–0.5)	56 718	(8,18,19,22,31,36,44,49,51,54,60,63,64,66,67,69,72)
Pathological tumor stage (weighted average, % (range))			
- ≤ T1	27.1% (6.4–54.9)	31 317	(10–12,14,15,17–21,25–27,30,31,35,37,42,43,45,46,48,52,54,55,59,60,62–64,71,72)
- T2	29.1% (11.9–56.7)	28 916	(10–12,14,15,17–21,25–27,30,31,35,37,43,45,46,48,49,52,54,55,60,62–64,71)
- T3	28.5% (10.8–42.4)	26 537	(10,12,14,17–21,25–27,30,31,35,43,46–49,52,54,55,60,62–64,71)
- T4	13.2% (2.4–25.9)	26 537	(10,12,14,17–21,25–27,30,31,35,43,46–49,52,54,55,60,62–64,71)
Lymph node positive disease (weighted average, % (%-range))	19.1% (6.3–44.4)	29 615	(10–12,14–16,18–21,25–27,29–31,35,43,45–49,52,54,60,62–64,71,72)
LOS			
- weighted median (%-range))	11 days (4–39)	77 038	(7,10,12–14,16,18,20–22,24,26,28,29,31,33,35,39,40,42,43,45,46,48,50,51,53,55,56,58,59,61–63,65,66,69,71,72)
- weighted mean (%-range)	12.5 days (8.2–27.6)	39 562	(8,19,25,38,39,44,47,48,50,53,54,58,64,67,68,70)

Abbreviations: BMI = Body Mass Index, ASA= American Society of Anesthesiologists, CCI = Charlson Comorbidity Index, LOS= Length of Stay, *not external beam radiation therapy due to bladder cancer

Complications

Fifty-two studies reported on short term complications as outlined in table 2. The most frequently reported follow-up period was 90 days. Three studies reporting short term complications did not state the exact

follow-up period and were therefore excluded from the complication rate analysis (33,40,67). During the primary hospitalisation, the overall complication rate was 34.9% (28.8–68.8). The complication rate increased with longer follow-up to 39.0% (27.3–80.0) 30 days, and 58.5% (36.1–80.5) 90 days postoperatively. Minor complications accounted for 40.0% (19.9–77.4) and 38.2% (19.0–80.8) of the complications reported at 30- and 90-days follow-up, respectively. Major complications after RC occurred in 15.5% (4.9–24.8) and 16.9% (13.4–32.0) of patients after 30 and 90 days, respectively. Rates of complications according to the Clavien-Dindo classification and reoperations are further outlined in Table 2.

Table 2. Complications and re-operations.

Outcome	Complication rate, weighted average (%-range)	Number of patients with data available (sum of references)	References
In-hospital complication rate	34.9%*[1] (28.8–68.8)	76171	(19,32,39,50,58,59,61)
30-day complication rate	39.0%*[2] (27.3–80.0)	19160	(9,18,23,28,30,43,44,46,47,51,53,55,60–62,70–72)
- CD grade I	9.2% (6.0–16.1)	1291	(30,35,45,70)
- CD grade II	29.8% (20.6–52.5)	1291	(30,35,45,70)
- CD grade IIIa+b	6.9% (5.6–14.4)	8749	(28,30,35,45,70)
- CD grade IVa+b	7.8% (0.7–11.0)	8749	(28,30,35,45,70)
- CD grade V	1.7% (0.0–2.1)	8982	(28,30,35,45,46,70)
- Minor complication rate*[3](%)	40.0% (19.9–77.4)	2536	(13,18,43,44,51,55,60,62)
- Major complication rate*[4]	15.5% (4.9–24.8)	4499	(13,18,30,43,44,46,51,55,60,62,70,72)
90-day complication rate	58.5*[5]% (36.1–80.5)	10625	(8,10,12,14,16,17,21,22,26,29–31,42,48,49,54,59–61,63–65,69,71,72)
- CD grade I	15.0% (4.0–31.6)	4442	(29,30,54,59,61,64,69)
- CD grade II	38.9% (27.0–67.4)	4442	(29,30,54,59,61,64,69,72)
- CD grade IIIa+b	20.5% (8.5–39,2)	5548	(29–31,54,59,61,64,69,72)
- CD grade IVa+b	3.0% (0.2–8.5)	5548	(29–31,54,59,61,64,69,72)
- CD grade V	3.5% (0.1–3.9)	55440	(29–31,36,48,54,59,61,64,69,72)
- Minor complication rate*[3]	38.2% (19.0–80.8)	56955	(8,12,16,17,21,26,31,36,42,59–61,63,69)
- Major complication rate*[4]	16.9% (13.4–32.0)	59068	(8,12,14,16,17,22,26,29–31,36,42,49,59–61,64,69,72)
Reoperation rate			
- 30-day	5.8% (3.0–8.7)	11598	(9,21,27,28,30,44–46,53,62,71)
- 90-day	12.3% (9.3–18.9)	1533	(10,26,30,54,69)

*[1]one study (25) did not report on overall complication rate, *[2]Three studies (13,35,45) did not report on overall complication rate. *[3] minor complications defined as Clavien-Dindo grade I–II, MSKCC grade 1–2 or minor complications. *[4] major complications defined as Clavien-Dindo grade III–V, MSKCC grade 3–5 or major complications. *[5] one study (36) did not report overall complication rate.

Thirty-four studies (8,10,12,14,16,18,19,22,26,28–31,33,35,36,42,45,46,48,49,54,55,59–64,67,69–72) classified complications according to the Clavien-Dindo classification (73), six (9,13,17,43,44,51) studies classified complications as minor and major complications, three studies (21,27,72) used the Memorial Sloan Kettering Cancer Centre modified Clavien-Dindo classification (61), one study (65) used Common Terminology Criteria for Adverse Events (74), and nine studies (23,25,32,39,40,47,50,53,58) did not use any system for grading complications.

Type of complications

Twenty-one studies reported on types of 90-day complications (Table 3). Gastrointestinal (GI) (29.0%) and infectious (26.4%) complications were the most frequent.

Table 3. Categories and type of 90-day complications.

