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## Short term outcomes after robot assisted and open cystectomy - A nation-wide population-based study

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## ABSTRACT

**Introduction:** We aimed to compare short term outcomes after robot assisted radical cystectomy (RARC) and open radical cystectomy (ORC) for urinary bladder cancer in a large population.

**Materials and methods:** We included all patients without distant metastases who underwent either RARC or ORC with ileal conduit between 2011 and 2019 registered in the Bladder cancer data Base Sweden (BladderBaSe) 2.0. Primary outcome was unplanned readmissions within 90 days, and secondary outcomes within 90 days of surgery were reoperations, Clavien 3–5 complications, total days alive and out of hospital, and mortality. The analysis was carried out using multivariate regression models.

**Results:** Out of 2905 patients, 832 were operated with RARC and 2073 with ORC. Robotic procedures were to a larger extent performed during later years, at high volume centers (47% vs 17%), more often for organ-confined disease (82% vs. 72%) and more frequently in patients with high socioeconomic status (26% vs. 21%). Patients operated with RARC were more commonly readmitted (29% vs. 25%). In multivariable analysis RARC was associated with decreased risk of Clavien 3–5 complications (OR 0.58, 95% CI 0.47–0.72), reoperations (OR 0.53, 95% CI 0.39–0.71) and had more days alive and out of hospital (mean difference 3.7 days, 95% CI 2.4–5.0).

**Conclusion:** This study illustrates the “real-world” effects of a gradual and nation-wide introduction of RARC. Patients operated with RARC had fewer major complications and reoperations but were more frequently readmitted compared to ORC. The observed differences were largely due to more wound related complications among patients treated with ORC.

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## 1. Introduction

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Muscle-invasive bladder cancer without metastases has

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generally been treated with open radical cystectomy (ORC), pelvic lymphadenectomy and urinary diversion. Such complex surgery is associated with a considerable risk of perioperative complications and even mortality. Robot assisted radical cystectomy (RARC) has increasingly been introduced during the last decade, in an attempt to mitigate these issues.

The first randomized trial comparing morbidity and complications as primary outcome measures was prematurely closed after an interim analysis due to lack of difference between the RARC and ORC-groups [1]. This trial applied an extracorporeal technique when constructing the urinary diversion. Three additional randomized single-center studies have shown improved peri- and postoperative parameters for RARC such as reduced blood loss and a shorter hospital stay. However, none of these studies have shown any major differences regarding the risk of postoperative complications or survival, and the operative time for RARC was generally longer [1–3]. Similarly, oncological outcomes in the RAZOR-study showed no major differences between RARC and ORC regarding adverse events and 2-year progression-free survival [4]. The large iROC-trial comparing RARC with intracorporeal urinary diversion to ORC was recently published, reporting more days alive and out of hospital within 90 days of surgery as well as fewer thromboembolic- and wound related complications. However, there were no larger differences regarding cancer recurrence and overall mortality [5]. Additionally, some observational studies have shown a lower proportion of postoperative complications after RARC [6–16], but larger population-based studies in a real-world setting with extensive information about confounding factors are lacking.

We investigated if the introduction of RARC into clinical practice led to any short term (within 90 days) improvements for patients diagnosed with invasive urinary bladder cancer regarding outcomes such as readmissions, reoperations, complications, days alive and out of hospital, and mortality, as compared to ORC. We utilized a linked nation-wide health care register with extensive information on confounding factors to enable further adjusting for potential bias.

## 2. Patients and methods

### 2.1. Data source

The Swedish National Registry of Urinary Bladder Cancer (SNRUBC) includes information on tumor characteristics, treatment and follow-up on virtually all Swedish patients with urinary bladder cancer since 1997. A radical cystectomy form containing information on pre-, peri-, and postoperative data is routinely collected since 2011. In 2014 and in 2019, the SNRUBC has been cross-linked to several other nation-wide population-based health care registries and demographic databases such as the in-patient register and the cause of death register in the Bladder cancer data Base Sweden (BladderBaSe) 2.0 to obtain additional information such as data on socioeconomic status and comorbidities [17].

