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Original Article

Morbidity and mortality after robot-assisted radical cystectomy with intracorporeal urinary diversion in octogenarians: results from the European Association of Urology Robotic Urology Section Scientific Working Group

Ashkan Mortezavi[1,2,3], Alessio Crippa[3], Sebastian Edeling[4], Sasa Pokupic[4], Paolo Dell'Oglio[5,6,7], Francesco Montorsi[5], Frederiek D'Hondt[6], Alexandre Mottrie[6,7], Karel Decaestecker[8], Carl J. Wijburg[9], Justin Collins[10], John D. Kelly[10], Wei Shen Tan[10], Ashwin Sridhar[10], Hubert John[11], Abdullah Erdem Canda[12], Christian Schwentner[13], Erik Peder Rönmark[1], Peter Wiklund[1,14] and Abolfazl Hosseini[1]

[1]Department of Molecular Medicine and Surgery, Section of Urology, Karolinska Institutet, Stockholm, Sweden, [2]Department of Urology, University Hospital Zurich, Zurich, Switzerland, [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [4]Department of Urology, Vinzenzkrankenhaus Hannover, Hannover, Germany, [5]Unit of Urology, Division of Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy, [6]Department of Urology, Onze Lieve Vrouw Hospital, Aalst, [7]ORSI Academy, Melle, [8]Department of Urology, Ghent University Hospital, Ghent, Belgium, [9]Department of Urology, Rijnstate Hospital, Arnhem, the Netherlands, [10]Department of Urology, University College London Hospital, London, UK, [11]Department of Urology, Kantonsspital Winterthur, Winterthur, Switzerland, [12]Department of Urology, School of Medicine, Koç University, Istanbul, Turkey, [13]Department of Urology, Diakonie Klinikum Stuttgart, Stuttgart, Germany, and [14]Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Objectives

To evaluate the postoperative complication and mortality rate following laparoscopic radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) in octogenarians.

Patients and Methods

We conducted a retrospective analysis comparing postoperative complication and mortality rates depending on age in a consecutive series of 1890 patients who underwent RARC with ICUD for bladder cancer between 2004 and 2018 in 10 European centres. Outcomes of patients aged <80 years and those aged ≥80 years were compared with regard to postoperative complications (Clavien–Dindo grading) and mortality rate. Cancer-specific mortality (CSM) and other-cause mortality (OCM) after surgery were calculated using the non-parametric Aalen-Johansen estimator.

Results

A total of 1726 patients aged <80 years and 164 aged ≥80 years were included in the analysis. The 30- and 90-day rate for high-grade (Clavien–Dindo grades III–V) complications were 15% and 21% for patients aged <80 years compared to 11% and 13% for patients aged ≥80 years (P = 0.2 and P = 0.03), respectively. In a multivariable logistic regression analysis adjusting for pre- and postoperative variables, age ≥80 years was not an independent predictor of high-grade complications (odds ratio 0.6, 95% confidence interval 0.3–1.1; P = 0.12). The non-cancer-related 90-day mortality was 2.3% for patients aged ≥80 years and 1.8% for those aged <80 years, respectively (P = 0.7). The estimated 12-month CSM and OCM rates for those aged <80 years were 8% and 3%, and for those aged ≥80 years, 15% and 8%, respectively (P = 0.009 and P < 0.001).

Conclusions

The minimally invasive approach to RARC with ICUD for bladder cancer in well-selected elderly patients (aged ≥80 years) achieved a tolerable high-grade complication rate; the 90-day postoperative mortality rate was driven by cancer progression and the non-cancer-related rate was equivalent to that of patients aged <80 years. However, an increased OCM rate in this elderly group after the first year should be taken into account. These results will support clinicians and patients when balancing cancer-related vs treatment-related risks and benefits.