Category/type	Rate, weighted average (%-range)	Number of patients with data available (sum of references)	References
Gastrointestinal	29.0% (6.7–42.7)	6188	(16,21,22,26,27,30,48,49,54,59,61,69)
- Ileus	16.5% (3.8–33.7)	5073	(12,14,21,22,30,31,42,48,49,54,61,64,65,69)
- Small bowel obstruction	4.6% (1.7–9.0)	3193	(14,21,26,31,48,49,54,61,64,65)
- Constipation	3.3% (0.5–11.4)	2491	(12,14,22,48,49,61)
- Clostridium Difficile Colitis	2.3% (0.7–3.8)	2574	(21,49,61,64,69)
- Diarrhoea	1.7% (0.6–5.6)	2392	(12,22,48,49,54,61)
- Anastomotic bowel leak	1.1% (0.3–1.9)	3254	(12,21,22,26,61,69)
- Gastrointestinal bleeding	1.0% (0.3–1.3)	2757	(12,21,22,61,69)
Infectious	26.4% (10.9–46.2)	5270	(14,16,21,22,26,27,30,48,49,54,61,69)
- UTI/pyelonephritis	14.1% (1.1–29.7)	4297	(12,21,22,26,42,48,49,54,61,64,65,69)
- Sepsis	4.2% (1.5–8.5)	3812	(21,22,26,42,48,49,54,61,65,69)
- Fever of unknown origin	3.1% (0.6–4.8)	2966	(12,21,22,49,61,69)
- Pelvic/intraabdominal abscess	2.4% (0.1–4.3)	2836	(21,22,48,61,65,69)
Genitourinary	16.0% (6.0–23.5)	5697	(17,21,22,27,30,54,59,61,69)
- Ureter stenosis	3.2% (1.7–7.0)	2539	(12,21,22,26,48,61,65)
- Ureter leakage	3.1% (0.4–5.3)	4282	(12,14,21,22,26,48,49,61,64,65,69)
Wound	13.1% (5.6–27.0)	6424	(12,16,17,21,22,26,27,30,48,59,64,69)
- Dehiscence	4.0% (1.3–4.9)	2722	(26,31,49,61,69)
- Fascial dehiscence	1.6% (0.4–3.5)	2139	(12,21,54,61,65)
- Infection	10.5% (2.4–19.3)	3827	(14,21,26,31,42,49,54,61,69)
Cardiac	6.1% (0.6–16.9)	5366	(12,16,17,21,30,48,49,59,61,64,69)
- Myocardial infarction	1.1% (0.2–3.5)	4170	(12,14,21,26,48,49,54,61,65,69)
- Arrhythmia	4.2% (0.2–14.4)	2923	(12,21,48,49,61,69)

Bleeding	3.5% (0.5–17.8)	2814	(16,30,61,64,69)
- Hematoma	0.9% (0.7–1.2)	1096	(12,14,65)
- Transfusion	23.2% (8.1–45.3)	2606	(12,14,31,48,54,61,64)
Respiratory	5.0% (1.3–11.5)	6845	(12,14,16,17,21,27,30,48,49,54,59,61,69)
- Pneumonia	2.8% (0.6–5.9)	3639	(12,21,26,31,42,48,54,61,69)
Thromboembolic	3.6% (0.2–8.1)	4933	(12,14,16,21,26,30,31,48,49,54,61,65,69)
Neurological	2.8% (0.6–7.7)	4557	(12,16,17,21,27,48,49,54,61,69)
Renal failure	2.3% (0.5–6.7)	4070	(12,14,21,22,48,49,61,65,69)
Other			
- Fistula	1.1% (0.6–1.4)	1560	(12,21,26,48,49,64,65)
- Lymphocele	2.1% (1.3–4.7)	3381	(12,14,21,26,48,49,54,61,64,65)

UTI: urinary tract infection

Mortality

Fifty-three studies were included in the mortality analysis (Table 4). The weighted average for the in-hospital mortality rate was 2.4% (0.9–4.7), the 30-day mortality rate 2.1% (0.0–4.0) and the 90-day mortality rate 4.7% (0.0–7.0). A total of 17 of 53 studies reporting on mortality stated the causes of death with 183 deaths reported (10,16,21,22,26,29–31,35,45,52,53,57,61,64,69,71). The most frequent cause of death was cardiopulmonary events accounting for 30% followed by progression of BC (15%) and sepsis (11%).

Table 4. In-hospital, 30-day, and 90-day mortality.

	Mortality rate, weighted average (%-range)	Number of patients with data available (sum of references)	References
In-hospital mortality	2.4% (0.9–4.7)	87848	(32,41,50,56,58,61,66)
30-day mortality	2.1% (0.0–3.7)	61299	(7–9,13–15,20,24,28,30,33,35,37,38,41,43–46,51,53,57,60–62,69–72)
90-day mortality	4.7% (0.0–7.0)	108717	(7,8,10–12,14,16,17,20–22,24,26,29–31,33,36–38,41,48,49,52,54,56,59–62,64,65,67–69,71,72)

Quality of studies

Only three of the included studies (22,61,75) met 10 of 10 Martin criteria (Appendix 2). The median number of fulfilled Martin criteria was 6 (range 2–10). The only criterion fulfilled by all studies was defining the method of accruing data. The level of evidence according to criteria from the Oxford Centre for Evidence-Based Medicine was rated as 3 or 4. The methodological quality across studies was “poor” to “good” assessed using the NOS (Appendix 2).

DISCUSSION

We systematically reviewed the literature to accurately describe short-term morbidity and mortality following RC and identify modifiable risk factors associated with these. The aim was to identify factors that could form the basis for the design of future randomised trials on postoperative interventions that can reduce the risk of complications.

Main results

RC is an extensive urological procedure and associated with a high risk of short-term minor and major morbidity. Mortality within 90-days of primary surgery is not negligible and occurs in 4.7% according to our review. Our systematic review underlines that complications occur in 1 in 3 patients during hospitalization and that 1 in 5 patients have major complications during the first 30 days after RC. This emphasizes the continuous need to identify and moderate risk factors for complications and optimize postoperative management plans to reduce both morbidity and mortality associated with RC.

Our analysis identified GI and infectious complications as the most frequently reported complications after RC. Overall, GI complications occurred in 29.0% with a postoperative ileus rate of 15.6%. Urinary tract infections (UTI) were the most frequently occurring infectious complications occurring in 14.1% of patients.

Risk factors for the development of GI complications

Based on the literature reviewed, it was not possible to identify the most important risk factors for GI complications and thus define whether these were potentially modifiable. The risk of ileus, which is often most clinically relevant, seems to be affected by many factors, most importantly increasing age. One study reported an increasing age as a statistically significant risk factor for ileus with an odds ratio (OR) of 1.30 (95% CI 1.1–1.5) per 10-year increase of age (23). This finding is supported by a large retrospective study (not included in this review) of 41 498 patients that found an increased OR of developing ileus with per one year increment in age (OR 1.012, 95% CI 1.009–1.014, $p<0.05$) (76). The study also found that the risk of ileus increased with several chronic conditions such as chronic pulmonary and neurological disease. This underlines that reducing GI complication rates relies primarily on an overall medical assessment and that alternative treatment options should be considered in medically ill patients. Surgeons performing RC must be aware that poor general health status increases the risk of GI complications and entails a poor short-term outcome. Several studies of RC have promoted the implementation of ERAS protocols, which originate from colorectal surgery where ERAS reduces GI complications. In this review, no studies investigated the impact on GI complications with the use of an ERAS protocol versus a non-ERAS protocol in the perioperative care. Generally, there is limited evidence for ERAS in an RC setting (77). Only the use of postoperative gum-chewing, the use of Alvimopan (a peripherally acting μ-opioid receptor antagonist currently not available in Europe) and controlled administration of perioperative fluid management (goal-directed fluid therapy) to avoid both fluid excess and hypovolemia have been shown to reduce GI complications after RC in randomised clinical trials (RCT) (78–80). Comparative studies indicate that omitting the nasogastric tube and mechanical bowel preparation result in lower GI complications after RC (81,82). ERAS offers good practical guidelines, but the various elements such as early mobilization, omitting pelvic drainage, perioperative body temperature monitoring, and early oral diet are not studied individually but introduced in different modified versions with several components used together. Consequently, it is