### 2.2. Study population and design

We included Swedish patients who underwent either RARC or ORC between 2011 and 2019, without distant metastasis at diagnosis, registered in the SNRUBC, and with complete information on outcomes in a cohort study comparing short term outcomes (within 90 days of the radical cystectomy). To assess unplanned readmissions, only patients receiving an ileal conduit without the need for readmissions to extract catheters and/or commencing catheterization of continent reconstructions were considered. Type of surgery (RARC or ORC) was reported in SNRUBC. Missing data on type of surgery was retrieved from the in-patient register ( $n = 5$ ).

Patients were analyzed according to an intention to treat approach, i.e. individuals where a RARC procedure was converted to ORC remained in the RARC group. Additionally, a “trial population” was defined excluding individuals not fulfilling the inclusion criteria for the randomized iROC study comparing RARC and ORC (5) and in which we investigated the same outcome measures as in the main analysis (Fig. 1). Consequently, this “trial population” used narrower inclusion criteria's and excluded patients with extensive nodal spread (cN2 or higher) or stage cT4b compared to the main cohort.

### 2.3. Outcomes

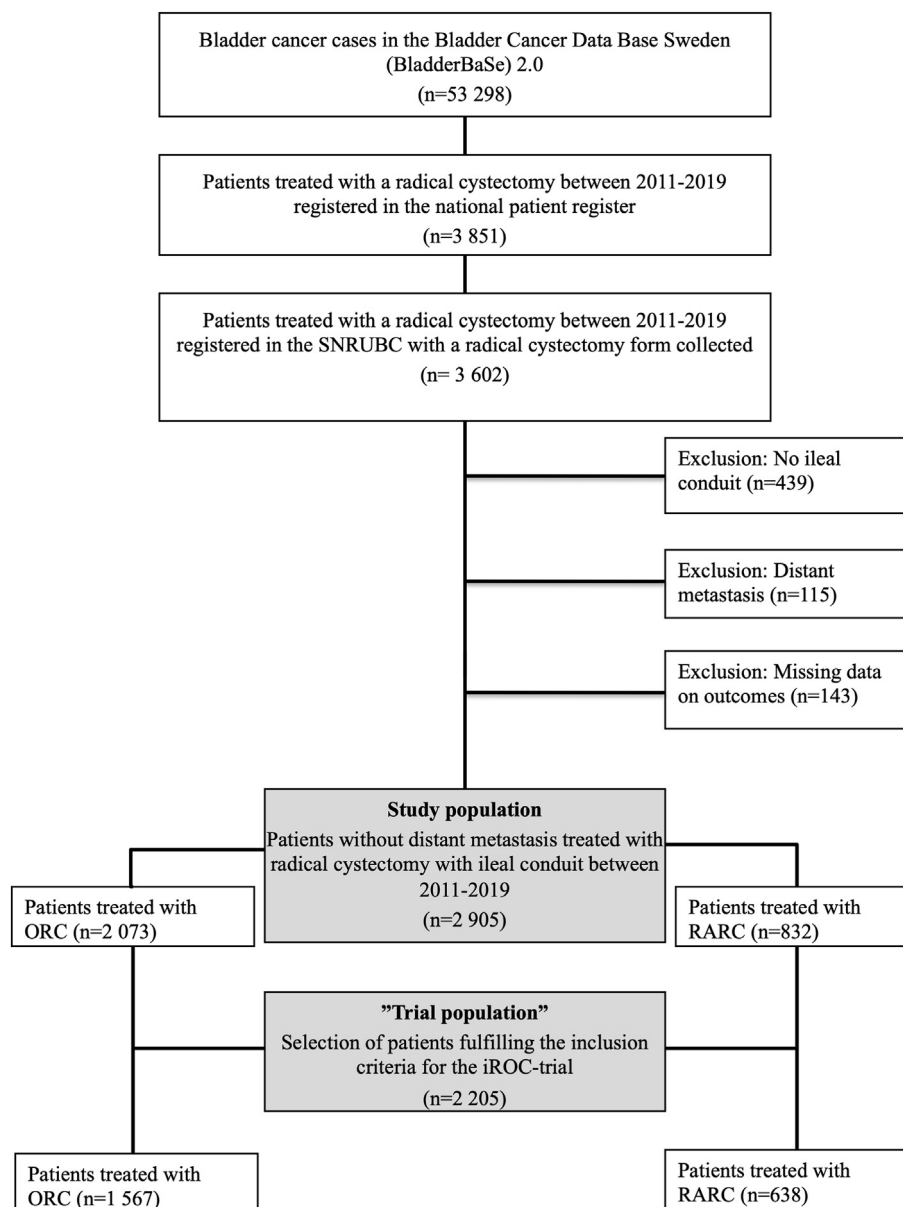
Our primary outcome measure was unplanned readmissions within 90 days of surgery. Secondary outcomes within 90 days were defined as Clavien 3–5 complications [18]; reoperations (categorized as reoperation for gastrointestinal complications, complications related to wound closure or stoma, urinary tract, postoperative bleeding and/or other); total days alive and out of hospital and mortality (including cause of death). Total days alive and out of hospital is a validated composite outcome measure for both morbidity and mortality, combining length of stay, readmissions and mortality into one outcome measure [19], calculated as previously described [20] and stratified in quartiles (0–69, 70–77, 78–80, and 81–90 days). All estimates except total days alive and out of hospital within 90 days, mortality, and cause of death were retrieved from the radical cystectomy form in the SNRUBC. Total days alive and out of hospital were calculated with data from the cause of death register and date of discharge from the in-patient register. Mortality and cause of death was retrieved from the cause of death register. Missing data on unplanned readmission from the radical cystectomy form was retrieved from the in-patient register ( $n = 104$ ). Missing data of highest Clavien complication grade was set to 0–2 if no reoperations or complications were reported in the SNRUBC.