Keywords
robot-assisted radical cystectomy, intracorporeal diversion, octogenarian, bladder cancer, complication, mortality, #BladderCancer, #blcsm, #uroonc, #EndoUrology

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) represents the 'gold standard' therapy for selected high-risk non-muscle-invasive and muscle-invasive bladder cancer (MIBC) [1]. Unfortunately, this major surgical procedure is associated with significant peri-operative morbidity and mortality [2]. In addition to the surgical complexity of RC and subsequent urinary diversion, patients with bladder cancer are diagnosed at a more advanced age (median 73 years) and harbour multiple risk factors, contributing to their known adverse event profile [3]. Specifically in elderly patients, concerns have been expressed about the higher morbidity and mortality rates associated with RC [4], resulting in <20% of octogenarians with MIBC undergoing RC, which indicates that a significant number of patients are not currently being offered definitive treatment [5]. The evidence indicates that 85% of untreated patients with localized MIBC succumb to the disease within 5 years of the diagnosis, whereas <10% die from other causes [6]. At the same time, reported high-grade complication rates in elderly populations for open RC (ORC) have been up to 33%, and the 90-day mortality rates are approximately 15% [7–9]. This adds to the complexity of the risk–benefit analysis that urologists face while evaluating the risk of death from tumour progression vs the risks of peri-operative mortality.

Significant efforts have been made to reduce the morbidity and mortality associated with RC. These measures include centralization of bladder cancer treatment to high-volume centres [10], introduction of enhanced recovery after surgery protocols [11], and standardization of surgical technique [12], together with the implementation of robot-assisted laparoscopic radical cystectomy (RARC) [13]. The latter is considered to offer benefits in terms of estimated blood loss (EBL) and length of hospital stay (LOS) [14]. However, outcome data for elderly patients treated by RARC with intracorporeal urinary diversion (ICUD) are sparse [15,16]. We hypothesized that this subgroup of patients may benefit differentially from a fully minimally invasive approach, and performed an analysis of complications, mortality rates and survival outcomes based on age in a contemporary bladder cancer population treated with RARC followed by ICUD at multiple high-volume European centres.

Patients and Methods

We retrospectively reviewed the records of 2039 consecutive patients who underwent RARC with ICUD between 2004 and 2018 at 10 European centres. All patients underwent surgery at a tertiary care hospital with access to geriatric and palliative care specialists. No specific geriatric assessment was performed routinely; however, treatment decisions were made by an interdisciplinary team at all participating sites. The techniques of RARC and ICUD, and the follow-up scheme differed among institutions. Bowel anastomoses were predominantly performed by the surgical assistant using a laparoscopic stapler. Data were reviewed for preoperative characteristics (age, gender, body mass index [BMI], neoadjuvant chemotherapy [NAC], American Society of Anesthesiologists [ASA] score), operative variables (operation time [skin-to-skin], EBL, type of diversion), and postoperative outcomes (staging, lymph node yield/invasion and LOS). A cut-off age of ≥80 years was used to define elderly patients [5,15–19].

Complications were reported by type and on a per-patient basis, categorized using the modified Clavien–Dindo classification [20], subdivided into short (30-day) and long-term (90-day) events. The quality criteria for reporting of surgical outcomes recommended by the European Association of Urological Guidelines were considered and fulfilled for 11/14 criteria (Table S1).

Descriptive statistics were used to summarize the data. Differences between the groups were statistically assessed using the Pearson chi-squared test for categorical and the Mann–Whitney *U*-test for continuous variables, respectively. A multivariable logistic regression model was fitted to assess the impact of age on complications. Univariate and multivariate Cox regression models were fit to evaluate preoperative, operative and postoperative predictors of all-cause mortality (ACM) and cause-specific mortality following RARC. Cumulative incidence functions for cancer-specific mortality (CSM) and other-cause mortality (OCM) were estimated non-parametrically with the Aalen-Johansen estimator and compared between age groups using the Gray's test [21]. Overall survival (OS) curves were derived as 1 – ACM, and compared between age groups with the log-rank test. Finally, to investigate a possible effect of the learning curve on outcome in the elderly cohort, we plotted the

Table 1 Peri-operative variables.