difficult to derive which factor has the largest impact on reducing GI complications. Four studies in this review investigated the impact on overall complications, but the results were conflicting (33,39,67,69). A meta-analysis of ERAS protocols versus traditional protocols have found a faster return of bowel function and lower overall complication rate in the group managed on an ERAS compared to a standard of care protocol, but the overall level of evidence in RC remains low with regard to ERAS implementation (83,84). A previous study described that only 20% of surgeons that endorse ERAS guidelines actually practised all interventions recommended by the ERAS society (85).

Risk factors for the development of infectious complications

The anatomical reconstruction of the urinary tract with the use of bowel as urinary diversion following RC will naturally increase the risk of UTI, which can prolong LOS and is leading to re-admittance. Only three of the included studies identified multivariable risk factors that were statistically significant predictors of infectious complications 30 and 90 days after RC (23,28,49). Two studies found that continent reservoirs were associated with a higher risk of UTI compared to ileal conduits. Johnson et al. found that any continent urinary diversion increased the risk of infectious complications compared to an incontinent urinary diversion (OR 1.68, p<0.001)(28). Nazmy et al. found that an Indiana pouch increased the risk of UTI compared to ileal conduit (OR 3.55, 95% CI 1.33–9.44, p=0.01), however, an orthotopic bladder substitute did not increase the risk of UTI compared to an ileal conduit (49). Other studies not included in this review investigating this association have shown conflicting results (86–89). Hollenbeck et al. found preoperative bleeding disorder, poor functional status, preoperative acute renal failure, and a >10% weight loss preoperatively to be associated with an increased risk of UTI (23). In general, the comorbid patient may be at the highest risk for UTI. A large retrospective study of 1133 patients found that a CCI > 2 was associated with a higher 90-day postoperative UTI rate (OR = 1.8, 95% CI 1.1–2.9, p = 0.05) compared to a CCI 0–2 (86). It remains unclear if UTI can be prevented. No studies in this review investigated this question which in general is not well-investigated. Pariser et al. demonstrated that a change in prophylactic antibiotic protocol from a narrow to a broader coverage did not reduce the UTI rate, although the 30-day risk of overall infectious complications was reduced following RC from 41% to 30% (p = 0.043) (90). A population-based American study reported a lower infectious event rate when using a combination of antibiotic prophylaxis compared to a single agent antibiotic (OR 0.79, 95% CI 0.70–0.89, p <0.001) (91). The authors also investigated if extended antibiotic treatment > 24 h after RC decreased the risk of infectious complications, but no such association was found. Currently, international guidelines recommend that broad-spectrum antibiotics are used in the prophylactic regimen considering the local microbiological environment (92,93). However, RCTs addressing antibiotic prophylaxis regarding type, timing and duration for the risk of UTI are lacking and warranted.

Risk factors for mortality

In several studies, patient-related factors, age and comorbidity, were identified as the most important factors for mortality at index hospitalization, as well as 30- and 90 days following surgery (11,17,24,27,32,38,41,52,66,68).

Other risk factors

In addition to patient-related factors, the impact of hospital volume, surgical experience, and surgical technique has been addressed. Studies included in this review investigating the impact of hospital volume has shown conflicting results (15,32,34,37,41,56,66). However, a previous meta-analysis of studies not all included in the present review found that the risk of postoperative mortality after RC was decreased by 45% when performed at a high-volume centre compared to a low volume centre (pooled estimated effect OR 0.55 (95% CI 0.44–0.69)) (94). Studies also show that complications are reduced with both increasing hospital and surgeon volume (32,36). Unfortunately, the distinction between low- vs high-volume is not well-defined and thus not comparable between studies. The European Association of Urology (EAU) Muscle-invasive and Metastatic Bladder Cancer Guideline Panel recommends RC to be performed at centres with at least 10 RC/year and preferably >20 RC/year (95). The surgical technique has been investigated in 12 of the included studies in this review (18,20,29,31,33,35,45,48,62,64). Open RC was compared to robotic-assisted RC in ten of these non-randomised papers. In seven of these publications, a significantly reduced complication rate was found. However, five RCTs comparing open and robotic surgery (not included in the review) did not find a difference in complication rates (96–100). All RCTs have been conducted with extracorporeal urinary diversion performed and it is speculated that robot-assisted RC with intracorporeal urinary diversion may have a lower complication rate compared to open RC. The question in hand is currently being studied in the ongoing iROC trial (101).

Limitations

There are limitations of this review that must be addressed. Most of the included studies were retrospective which limits the clinical utility. It is important to notice that we excluded studies with less than 100 patients and studies investigating subgroups of patients such as certain age groups, types of urinary diversion or T-stages of BC. Since most RCTs on RC have less than 100 participants and often exclude patients with certain characteristics they were not included in this review.

Challenges in the comparison of RC studies

The difficulties of comparing RC studies are manifold. Firstly, selection bias between cohorts must be expected. This is reflected by the wide range for the estimates of the weighted averages for ASA score and CCI (Table 1). The selection of patients fit for RC is known to be associated with great variation among centres (102). Secondly, there was no standardized reporting of complications. Most used different classification systems for severity grade of complications with the Clavien-Dindo classification being the most frequent. Thirdly, even when using a grading system as Clavien-Dindo with certain criteria, the scale can be interpreted differently or modified in some way. For example, some studies do not calculate blood transfusions as a complication even though it could be argued to be a grade II complication. Fourthly, measures of morbidity can be defined differently across studies. For example, ileus is reported in up to 20% of patients undergoing RC. However, the reporting of ileus may be questioned as a previous systematic review found that ileus was defined differently across studies, and in the majority of included studies it was not defined at all (103). There is an increased focus on more uniform reporting of morbidity following RC and the EAU have proposed authors to use quality criteria originally proposed by Martin et al. (4,104). In the present review, only three studies fulfilled all the Martin criteria. A previous non-systematic review from 2007 found no study reporting on complications after RC fulfilling all the Martin criteria. Lastly, publication bias must be emphasized as an important limitation.