### 2.4. Statistical analysis

Potential confounders were identified as gender, age, BMI, comorbidity according to Charlson Comorbidity Index (CCI) and Drug Comorbidity Index (DCI) [21], socioeconomic status, previous pelvic surgery or radiotherapy, tumor stage group, and preoperative chemotherapy. CCI was calculated on the date of diagnosis and handled as a categorical variable in the analysis and DCI was calculated on the date of surgery and handled as a continuous variable in the analysis. Socioeconomic status was defined as the highest educational level (mandatory school, high school or university). Clinical tumor stage group was stratified into Ta/CIS/T1 and N0, T2 and N0, T3–4 and N0, or any T-stage and N+, respectively. Preoperative chemotherapy was either neoadjuvant or induction chemotherapy for cT4b and/or N+ disease.

Year of radical cystectomy was stratified into 2011–2013, 2014–2016, and 2017–2019. Hospital experience was calculated using data from the in-patient register and defined as the average number of type specific radical cystectomies per year during the three preceding years for patients included in the study population (calculated separately for each hospital unit and year of operation for the individual patient, i.e. number of ORC three years prior to an open surgery and number of RARC prior to a robot surgery) stratified into groups of equal size as follows; at most 15 surgeries per year (independent of surgery type), 16–24 type specific surgeries per year, 25–44 type specific surgeries per year and >44 type specific surgeries per year.

Multivariable analysis was performed after imputing missing data on the variables BMI, previous surgery or radiotherapy, clinical



**Fig. 1.** CONSORT-diagram describing the study population. SNRUBC = The Swedish National Registry of Urinary Bladder Cancer.

tumor stage group and perioperative chemotherapy in 20 imputation datasets created using chained equations implemented in R by the MICE algorithm [22]. Logistic regression presenting odds ratios (ORs) with 95% confidence intervals were calculated for dichotomous variables adjusting for the confounders described above. For continuous variables linear regression models were applied presenting mean values with 95% confidence intervals. ORC was the reference group in all analyses. The analyses were made with and without adjusting for the effect modifiers year of surgery and hospital experience, to assess a presumed more liberal use of early discharge during later years and the effect of hospital experience on outcomes. All analyses were performed utilizing the R statistical software version 4.1.2.

#### Ethical approval

Ethical approval was obtained (approval numbers 2015/277 and 2020/05123).