	<80 years (*n* = 1726)	≥80 years (*n* = 164)	*P*
Age, years	67 (60, 73)	82 (81, 83)	**<0.001**
Men, *n* (%)	1378 (79.8)	125 (79.5)	0.3
BMI, kg/m^2	26 (23, 28)	25 (23, 28)	0.2
Missing, *n* (%)	496 (28.7)	34 (20.7)	
NAC, *n* (%)	466 (27.9)	8 (5.0)	**<0.001**
Missing, *n* (%)	57 (3.3)	4 (2.4)	
ASA score, *n* (%)			
I	202 (12.8)	3 (1.9)	**<0.001**
II	831 (52.5)	67 (43.5)	
III	521 (32.9)	81 (52.6)	
IV	30 (1.9)	3 (1.9)	
Missing	142 (8.2)	10 (6.1)	
Preoperative T stage, *n* (%)			0.2
Ta/ T1/ Tis	535 (31.0)	42 (25.6)	
T2	984 (57.0)	105 (64.0)	
T3/ T4	207 (12.0)	17 (10.4)	
Operating time, min	340 (284, 410)	299 (240, 343)	**<0.001**
Missing, *n* (%)	461 (26.7)	44 (26.8)	
EBL, mL	200 (100, 350)	150 (100, 288)	**0.005**
Missing, *n* (%)	427 (24.7)	40 (24.4)	
Type of diversion, *n* (%)			
Conduit	1172 (67.9)	161 (98.2)	**<0.001**
Neobladder	554 (32.1)	3 (1.8)	
PLND, *n* (%)	1610 (96.4)	135 (84.4)	**<0.001**
Missing, *n* (%)	56 (3.2)	4 (2.4)	
No. of nodes*	19 (13, 25)	16 (11, 23)	**0.003**
Missing, *n* (%)	15 (0.9)	2 (1.5)	
pN+, *n* (%)	321 (19.1)	35 (22.0)	0.4
Missing, *n* (%)	48 (2.8)	5 (3.0)	
pT stage, *n* (%)			**0.002**
pT0	388 (22.6)	25 (15.2)	
pTa	76 (4.4)	4 (2.4)	
pTis	136 (7.9)	10 (6.1)	
pT1	184 (10.7)	11 (6.7)	
pT2	350 (20.4)	29 (17.7)	
pT3	432 (25.2)	60 (36.6)	
pT4	148 (8.6)	25 (15.2)	
Missing	11 (0.6)	0 (0)	
LOS, days	9 (7.0, 14.0)	10 (8.0, 14.3)	**0.014**
Missing	322 (18.7)	9 (8.5)	

*ASA, American Society of Anaesthesiologists; BMI, body mass index; EBL, estimated blood loss LOS, length of hospital stay; NAC, neoadjuvant chemotherapy; PLND, pelvic lymph node dissection. Data presented as median (quartile 1, quartile 3), unless otherwise specified. *In patients with PLND. Bold face indicates P < 0.05.*

number of cases per year, classified for each age group and centre. Values were considered statistically significant at $P < 0.05$. Statistical analyses were performed using SPSS statistical software (v25; IBM Corp.) and R (survival and cmprsk packages).

Results

After exclusion of 149 cases (no cancer, non-urothelial cancer, uretero-cutaneostomy, extracorporeal urinary diversion [ECUD], missing variables), a total of 1890 patients were included in this analysis (Fig. S1), with 164 (8.7%) of these identified as aged ≥80 years. Peri-operative variables are presented in Table 1. There were significant differences between younger patients and patients aged ≥80 years, including the rate of NAC, ASA score, LOS, operating time, diversion type, PLND, overall lymph node yield, EBL, and tumour stage.

To further investigate the difference in PLND rates between the age groups, we performed a multivariable logistic regression analysis; age ≥80 years remained a predictor of not undergoing PLND after adjusting for other baseline covariates such as BMI, NAC, ASA score and tumour stage (odds ratio [OR] 0.46, 95% CI 0.24–0.89; $P = 0.021$).

The per-patient 30- and 90-day rates for high-grade (Clavien–Dindo III–V) complications were 15.0% and 21.3% for patients aged <80 years compared to 11.0% and 13.3% for patients aged ≥80 years (Table 2; $P = 0.2$ and $P = 0.031$), respectively. Comparable rates were observed when only patients receiving an ileal conduit were included (14.2% and 20.1% for age <80 years vs 11.2% and 13.3% for age ≥80 years; $P = 0.332$ and $P = 0.074$). The two most common complication types were infectious and gastrointestinal in both age groups (Table 3). A larger proportion of complications in these two categories were graded as Clavien–Dindo ≥III in the age group <80 years (47% and 34%) than in the age group ≥80 years (29% and 26%), implying lower intervention or intensive care unit admission rates. Notably, cardiac and neurological low-grade complications occurred more frequently in the elderly ($P = 0.045$) without effects on the high-grade complication rate.

In multivariable logistic regression analyses, age ≥80 years was not an independent predictor of high-grade complications (OR 0.6, 95% CI 0.3–1.1; $P = 0.12$) after adjusting for multiple variables including type of diversion and PLND (Table 4). Interestingly, a higher BMI (≥26 kg/m^2) was associated with a decreased risk of high-grade complications (OR 0.7, 95% CI 0.5–0.98; $P = 0.036$) while longer operating time was associated with an increased rate of such an event (per 30 min, OR 1.1, 95% CI 1.01–1.1; $P = 0.034$).