We refrained from a meta-analysis of predictors of morbidity and mortality in this review as the number of studies investigating the same risk variable and outcome were too small for analysis. Identifying clinical predictors may aid in the prevention of postoperative morbidity and mortality. Currently, there is no risk-assessment tool to predict postoperative outcomes after RC, and little correlation is found between the most frequently used risk-scoring systems (e.g. CCI and ASA score) and postoperative outcomes (70). Nevertheless, in the included studies of this review, comorbidity was in multivariate logistic regression analysis consistently associated with a significantly increased OR of both complications (12,17,22,23,32,49,51,58,60,61,72) and mortality (11,17,24,32,41,52,66). Surprisingly, there is a paucity of prospective studies studying the subjects of the most common complications after RC in order to identify clinical predictors of these. Furthermore, prospective randomised studies comparing different interventions/regimens are lacking.

CONCLUSION

This review shows that RC is associated with a high risk of morbidity and mortality. However, with thorough patient selection, experienced surgeons, treatment at a high-volume hospital and the implementation of an ERAS protocol morbidity and mortality can likely be reduced. Trials addressing medical or surgical interventions to reduce short-term complication are needed.

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COMPETING INTERESTS

None declared.

AUTHORS CONTRIBUTIONS

S.L.M., U.N.J., A.M.P., H.K., K.B., M.A.R. contributed to the research idea and the question. S.L.M., U.N.J., and M.A.R. wrote the protocol. S.L.M. and M.A.R. screened all abstracts and full texts for inclusion. S.L.M. did all the data extraction and statistics. S.L.M. drafted the manuscript and U.N.J., A.M.P., H.K., K.B., M.A.R. contributed to the editing of the manuscript and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data are stored and available from the corresponding author (S.L.M.) upon reasonable request and can be reused without any further permission.

REFERENCES

1. Alfred Witjes J, Lebret T, Compérat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. *Eur Urol*. 2017 Mar;71(3):462–75.

2. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015 Jan 1;4(1):1.

3. Covidence Systematic Review Software [Internet]. Veritas Health Innovation Ltd, Melbourne, Australia. Available from: www.covidence.org

4. Martin RCG, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg*. 2002 Jun;235(6):803–13.

5. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati, Alessandro Moschetti I, et al. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. [Internet]. Available from: http://www.cebm.net/index.aspx?o=5653

6. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. [cited 2020 May 6]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

7. Afshar M, Goodfellow H, Jackson-Spence F, et al. Centralisation of radical cystectomies for bladder cancer in England, a decade on from the "Improving Outcomes Guidance": the case for super centralisation. *BJU Int.* 2018 Feb;121(2):217–24.

8. Al-Daghmin A, Kauffman EC, Shi Y, et al. Efficacy of robot-assisted radical cystectomy (RARC) in advanced bladder cancer: results from the International Radical Cystectomy Consortium (IRCC). *BJU Int.* 2014 Jul;114(1):98–103.

9. Arora K, Hanson KT, Habermann EB, Tollefson MK, Psutka SP. Early Complications and Mortality following Radical Cystectomy: Associations with Malnutrition and Obesity. *Bl cancer* (Amsterdam, Netherlands). 2018 Oct;4(4):377–88.

10. Björnsson O, Gudmundsson EO, Marteinsson VT, et al. Radical cystectomy in the treatment of bladder cancer in Iceland: A population-based study. *Scand J Urol.* 2016 Jan 2;50(1):65–70.

11. Boorjian SA, Kim SP, Tollefson MK, et al. Comparative performance of comorbidity indices for estimating perioperative and 5-year all cause mortality following radical cystectomy for bladder cancer. *J Urol.* 2013 Jul;190(1):55–60.

12. Cantiello F, Cicione A, Autorino R, et al. Metabolic Syndrome, Obesity, and Radical Cystectomy Complications: A Clavien Classification System-Based Analysis. *Clin Genitourin Cancer.* 2014 Oct;12(5):384–93.

13. Chang SS, Cookson MS, Baumgartner RG, Wells N, Smith JA. Analysis of early complications after radical cystectomy: results of a collaborative care pathway. *J Urol.* 2002 May;167(5):2012–6.

14. De Nunzio C, Cindolo L, Leonardo C, et al. Analysis of radical cystectomy and urinary diversion complications with the Clavien classification system in an Italian real life cohort. *Eur J Surg Oncol.* 2013 Jul;39(7):792–8.

15. de Vries RR, Visser O, Nieuwenhuijzen JA, Horenblas S. Outcome of treatment of bladder cancer: a

comparison between low-volume hospitals and an oncology centre. *World J Urol.* 2010 Aug;28(4):431–7.

16. Djaladat H, Katebian B, Bazargani ST, et al. 90-Day complication rate in patients undergoing radical cystectomy with enhanced recovery protocol: a prospective cohort study. *World J Urol.* 2017 Jun 12;35(6):907–11.

17. Fairey A, Chetner M, Metcalfe J, et al. Associations Among Age, Comorbidity and Clinical Outcomes After Radical Cystectomy: Results From the Alberta Urology Institute Radical Cystectomy Database. *J Urol.* 2008 Jul;180(1):128–34.

18. Flamiatos JF, Chen Y, Lambert WE, et al. Open versus robot-assisted radical cystectomy: 30-day perioperative comparison and predictors for cost-to-patient, complication, and readmission. *J Robot Surg.* 2019 Feb;13(1):129–40.

19. Gschliesser T, Eredics K, Berger I, et al. The Impact of Gender on Tumour Stage in In-House Complications and Choice of Urinary Diversion: Results of the Austrian Cystectomy Registry. *Urol Int.* 2017;99(4):429–35.

20. Hanna N, Leow JJ, Sun M, et al. Comparative effectiveness of robot-assisted vs. open radical cystectomy. *Urol Oncol.* 2018 Mar;36(3):88.e1-88.e9.

21. Hayn MH, Hellenthal NJ, Hussain A, Stegemann AP, Guru KA. Defining Morbidity of Robot-Assisted Radical Cystectomy Using a Standardized Reporting Methodology. *Eur Urol.* 2011 Feb;59(2):213–8.

22. Hirobe M, Tanaka T, Shindo T, et al. Complications within 90 days after radical cystectomy for bladder cancer: results of a multicenter prospective study in Japan. *Int J Clin Oncol.* 2018 Aug 13;23(4):734–41.

23. Hollenbeck BK, Miller DC, Taub D, et al. Identifying risk factors for potentially avoidable complications following radical cystectomy. *J Urol.* 2005 Oct;174(4 Pt 1):1231–7.

24. Hollenbeck BK, Miller DC, Taub DA, et al. The Effects of Adjusting for Case Mix on Mortality and Length of Stay Following Radical Cystectomy. *J Urol.* 2006 Oct;176(4):1363–8.

25. Hu JC, Chughtai B, O'Malley P, et al. Perioperative Outcomes, Health Care Costs, and Survival After Robotic-assisted Versus Open Radical Cystectomy: A National Comparative Effectiveness Study. *Eur Urol.* 2016 Jul;70(1):195–202.