### 3. Results

#### 3.1. Baseline characteristics

In all, 2905 patients were included of which 832 were operated with a RARC and 2073 with an ORC (Table 1). RARC was increasingly utilized during the study period, from 114/776 (15%) procedures during 2011–2013 to 445/1046 (43%) procedures during 2017–2019. RARC was to a larger extent performed at high-volume centers (defined as more than 45 type specific procedures per year), 395/832 (47%) procedures versus 346/2073 (17%) procedures for ORC (Table 1). Patients treated with RARC more often had organ-confined (cTa–cT2N0) disease (82% versus 72%), had a higher socioeconomic status with 26% having attended higher education compared to 21% among patients treated with ORC, and less often received preoperative chemotherapy (28% versus 34%) (Table 1). The proportions of sex, age, BMI, comorbidity and previous pelvic surgery/radiotherapy were similar between the groups.

**Table 1**

Baseline characteristics for all study participants. RARC = Robot assisted radical cystectomy; ORC = Open radical cystectomy; CCI = Charlson comorbidity index; DCI = Drug comorbidity index.

	RARC (n = 832)		ORC (n = 2073)		All (n = 2905)	
<b>Gender, n (%)</b>						
Men	601	(72.2)	1544	(74.5)	2145	(73.8)
Women	231	(27.8)	529	(25.5)	760	(26.2)
<b>Age, n (%)</b>						
≤65	164	(19.7)	430	(20.7)	594	(20.4)
66–70	157	(18.9)	469	(22.6)	626	(21.5)
71–75	233	(28.0)	539	(26.0)	772	(26.6)
76–80	178	(21.4)	446	(21.5)	624	(21.5)
81+	100	(12.0)	189	(9.1)	289	(9.9)
<b>BMI, n (%)</b>						
<18.5	18	(2.2)	41	(2.0)	59	(2.0)
18.5–25	348	(41.8)	855	(41.2)	1203	(41.4)
25–30	342	(41.1)	827	(39.9)	1169	(40.2)
30+	122	(14.7)	330	(15.9)	452	(15.6)
Missing	2	(0.2)	20	(1.0)	22	(0.8)
<b>CCI, n (%)</b>						
0	496	(59.6)	1274	(61.5)	1770	(60.9)
1	114	(13.7)	291	(14.0)	405	(13.9)
2	145	(17.4)	349	(16.8)	494	(17.0)
3+	77	(9.3)	159	(7.7)	236	(8.1)
<b>DCI, n (%)</b>						
≤1	146	(17.5)	462	(22.3)	608	(20.9)
1.01–2.00	179	(21.5)	511	(24.7)	690	(23.8)
2.01–3.00	179	(21.5)	392	(18.9)	571	(19.7)
3.01–4.00	148	(17.8)	308	(14.9)	456	(15.7)
4.01–5.00	92	(11.1)	212	(10.2)	304	(10.5)
5.01+	88	(10.6)	188	(9.1)	276	(9.5)
<b>Educational level, n (%)</b>						
Mandatory school	263	(31.6)	804	(38.8)	1067	(36.7)
High school	353	(42.4)	825	(39.8)	1178	(40.6)
University	216	(26.0)	444	(21.4)	660	(22.7)
<b>Previous pelvic surgery or radiotherapy, n (%)</b>						
No	659	(79.2)	1601	(77.2)	2260	(77.8)
Yes	170	(20.4)	419	(20.2)	589	(20.3)
Missing	3	(0.4)	53	(2.6)	56	(1.9)
<b>Year of radical cystectomy, n (%)</b>						
2011–2013	114	(13.7)	662	(31.9)	776	(26.7)
2014–2016	273	(32.8)	810	(39.1)	1083	(37.3)
2017–2019	445	(53.5)	601	(29.0)	1046	(36.0)
<b>Clinical tumor stage group, n (%)</b>						
Ta/CIS/T1, NO	200	(24.0)	510	(24.6)	710	(24.4)
T2, NO	483	(58.1)	989	(47.7)	1472	(50.7)
T3–4, NO	93	(11.2)	347	(16.7)	440	(15.1)
N+	51	(6.1)	215	(10.4)	266	(9.2)
Missing	5	(0.6)	12	(0.6)	17	(0.6)
<b>Preoperative chemotherapy, n (%)</b>						
Yes	233	(28.0)	698	(33.7)	931	(32.0)
No	597	(71.8)	1365	(65.8)	1962	(67.5)
Missing	2	(0.2)	10	(0.5)	12	(0.4)
<b>Hospital experience, n (%)</b>						
At most 15 surgeries/year	48	(5.8)	603	(29.1)	651	(22.4)
16–24 type specific surgeries/year	273	(32.8)	530	(25.6)	803	(27.6)
25–44 type specific surgeries/year	116	(13.9)	594	(28.7)	710	(24.4)
45+ type specific surgeries/year	395	(47.5)	346	(16.7)	741	(25.5)