The median (interquartile range) follow-up time for survivors was 18 (8, 35) months. The estimated 30-day and 90-day ACM rates in the age group ≥80 years were 2.8% ($n = 4$) and 7.5% ($n = 10$) and in the age group <80 years 1.0% ($n = 16$) and 2.7% ($n = 40$), respectively ($P = 0.06$ and $P < 0.02$). We performed an in-depth analysis of cause of death for 90-day mortality. In the age group ≥80 years, seven (70%) of the deaths were attributed directly to bladder cancer progress, two (20%) to an infection/sepsis and one (10%) to a cardiac event. In the age group <80 years, data were available for 29 patients (73%), and the respective event rates were 13 (45%), three (10%), and eight (28%), respectively. Five patients (17%) died from other causes (ileus, other cancer, gastric ulcer/bleeding, suicide). The estimated non-cancer-related 90-day mortality was 2.3% ($n = 3$) for patients aged ≥80 years and 1.8% for those aged <80 years (*n* = 27), respectively (*P* = 0.726).

Estimates for CSM, OCM and OS are shown in Fig. 1 and Fig. 2. One centre did not differentiate between CSM and OCM, therefore, these patients were excluded from the survival analysis. The estimated 12-month CSM, OCM and OS for the age group <80 years were 8%, 3% and 89% and, for the age group ≥80 years, 15%, 8% and 77%, respectively (*P* = 0.009, *P* < 0.001 and *P* < 0.001). While the OCM difference between the age groups was significant through all subgroups (pT0–2N0, pT3–4N0, pTanyN+; *P* < 0.05), CSM was comparable after adjusting for tumour stage (*P* = 0.13 and *P* = 0.63). Survival curves and cause-specific mortality for patients with different ASA score groups are shown in Fig. 2. For the age group ≥80 years, the OCM and OS estimates for 12 months were comparable between those with ASA scores I–II and those with ASA scores III–IV (7% and 77% vs 9% and 76%). However, mortality and survival differences were observed for the 60-month estimates (24% and 54% vs 29% and 24%).

In the univariate Cox regression model, age ≥80 years was a predictor of CSM, OCM and ACM (hazard ratio [HR] 1.7 [95% CI 1.2–2.5], HR 4.4 [95% CI 2.7–7.1] and HR 2.3 [95% CI 1.7–3.1]; *P* = 0.007, *P* < 0.001 and *P* < 0.001, respectively [Table 5A]. However, in the multivariate analysis, age was not an independent predictor for CSM and ACM (HR 1.1 [95% CI 0.7–1.8] and 1.3 [95% CI 0.9–2.0]; *P* = 0.8 and *P* = 0.02, respectively [Table 5B] after adjustment for sex, BMI, ASA score, tumour stage, operating time, EBL, pN and complications. Notably, occurrence of high-grade complications remained an independent predictor of OCM and ACM, with an HR of 5.2 (95% CI 2.2–12.4) and 1.6 (95% CI 1.1–2.2; *P* < 0.001 and *P* = 0.009, respectively). Finally, although an ASA score of III–IV was observed to be prognostic in the univariate analysis for OCM and ACM (HR 2.2 [95% CI 1.5–3.3] and 1.5 [95% CI 1.2–1.8]; *P* < 0.001 and *P* < 0.001), it did not show an independent association in the multivariate analysis.

Analysing annual cases in each centre and stratifying them for age groups revealed that seven out of 10 centres did not offer RARC to patients aged ≥80 years in the first year of the observation period (Fig. S2).

Discussion

Despite many advances in medical and surgical therapies, population-based mortality rates resulting from bladder cancer have remained unchanged for more than 30 years [22]. However, recent publications focusing on selected cohorts treated with curative intent report far better survival rates [23]. This discrepancy is partly explained by an undertreatment of patients with localized bladder cancer on a population level. Analyses in the USA and Sweden revealed that 55–79% of patients with non-metastatic MIBC do not undergo treatment with curative intent, resulting in significantly lower OS rates in the surveillance groups [24,25]. Indeed, in a population-based analysis for localized MIBC, the median time to CSM was 71 months if patients were treated with curative intent and 10 months if not. Notably, at 6 months after diagnosis, 38% of the untreated patients had died from bladder cancer vs 6.5% in the treated group [6]. Based on these findings, balancing the risks of cancer- and treatment-related mortality clearly favours a curative approach in younger and healthier patients, however, in older patients treatment decisions may

Table 2 Thirty- and ninety-day complication rate according to the Clavien–Dindo classification system.