26. Jerlström T, Gårdmark T, Carringer M, et al. Urinary bladder cancer treated with radical cystectomy: Perioperative parameters and early complications prospectively registered in a national population-based database. *Scand J Urol.* 2014 Aug 21;48(4):334–40.

27. Johar RS, Hayn MH, Stegemann AP, et al. Complications After Robot-assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium. *Eur Urol.* 2013 Jul;64(1):52–7.

28. Johnson SC, Smith ZL, Golan S, Rodriguez JF, Smith ND, Steinberg GD. Temporal trends in perioperative morbidity for radical cystectomy using the National Surgical Quality Improvement Program database. *Urol Oncol Semin Orig Investig.* 2017 Nov;35(11):659.e13-659.e19.

29. Kader AK, Richards KA, Krane LS, Pettus JA, Smith JJ, Hemal AK. Robot-assisted laparoscopic vs open radical cystectomy: comparison of complications and perioperative oncological outcomes in 200 patients. *BJU Int.* 2013 Aug;112(4):E290–4.

30. Kanno T, Ito K, Sawada A, et al. Complications and reoperations after laparoscopic radical cystectomy in a Japanese multicenter cohort. *Int J Urol.* 2019 Apr;26(4):493–8.

31. Khan MS, Challacombe B, Elhage O, et al. A dual-centre, cohort comparison of open, laparoscopic and robotic-assisted radical cystectomy. *Int J Clin Pract.* 2012 Jul;66(7):656–62.

32. Kim SP, Boorjian SA, Shah ND, et al. Contemporary trends of in-hospital complications and mortality for radical cystectomy. *BJU Int.* 2012 Oct;110(8):1163–8.

33. Koupparis A, Villeda-Sandoval C, Weale N, El-Mahdy M, Gillatt D, Rowe E. Robot-assisted radical cystectomy with intracorporeal urinary diversion: impact on an established enhanced recovery protocol. *BJU Int.* 2015 Dec;116(6):924–31.

34. Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A. Impact of provider volume on operative mortality after radical cystectomy in a publicly funded healthcare system. *Can Urol Assoc J.* 2013;7(11–12):425–9.

35. Lenfant L, Campi R, Parra J, et al. Robotic versus open radical cystectomy throughout the learning phase: insights from a real-life multicenter study. *World J Urol.* 2019 Nov;

36. Leow JJ, Reese S, Trinh Q-D, et al. Impact of surgeon volume on the morbidity and costs of radical cystectomy in the USA: a contemporary population-based analysis. *BJU Int.* 2015 May;115(5):713–21.

37. Liedberg F, Holmberg E, Holmäng S, et al. Long-term follow-up after radical cystectomy with emphasis on complications and reoperations: A Swedish population-based survey. *Scand J Urol Nephrol*. 2012 Feb 19;46(1):14–8.

38. Lin W-Y, Wu C-T, Chen M-F, Chang Y-H, Lin C-L, Kao C-H. Cystectomy for bladder cancer in elderly patients is not associated with increased 30- and 90-day mortality or readmission, length of stay, and cost: propensity score matching using a population database. *Cancer Manag Res.* 2018;10:1413–8.

39. Liu B, Domes T, Jana K. Evaluation of an enhanced recovery protocol on patients having radical cystectomy for bladder cancer. *Can Urol Assoc J.* 2018 Jul;12(12):421–6.

40. Llorente C, Lopez B, Hernandez V, Guijarro A, Perez-Fernandez E. Variability in complications and operative mortality after radical cystectomy in Spain. *Actas Urol Esp.* 2017 Jan;41(1):32–8.

41. Llorente C, Guijarro A, Hernandez V, Fernández-Conejo G, Perez-Fernandez E, Pocock S. Effect of hospital volume on 90-day mortality after radical cystectomy for bladder cancer in Spain. *World J Urol.* 2020 May;38(5):1221–8.

42. Llorente C, Guijarro A, Hernández V, et al. Outcomes of an enhanced recovery after radical cystectomy program in a prospective multicenter study: compliance and key components for success. *World J Urol.* 2020 Mar;

43. Lowrance WT, Rumohr JA, Chang SS, Clark PE, Smith JA, Cookson MS. Contemporary open radical cystectomy: analysis of perioperative outcomes. *J Urol.* 2008 Apr;179(4):1313–8.

44. Malavaud B, Vaessen C, Mouzin M, Rischmann P, Sarramon J, Schulman C. Complications for radical cystectomy. Impact of the American Society of Anesthesiologists score. *Eur Urol*. 2001 Jan;39(1):79–84.

45. Mazzone E, D'Hondt F, Beato S, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion decreases postoperative complications only in highly comorbid patients: findings that rely on a standardized methodology recommended by the European Association of Urology Guidelines. *World J Urol.* 2020 May;

46. Monn MF, Kaimakliotis HZ, Cary KC, et al. Short-term morbidity and mortality of Indiana pouch, ileal conduit, and neobladder urinary diversion following radical cystectomy. *Urol Oncol Semin Orig Investig*. 2014 Nov;32(8):1151–7.

47. Moschini M, Gandaglia G, Dell'Oglio P, et al. Incidence and Predictors of 30-Day Readmission in Patients Treated With Radical Cystectomy: A Single Center European Experience. *Clin Genitourin Cancer*. 2016 Aug;14(4):e341-6.

48. Musch M, Janowski M, Steves A, et al. Comparison of early postoperative morbidity after robot-assisted and open radical cystectomy: results of a prospective observational study. *BJU Int.* 2014 Mar;113(3):458–67.

49. Nazmy M, Yuh B, Kawachi M, et al. Early and Late Complications of Robot-Assisted Radical Cystectomy: A Standardized Analysis by Urinary Diversion Type. *J Urol*. 2014 Mar;191(3):681–7.

50. Nazzani S, Mazzone E, Preisser F, et al. Comparison of Perioperative Outcomes Between Open and Robotic Radical Cystectomy: A Population-Based Analysis. *J Endourol.* 2018 Aug;32(8):701–9.

51. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary Diversions after Cystectomy: The Association of Clinical Factors, Complications and Functional Results of Four Different Diversions. *Eur Urol*. 2008 Apr;53(4):834–44.

52. Novotny V, Froehner M, Koch R, et al. Age, American Society of Anesthesiologists physical status classification and Charlson score are independent predictors of 90-day mortality after radical cystectomy. *World J Urol.* 2016 Aug;34(8):1123–9.

53. Novotny V, Hakenberg OW, Wiessner D, et al. Perioperative Complications of Radical Cystectomy in a Contemporary Series. *Eur Urol.* 2007 Feb;51(2):397–402.

54. Patidar N, Yadav P, Sureka SK, Mittal V, Kapoor R, Mandhani A. An audit of early complications of radical cystectomy using Clavien-Dindo classification. *Indian J Urol.* 2016;32(4):282–7.