### 3.2. Outcomes

Regarding our primary outcome measure, 238 (29%) patients treated with RARC were readmitted within 90 days of surgery compared to 516 (25%) patients treated with ORC (Table 2).

A lower proportion of patients in the RARC group had a major complication (Clavien grade 3–5), 128 (15%) compared to 480 (23%) of patients in the ORC group. Sixty-one patients (7%) operated with RARC were subjected to a reoperation compared to 266 (13%) treated with ORC, and 182 (22%) had less than 70 days alive and out of hospital within 90 days after surgery compared to 565 (27%) in the ORC group. The differences seen in reoperations were at large

**Table 2**

Primary and secondary outcomes within 90 days for all patients treated with radical cystectomy and ileal conduit in Sweden between 2011 and 2019. RARC = Robot assisted radical cystectomy; ORC = Open radical cystectomy.

	RARC (n = 832)		ORC (n = 2073)	
<b>Unplanned readmission, n(%)</b>				
No	594	(71.4)	1557	(75.1)
Yes	238	(28.6)	516	(24.9)
<b>Clavien 3–5 complications, n(%)</b>				
No	704	(84.6)	1593	(76.8)
Yes	128	(15.4)	480	(23.2)
<b>Reoperation, n(%)</b>				
No	771	(92.7)	1807	(87.2)
Yes	61	(7.3)	266	(12.8)
<b>Total days alive out of hospital, n(%)</b>				
0–69	182	(21.9)	565	(27.3)
70–77	225	(27.0)	658	(31.7)
78–80	170	(20.4)	521	(25.1)
81–90	255	(30.6)	329	(15.9)
<b>Mortality, n(%)</b>				
No	808	(97.1)	1997	(96.3)
Yes	24	(2.9)	76	(3.7)

caused by reoperations due to wound dehiscence in patients operated with ORC (6.2% compared to 1.7% in patients operated with RARC) (Supplementary Table 1). Bladder cancer was the dominating cause of death at 90 days in both groups (Supplementary Table 2).

In multivariable regression analysis, RARC was associated with decreased risk of Clavien 3–5 complications OR 0.58 (95% CI 0.47–0.72), reoperation within 90 days of cystectomy OR 0.53 (95% CI 0.39–0.71), and days alive and out of hospital (mean difference in days was 3.7, 95% CI 2.4–5.0). The OR for unplanned readmission within 90 days of surgery after RARC was 1.2 (95% CI 0.98–1.42) adjusting for confounders, without any discernible difference between treatment groups when also including year of surgery and hospital experience in the model (Table 3). In a subset of all patients fulfilling all inclusion criteria for the iROC-trial (n = 2205) (Supplementary Table 3), the results for the outcome measures were similar (Supplementary Table 4), as were the negative association with major complications and reoperations for patients operated with RARC (Supplementary Table 5).

### 4. Discussion

In this Swedish population-based study on the effects of the introduction of RARC in clinical practice on short term outcomes after radical cystectomy, we found that patients subjected to RARC had fewer major complications, less often required reoperations, had more unscheduled readmissions but had more days alive and out of hospital within 90 days. The clinical events causing these differences were at large caused by differences in reoperations due to wound dehiscence in patients operated with ORC. Further, we performed a subgroup analysis of patients fulfilling the inclusion criteria in the iROC trial [5], which showed similar results.

The strengths of the present study include the large sample size, the population-based and nation-wide design, the high quality and high coverage in the SNRUBC [17], and the use of national register data with high capture ratios and no losses to follow-up when comparing the two surgical methods in a “real-world” setting. Furthermore, linkage of several other nation-wide health care registries to BladderBaSe 2.0 enables adjusting for potential bias. For example, we adjusted for comorbidity by applying both CCI and DCI, which adds information beyond using CCI only [21], and for educational level which is a relevant proxy for socioeconomic status.