	0–30 days			0–90 days*		
	<80 years (*n* = 1726)	≥80 years (*n* = 164)	*P*	<80 years (*n* = 1524)	≥80 years (*n* = 128)	*P*
All complications	835 (48.4)	84 (51.2)	0.14	856 (56.2)	71 (55.5)	0.06
Number of complications						
1	663 (38.4)	66 (40.2)	0.9	553 (36.4)	46 (35.9)	0.9
2	131 (7.6)	14 (8.5)		217 (14.2)	19 (14.8)	
3	28 (1.6)	4 (2.4)		61 (4.0)	4 (3.1)	
4	6 (0.3)	0 (0)		15 (1.0)	2 (1.6)	
5–6	1 (0.1)	0 (0)		8 (0.5)	0 (0)	
N/A	3 (0.2)	0 (0)		3 (0.2)	0(0)	
Low-Grade (Clavien I–II)	576 (33.4)	66 (40.2)	0.084	532 (34.9)	54 (42.2)	0.1
High grade (Clavien III-V)	259 (15.0)	18 (11.0)	0.2	324 (21.3)	17 (13.3)	**0.031**
Clavien I	124 (7.2)	16 (9.8)	0.4	100 (6.6)	12 (9.4)	0.2
Clavien II	452 (26.2)	50 (30.5)		432 (28.3)	42 (32.8)	
Clavien IIIa	102 (5.9)	4 (2.4)		135 (8.9)	6 (4.7)	
Clavien IIIb	89 (5.2)	6 (3.7)		117 (7.7)	5 (3.9)	
Clavien IV	56 (3.2)	7 (4.3)		51 (3.4)	6 (4.7)	
Clavien V	12 (0.7)	1 (0.6)		21 (1.4)	0 (0)	

*Variables reported as frequency (percentage). Only the complication with the highest grade was considered and reported on a per-patient basis for each time period. *Differences in the patient numbers are due to one centre not reporting 90-day complication rates. Includes all postoperative complications up to 90 days. Bold face indicates P < 0.05.*

Table 3 Summary of 90-day postoperative complications classified for organ categories.