55. Peyton CC, Reich RR, Tang D, et al. Identifying and Codifying Complications after Radical Cystectomy: Comparison of Administrative Diagnostic and Procedure Codes, and Clinical Chart Review. *J Urol.* 2019 Nov;202(5):913–9.

56. Porter MP, Gore JL, Wright JL. Hospital volume and 90-day mortality risk after radical cystectomy: a population-based cohort study. *World J Urol.* 2011 Feb;29(1):73–7.

57. Quek ML, Stein JP, Daneshmand S, et al. A Critical Analysis of Perioperative Mortality From Radical Cystectomy. *J Urol.* 2006 Mar;175(3):886–90.

58. Roghmann F, Sukumar S, Ravi P, et al. Radical Cystectomy in the Elderly: National Trends and Disparities in Perioperative Outcomes and Quality of Care. *Urol Int.* 2014;92(1):27–34.

59. Salminen AP, Koskinen I, Perez IM, et al. Neoadjuvant Chemotherapy Does Not Increase the Morbidity of Radical Cystectomy: A 10-year Retrospective Nationwide Study. *Eur Urol Oncol.* 2018 Dec;1(6):525–30.

60. Schmid M, Rink M, Traumann M, et al. Evidence from the "PROspective MulticEnTer RadIcal Cystectomy Series 2011 (PROMETRICS 2011)" Study: How are Preoperative Patient Characteristics Associated with Urinary Diversion Type After Radical Cystectomy for Bladder Cancer? *Ann Surg Oncol.* 2015 Mar 28;22(3):1032–42.

61. Shabsigh A, Korets R, Vora KC, et al. Defining Early Morbidity of Radical Cystectomy for Patients with Bladder Cancer Using a Standardized Reporting Methodology. *Eur Urol.* 2009 Jan;55(1):164–76.

62. Styn NR, Montgomery JS, Wood DP, et al. Matched Comparison of Robotic-assisted and Open Radical Cystectomy. *Urology*. 2012 Jun;79(6):1303–9.

63. Su S, Gu L, Ma X, et al. Comparison of Laparoscopic and Robot-assisted Radical Cystectomy for Bladder Cancer: Perioperative and Oncologic Outcomes. *Clin Genitourin Cancer*. 2019 Oct;17(5):e1048–53.

64. Sung HH, Ahn J-S, Seo S Il, et al. A Comparison of Early Complications Between Open and Robot-Assisted Radical Cystectomy. *J Endourol.* 2012 Jun;26(6):670–5.

65. Svatek RS, Fisher MB, Matin SF, et al. Risk Factor Analysis in a Contemporary Cystectomy Cohort Using Standardized Reporting Methodology and Adverse Event Criteria. *J Urol.* 2010 Mar;183(3):929–34.

66. Udovicich C, Perera M, Huq M, Wong L-M, Lenaghan D. Hospital volume and perioperative outcomes for radical cystectomy: a population study. *BJU Int.* 2017 May;119 Suppl:26–32.

67. Wei C, Wan F, Zhao H, Ma J, Gao Z, Lin C. Application of enhanced recovery after surgery in patients undergoing radical cystectomy. *J Int Med Res.* 2018 Dec;46(12):5011–8.

68. Wissing MD, Santos F, Zakaria AS, et al. Short- and long-term survival has improved after radical cystectomy for bladder cancer in Québec during the years 2000-2015. *J Surg Oncol.* 2019 Jun;119(8):1135–44.

69. Takada N, Abe T, Shinohara N, et al. Peri-operative morbidity and mortality related to radical cystectomy: a multi-institutional retrospective study in Japan. *BJU Int.* 2012 Dec;110(11b):E756–64.

70. Woldu SL, Sanli O, Clinton TN, Lotan Y. Validating the predictors of outcomes after radical cystectomy for bladder cancer. *Cancer*. 2019 Jan 15;125(2):223–31.

71. Xylinas E, Green DA, Otto B, et al. Robotic-assisted Radical Cystectomy With Extracorporeal Urinary Diversion for Urothelial Carcinoma of the Bladder: Analysis of Complications and Oncologic Outcomes in 175 Patients With a Median Follow-up of 3 Years. *Urology*. 2013 Dec;82(6):1323–9.

72. Zhang JH, Ericson KJ, Thomas LJ, et al. Large Single Institution Comparison of Perioperative Outcomes and Complications of Open Radical Cystectomy, Intracorporeal Robot-Assisted Radical Cystectomy and Robotic Extracorporeal Approach. *J Urol*. 2020 Mar;203(3):512–21.

73. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo Classification of Surgical Complications. *Ann Surg*. 2009 Aug;250(2):187–96.

74. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003;13(3):176–81.

75. Hayn MH, Hellenthal NJ, Seixas-Mikelus SA, et al. Is patient outcome compromised during the initial

experience with robot-assisted radical cystectomy? Results of 164 consecutive cases. *BJU Int*. 2011 Jan;108(6):no-no.

76. Nutt M, Scaief S, Dynda D, Alanee S. Ileus and small bowel obstruction after radical cystectomy for bladder cancer: Analysis from the Nationwide Inpatient Sample. *Surg Oncol.* 2018 Sep;27(3):341–5.

77. Cerantola Y, Valerio M, Persson B, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) society recommendations. *Clin Nutr*. 2013 Dec;32(6):879–87.

78. Pillai P, McEleavy I, Gaughan M, et al. A Double-Blind Randomized Controlled Clinical Trial to Assess the Effect of Doppler Optimized Intraoperative Fluid Management on Outcome Following Radical Cystectomy. *J Urol.* 2011 Dec;186(6):2201–6.

79. Choi H, Kang SHSG, Yoon DK, et al. Chewing Gum Has a Stimulatory Effect on Bowel Motility in Patients After Open or Robotic Radical Cystectomy for Bladder Cancer: A Prospective Randomized Comparative Study. *Urology*. 2011 Apr;77(4):884–90.

80. Lee CT, Chang SS, Kamat AM, et al. Alvimopan Accelerates Gastrointestinal Recovery After Radical Cystectomy: A Multicenter Randomized Placebo-Controlled Trial. *Eur Urol.* 2014 Aug;66(2):265–72.

81. Inman BA, Harel F, Tiguert R, Lacombe L, Fradet Y. Routine Nasogastric Tubes Are Not Required Following Cystectomy With Urinary Diversion: A Comparative Analysis of 430 Patients. *J Urol.* 2003 Nov;170(5):1888–91.

82. Shafii M, Murphy DM, Donovan MG, Hickey DP. Is mechanical bowel preparation necessary in patients undergoing cystectomy and urinary diversion? *BJU Int.* 2002 May 12;89(9):879–81.

83. Wessels F, Lenhart M, Kowalewski KF, et al. Early recovery after surgery for radical cystectomy: comprehensive assessment and meta-analysis of existing protocols. *World J Urol*. 2020 Mar 2;

84. Williams SB, Cumberbatch MGK, Kamat AM, et al. Reporting Radical Cystectomy Outcomes Following Implementation of Enhanced Recovery After Surgery Protocols: A Systematic Review and Individual Patient Data Meta-analysis. *Eur Urol*. 2020;1–12.