**Table 3**

Primary- and secondary outcomes within 90 days for all participants. Odds ratios presented for all outcomes except total days alive and out of hospital where mean difference in days is reported. Open radical cystectomy was chosen as the reference group.<sup>#</sup> Adjusted for gender, age, BMI, Charlson Comorbidity Index, Drug Comorbidity Index, socioeconomic status, previous pelvic surgery or radiotherapy, tumor stage group and preoperative chemotherapy. <sup>\*</sup> Adjusted for<sup>#</sup> year of radical cystectomy and hospital experience. RARC = Robot assisted radical cystectomy; ORC = Open radical cystectomy.

	Crude		Adjusted <sup>#</sup>		Adjusted <sup>§</sup>	
<b>Unplanned readmission, OR (95% CI)</b>						
ORC	1		1		1	
RARC	1.21	(1.01–1.45)	1.18	(0.98–1.42)	1.06	(0.87–1.30)
<b>Clavien 3–5 complication, OR (95% CI)</b>						
ORC	1		1		1	
RARC	0.60	(0.49–0.75)	0.58	(0.47–0.72)	0.59	(0.47–0.75)
<b>Reoperation, OR (95% CI)</b>						
ORC	1		1		1	
RARC	0.54	(0.40–0.72)	0.53	(0.39–0.71)	0.56	(0.41–0.77)
<b>Mortality, OR (95% CI)</b>						
ORC	1		1		1	
RARC	0.78	(0.49–1.24)	0.63	(0.39–1.02)	0.79	(0.47–1.34)
<b>Total days alive and out of hospital</b>						
Mean difference in days (95% CI)	2.89	(1.55–4.24)	3.69	(2.35–5.03)	2.74	(1.28–4.20)

More liberal discharge policies during later years might modify the risk of unplanned readmissions [23]. Additionally, the study is undertaken during a transition where the centralization of cystectomy care and the introduction of RARC in a population-based setting occurred simultaneously. To evaluate how altered discharge policies and surgical volume modified the outcomes, we performed a multivariable analysis with and without adjusting for year of surgery and hospital experience. The increased risk of unplanned readmission after RARC compared to ORC might be an effect of patients treated with RARC having more days alive and out of hospital and earlier discharge resulting in more readmissions due to complications that would otherwise have happened during hospitalization. However, no discernible difference between treatments groups remained after adjusting for year of surgery and hospital experience suggesting beneficial effects of centralization of the Swedish cystectomy care during later years [24]. Another Swedish study by Mortezaei et al. compared perioperative outcomes between RARC and ORC and also found an increased risk of unplanned readmissions after RARC compared to ORC [16].

In a single-center randomized trial comparing RARC and ORC from a high-volume hospital, similar readmission rates as well as major complications were reported for both methods [25]. On the contrary, the recently published iROC-trial found similar distribution of major complications but higher readmission rates after ORC compared to RARC (5). Whether the required 30 robotic cystectomies as sole operator prior to study start for the robotic surgeons participating in that trial might have influenced that outcome is not known. The dissimilarities between the complication outcomes reported from one of the mentioned trials above (26) and our study could be related to ORC being spread out over a larger number of hospitals with a varying number of performed procedures and that a larger proportion of patients in the RARC group being operated at high volume centers in the current study. The learning curve regarding complications after RARC is estimated to be between 10 and 75 procedures, albeit without a clear plateau [26]. On the other hand, the main difference seen in major complications was explained both in our study and in the iROC-trial (5) by wound related complications in the ORC group. It is possible that the differences seen in complications and reoperation rates would diminish if applying a better surgical technique for wound closure during ORC such as to close the fascia in a single aponeurotic layer with small bites and a suture to wound length ratio at least 4:1 [27,28].