85. Baack Kukreja JE, Messing EM, Shah JB. Are we doing "better"? The discrepancy between perception and practice of enhanced recovery after cystectomy principles among urologic oncologists. *Urol Oncol.* 2016 Mar;34(3):120.e17-21.

86. Clifford TG, Katebian B, Van Horn CM, et al. Urinary tract infections following radical cystectomy and urinary diversion: a review of 1133 patients. *World J Urol.* 2018 May 25;36(5):775–81.

87. van Hemelrijck M, Thorstenson A, Smith P, Adolfsson J, Akre O. Risk of in-hospital complications after radical cystectomy for urinary bladder carcinoma: population-based follow-up study of 7608 patients. *BJU Int*. 2013 Dec;112(8):1113–20.

88. Kolwijck E, Seegers AEM, Tops SCM, Heijden AG van der, Sedelaar JPM, Oever J ten. Incidence and microbiology of postoperative infections after radical cystectomy and ureteral stent removal; a retrospective cohort study. *BMC Infect Dis.* 2019;19(1):303.

89. Parker WP, Tollefson MK, Heins CN, et al. Characterization of perioperative infection risk among patients undergoing radical cystectomy: Results from the national surgical quality improvement program. *Urol Oncol*. 2016 Dec;34(12):532.e13-532.e19.

90. Pariser JJ, Anderson BB, Pearce SM, et al. The effect of broader, directed antimicrobial prophylaxis including fungal coverage on perioperative infectious complications after radical cystectomy. *Urol Oncol Semin Orig Investig.* 2016;34(3):121.e9-121.e14.

91. Krasnow RE, Mossanen M, Koo S, et al. Prophylactic Antibiotics and Postoperative Complications of Radical Cystectomy: A Population Based Analysis in the United States. *J Urol.* 2017;198(2):297–304.

92. European Association of Urology. Guideline on urological infections [Internet]. [cited 2020 Apr 20]. Available from: https://uroweb.org/guideline/urological-infections/#3

93. American Urological Association. Urologic Procedures and Antimicrobial Prophylaxis (2019) [Internet]. [cited 2020 May 11]. Available from: https://www.auanet.org/guidelines/urologic-procedures-and-antimicrobial-prophylaxis-(2019)

94. Goossens-Laan CA, Gooiker GA, van Gijn W, et al. A systematic review and meta-analysis of the relationship between hospital/surgeon volume and outcome for radical cystectomy: an update for the ongoing debate. *Eur Urol.* 2011 May;59(5):775–83.

95. Bruins HM, Veskimäe E, Hernández V, et al. The Importance of Hospital and Surgeon Volume as Major Determinants of Morbidity and Mortality After Radical Cystectomy for Bladder Cancer: A Systematic Review and Recommendations by the European Association of Urology Muscle-invasive and Metastatic Bladd. *Eur Urol Oncol.* 2019 Dec 19;

96. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label , randomised , phase 3 , non-inferiority trial. *Lancet*. 2018 Jun;391(10139):2525–36.

97. Nix J, Smith A, Kurpad R, Nielsen ME, Wallen EM, Pruthi RS. Prospective Randomized Controlled Trial of Robotic versus Open Radical Cystectomy for Bladder Cancer: Perioperative and Pathologic Results. *Eur Urol.* 2010 Feb;57(2):196–201.

98. Bochner BH, Dalbagni G, Sjoberg DD, et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. *Eur Urol.* 2015 Jun;67(6):1042–50.

99. Parekh DJ, Messer J, Fitzgerald J, Ercole B, Svatek R. Perioperative Outcomes and Oncologic Efficacy from a Pilot Prospective Randomized Clinical Trial of Open Versus Robotic Assisted Radical Cystectomy. *J Urol*. 2013 Feb;189(2):474–9.

100. Khan MS, Gan C, Ahmed K, et al. A Single-centre Early Phase Randomised Controlled Three-arm Trial of Open, Robotic, and Laparoscopic Radical Cystectomy (CORAL). *Eur Urol.* 2016 Apr;69(4):613–21.

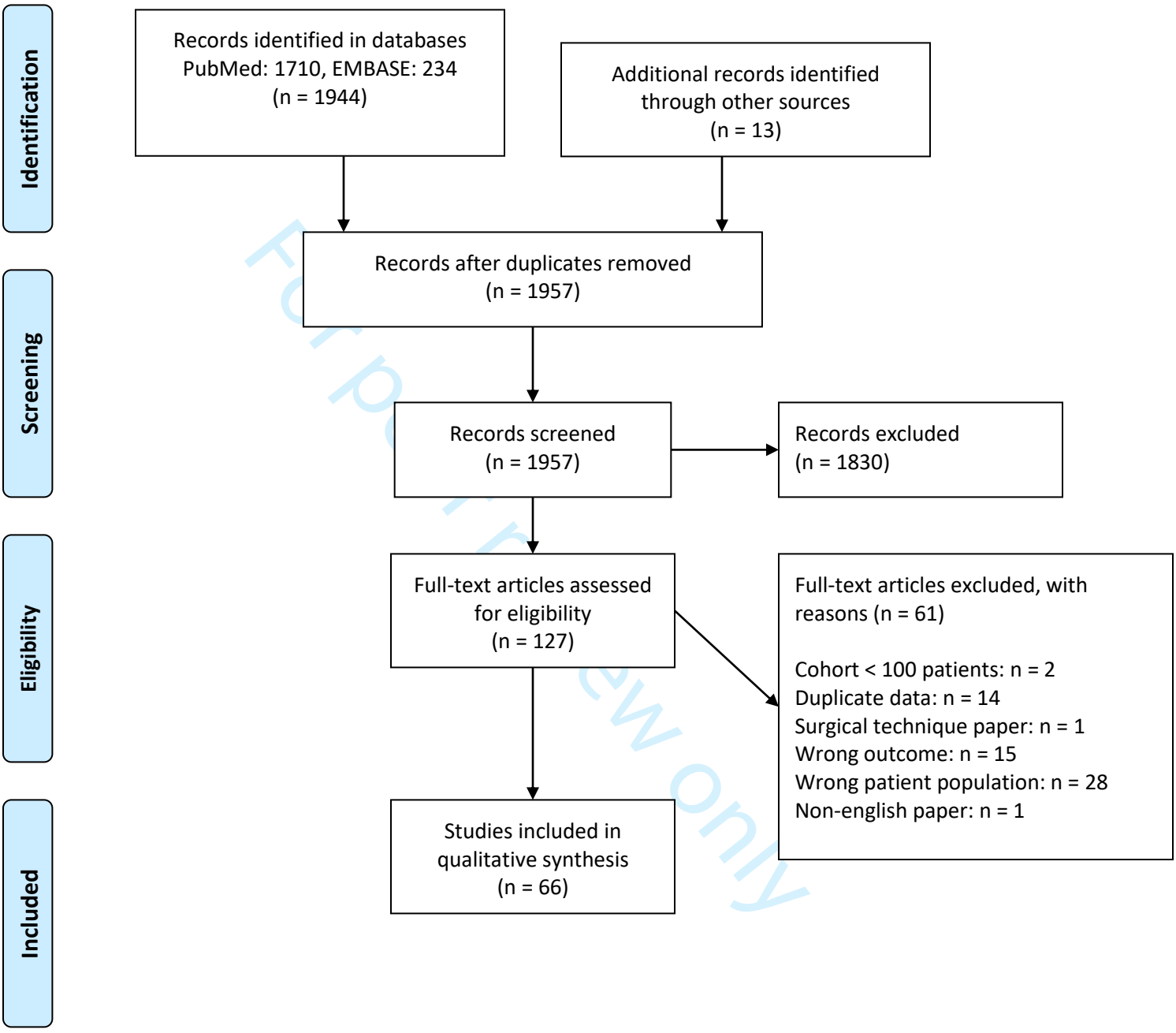
101. Catto JWF, Khetrapal P, Ambler G, et al. Robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy (iROC): Protocol for a randomised controlled trial with internal feasibility study. *BMJ Open.* 2018;8(8):1–10.

102. Williams SB, Huo J, Chamie K, et al. Underutilization of Radical Cystectomy Among Patients Diagnosed with Clinical Stage T2 Muscle-invasive Bladder Cancer. *Eur Urol Focus.* 2017 Apr;3(2–3):258–64.

103. Ramirez JA, McIntosh AG, Strehlow R, Lawrence VA, Parekh DJ, Svatek RS. Definition, incidence, risk factors, and prevention of paralytic ileus following radical cystectomy: a systematic review. *Eur Urol.* 2013 Oct;64(4):588–97.

104. Mitropoulos D, Artibani W, Graefen M, et al. Reporting and Grading of Complications After Urologic Surgical Procedures: An ad hoc EAU Guidelines Panel Assessment and Recommendations. *Eur Urol.* 2012 Feb;61(2):341–9.

Legend for Figure 1: Figure 1. PRISMA flowchart



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Appendix 1

Database	Search string
PubMed/MEDLINE	**#1**: “urinary bladder neoplasms” [MeSH Terms] OR "urothelial carcinoma"[Title/Abstract]) OR "invasive urothelial bladder carcinomas"[Title/Abstract]) OR "bladder cancer"[Title/Abstract] **#2**: "cystectomy"[Text Word] OR "cystoprostatectomy"[Title/Abstract] **#3**: “postoperative complications”[Text Word] OR “length of stay”[Text Word] OR “complication*”[Title/Abstract] OR “clavien*”[Title/Abstract] OR “reoperation*”[Title/Abstract] OR “mortality”[Title/Abstract] **#4**: #1 AND #2 AND #3 **#5**: #4 NOT (“review” [Publication Type] OR “letter”[Publication Type] OR “comment”[Publication Type]) Filter: English, humans, publication date 1990-
EMBASE	**#1**: exp bladder cancer/ OR bladder carcinoma.mp/ OR muscle invasive bladder cancer.mp OR bladder cancer.mp OR invasive urothelial cancer.mp OR urothelial carcinoma.mp **#2**: exp cystectomy/ OR cystectomy.mp OR cystoprostatectomy.mp **#3**: exp postoperative complication/ OR exp length of stay/ OR complication/ OR exp reoperation/ OR clavien*.mp OR complication*.mp OR reoperation*.mp OR length of stay.mp OR mortality.mp **#4**: #1 AND #2 AND #3 Limits: human, English language, exclude Medline journals

Appendix 2

Reference	Number of Martin criteria fulfilled	New Castle-Ottawa Scale score		
		Selection	Comparability	Outcome
Afshar et al.	NA	****	**	**
Al-Daghmin et al.	5	****	*	***
Arora et al.	5	****	**	***
Björnsson et al.	7	****	0	***
Boorjian et al.	NA	***	**	***
Cantiello et al.	9	****	0	***
Chang et al.	6	****	*	***
De Nunzio et al.	7	****	**	**
de Vries et al.	NA	****	**	***
Djaladat et al.	9	****	**	**
Fairey et al.	5	****	**	***
Flamiatos et al.	6	****	*	***
Gschliesser et al.	5*	****	**	***
Hanna et al.	NA	****	**	**
Hayn et al.	10	****	**	***
Hirobe et al.	10	****	**	***
Hollenbeck et al. (2005)	5	****	*	***
Hollenbeck et al. (2006)	NA	****	**	***
Hu et al.	4*	****	**	***
Jerlström et al.	7	****	*	***
Johar et al.	8	****	**	***
Johnson et al.	6	****	**	***

Kader et al.	5	****	0	***
Kanno et al.	7	****	0	***
Khan et al.	8	****	**	***
Kim et al.	6*	****	*	***
Koupparis et al.	5	****	0	***
Kulkarni et al.	NA	****	**	***
Lenfant et al.	6	****	0	***
Leow et al.	3	****	**	***
Liedberg et al.	NA	****	0	***
Lin et al.	NA	****	**	***
Liu et al.	5*	****	0	***
Llorente et al. (2017)	2	****	*	***
Llorente et al. (2020)	7	****	**	***
Llorente et al. (2020)	NA	****	**	***
Lowrance et al.	7	****	0	***
Malavaud et al.	6	****	0	***
Mazzone et al.	9	****	**	***
Monn et al.	8	****	**	***
Moschini et al.	2	****	*	***
Musch et al.	7	****	0	***
Nazmy et al.	8	****	**	***
Nazzani et al.	4*	****	**	***
Nieuwenhuijzen et al.	8	****	*	***
Novotny et al. (2007)	NA	****	0	***
Novotny et al. (2016)	5	****	**	***

Patidar et al.	7	****	0	***
Peyton et al.	5	****	0	***
Porter et al.	NA	****	**	***
Quek et al.	NA	****	0	***
Roghmann et al.	5	****	**	***
Salminen et al.	7	****	**	***
Schmid et al.	4	****	*	***
Shabsigh et al.	10	****	**	***
Styn et al.	6	****	**	***
Su et al.	5	****	0	***
Sung et al.	9	****	*	***
Svatek et al.	9	****	*	***
Takada et al.	9	****	*	***
Udovicuch et al.	NA	****	0	***
Wei et al.	3	****	0	*
Wissing et al.	NA	****	**	***
Woldu et al.	4	****	**	***
Xylinas et al.	7	****	0	***
Zhang et al.	7	****	**	***

NA: Not applicable (study not reporting complications). *Studies have been scored as fulfilling the criteria of "outpatient information included" as this criterium does not apply to the studies with an outcome period including in-house complications only.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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