A recent study reporting a high level of short-term morbidity following a radical cystectomy included days alive and out of

hospital within 90 days of surgery as an outcome variable, and concluded that this outcome measure was a suitable marker for overall morbidity [20]. Days alive and out of hospital within 90 days of surgery was also the primary outcome measure in the randomized multicenter iROC-trial, and thus the basis for power calculations when designing that trial (5). We found similar difference between the treatment groups with on average 3.7 days alive and out of hospital extra among patients treated with RARC compared to the median 2 days reported after RARC in the iROC-trial (5). The clinical importance of these differences remains uncertain, and furthermore no statistically significant differences in cystectomy-specific health-related quality of life were observed at 12 weeks postoperatively in that trial (5).

The main study limitations in the present study are missing cystectomy forms in 249 individuals (6%), where an underreporting of complications cannot be ruled out, and lack of information about the true proportion of extracorporeal reconstruction that was applied among patients subjected to RARC, although the majority of patients subjected to RARC were reconstructed intracorporeally. Another limitation is the difference in number of patients receiving preoperative chemotherapy and the lack of information on time elapsed between preoperative chemotherapy and surgery. Although adjusted for in multivariate regression models, this might have contributed to poorer preoperative status among patients treated with ORC. Additionally, the lack of health-related quality of life data is a limitation, although the Functional Assessment of Cancer Therapy scale Vanderbilt Cystectomy Index (FACT-G and FACT-VCI, respectively) has been translated into Swedish and been psychometrically validated [29], and is now distributed prior to and at 12 months postoperatively to all patients subjected to radical cystectomy in Sweden.

Interpretation of our findings needs to consider the complex relation between surgical volume and outcomes, the centralization of Swedish cystectomy care and altered discharge policies during the study period. Nonetheless, the early adoption of RARC in Sweden in 2004 [30] suggests that the current study outcomes, including patients who underwent surgery between 2011 and 2019, can be interpreted as real-world data not including the complete learning curve for RARC.

## 5. Conclusions

The current study illustrates the “real-world” effects of a gradual and nation-wide introduction of RARC and supports the findings of

the recently published iROC-trial with more days alive and out of hospital within 90 days among patients treated with RARC. The observed differences were largely due to more wound related complications among patients treated with ORC, and thus an improved surgical technique for wound closure should be emphasized to mitigate these issues. Additional perspectives to consider when introducing RARC into clinical practice is incremental cost per quality-adjusted life year in conjunction with longitudinal and publicly available complication and mortality data.

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## CRediT authorship contribution statement

**Oskar Bergengren:** Study design, Study concepts, Formal analysis, and interpretation, Manuscript preparation, Writing – review & editing, Manuscript editing, Manuscript review. **Alexej Belozerov:** Manuscript preparation, Writing – review & editing, Manuscript editing, Manuscript review. **Anna Bill-Axelsson:** Study concepts, Study design, Formal analysis, and interpretation, Writing – review & editing, Manuscript editing, Manuscript review. **Hans Garmo:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Formal analysis, and, interpretation, Statistical analysis, Writing – review & editing, Manuscript editing, Manuscript review. **Oskar Hagberg:** Manuscript editing, Manuscript review. **Firas Aljabery:** Manuscript editing, Manuscript review. **Truls Gårdmark:** Writing – review & editing, Manuscript editing, Manuscript review. **Staffan Jahnson:** Manuscript editing, Manuscript review. **Tomas Jerlström:** Writing – review & editing, Manuscript editing, Manuscript review. **Per-Uno Malmström:** Manuscript editing, Manuscript review. **Amir Sherif:** Manuscript editing, Manuscript review. **Viveka Ströck:** Writing – review & editing, Manuscript editing, Manuscript review. **Karin Söderkvist:** Manuscript editing, Manuscript review. **Anders Ullén:** Writing – review & editing, Manuscript editing, Manuscript review. **Lars Holmberg:** Study concepts, Study design, Formal analysis, and interpretation, Writing – review & editing, Manuscript editing, Manuscript review. **Christel Häggström:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Writing – review & editing, Manuscript editing, Manuscript review. **Fredrik Liedberg:** Study concepts, Study design, Formal analysis, and interpretation, Writing – review & editing, Manuscript editing, Manuscript review, Manuscript preparation, Manuscript editing, Manuscript review.

## Declaration of competing interest

We certify that there are no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2023.01.023>.

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