Category	0–90 days (all complications*)			0–90 days (Clavien–Dindo III–V†)		
	<80 years (n = 1524)	≥80 years (n = 128)	P	<80 years (n = 1524)	≥80 years (n = 128)	P
Gastrointestinal	209 (13.7)	21 (16.4)	0.4	98 (6.4)	6 (4.7)	0.6
Paralytic ileus	151(9.9)	18 (14.1)	0.17	47 (3.1)	4 (3.1)	1
Mechanical ileus	26 (1.7)	2 (1.6)	1	25 (1.6)	2 (1.6)	1
Bowel anastomotic leakage	18 (1.2)	0 (0)	0.4	17 (1.1)	0 (0)	1
Other	14 (0.9)	1 (0.8)	1	9 (0.6)	0 (0)	1
Infectious	380 (24.9)	38 (29.7)	0.2	130 (8.5)	10 (7.8)	0.9
Fever/ UTI/ pyelonephritis	245 (16.1)	20 (15.6)	1	71 (4.7)	7 (5.5)	0.7
Sepsis	66 (4.3)	7 (5.5)	0.5	24 (1.6)	2 (1.6)	1
Pneumonia	32 (2.1)	3 (2.3)	0.8	13 (0.9)	0 (0)	0.6
Abscess	25 (1.6)	1 (0.8)	0.7	16 (1.0)	1 (0.8)	1
Wound	4 (0.3)	0 (0)	1	3 (0.2)	0 (0)	1
Other	8 (0.5)	7 (0.8)	0.5	3 (0.2)	0 (0)	1
Genitourinary	185 (12.1)	12 (9.3)	0.4	144 (9.4)	8 (6.3)	0.3
Urine leakage (intra-abdominal)	61 (4.0)	3 (2.3)	0.5	47 (3.1)	3 (2.3)	1
Ureteric stricture	38 (2.5)	2 (1.6)	0.8	35 (2.3)	2 (1.6)	1
Hydronephrosis	27 (1.8)	2 (1.6)	1	22 (1.4)	1 (0.8)	1
Stent/catheter malfunction/dislocation	16 (1.0)	0 (0.0)	0.6	12 (0.8)	0 (0)	0.6
Acute renal failure	13 (0.9)	1 (0.8)	1	9 (0.6)	1 (0.8)	0.6
Fistula	12 (0.8)	0 (0.0)	0.6	10 (0.7)	0 (0)	1
Other	18 (1.2)	4 (3.1)	0.09	9 (0.6)	1 (0.8)	0.6
Cardiac	20 (1.3)	5 (3.9)	**0.039**	14 (0.9)	1 (0.8)	1
Atrial fibrillation	6 (0.4)	3 (2.3)	**0.027**	4 (0.3)	0 (0)	1
Myocardial infarction	3 (0.2)	1 (0.8)	0.3	2 (0.1)	1 (0.8)	1
Hyper-/hypotension	5 (0.3)	1 (0.8)	0.4	2 (0.1)	0 (0)	1
Other	6 (0.4)	0 (0)	1	6 (0.4)	0 (0)	1
Pulmonary	17 (1.1)	1 (0.8)	1	10 (0.7)	0 (0)	1
Pulmonary embolism	12 (0.8)	0 (0)	0.6	7 (0.5)	0 (0)	1
Other	5 (0.3)	1 (0.8)	0.4	3 (0.2)	0 (0)	1
Haematological/vascular	56 (3.7)	5 (3.9)	0.8	27 (1.8)	0 (0)	0.3
Anaemia due to postoperative bleeding	41 (2.7)	4 (3.1)	0.8	20 (1.3)	0 (0)	0.4
Thromboembolic event	12 (0.8)	0 (0)	0.6	5 (0.3)	0 (0)	1
Other	3 (0.1)	1 (0.8)	0.2	2 (0.1)	0 (0)	1
Abdominal wall/ stoma	40 (2.4)	2 (1.6)	0.8	34 (2.2)	2 (1.6)	1
Hernia/ fascial dehiscence	27 (1.8)	1 (0.8)	0.7	25 (1.6)	1 (0.8)	0.7
Parastomal hernia	5 (0.3)	1 (0.8)	0.4	3 (0.2)	1 (0.8)	0.3
Stoma dysfunction/necrosis	8 (0.5)	0 (0)	1	6 (0.4)	0 (0)	1
Neurological	14 (0.9)	4 (3.1)	**0.045**	1 (0.1)	0 (0)	1
Delirium	6 (0.4)	3 (2.3)	**0.027**	0 (0)	0 (0)	-
Peripheral neuropathy	5 (0.3)	1 (0.8)	0.4	0 (0)	0 (0)	-
Transient ischaemic attack	1 (0.1)	0 (0)	1	0 (0)	0 (0)	-
Other	2 (0.1)	0 (0)	1	1 (0)	0 (0)	1
Bleeding	27 (1.8)	0 (0)	0.3	22 (1.4)	0 (0)	0.4
Lymphocele	27 (1.8)	0 (0)	0.3	16 (1.0)	0 (0)	0.6
Metabolic	15 (1.09	0 (0)	0.6	8 (0.5)	0 (0)	1
Compartment syndrome	3 (0.2)	0 (0)	1	3 (0.2)	0 (0)	1
Other	18 (1.2)	1 (0.8)	1	8 (0.5)	0 (0)	1

*Variables reported as frequency (percentage). *All reported complications regardless of grade. †Only complications that occurred in patients with a Clavien–Dindo grade of ≥III. The denominator is the number of patients in each group. Bold face indicates P < 0.05.*

focus on perceived risks of life-threatening or fatal complications associated with RC, and a dovish strategy may be preferred. Therefore, outcome data on peri-operative morbidity and mortality are needed for accurate counselling and decision making in this steadily growing cohort of elderly patients with bladder cancer [26].

The present study is the first investigation reporting on morbidity and mortality risks in a contemporary multicentre cohort of elderly patients treated by RARC with ICUD, and provides evidence that the complication and mortality rates associated with RC with a fully minimally invasive approach in carefully selected octogenarians is favourable.

Minimally invasive strategies have gained popularity because of their potential to reduce surgical morbidity and shorten LOS. Two prospective randomized trials have shown a significantly lower EBL, transfusion rate and LOS for RARC with ECUD compared to ORC [27,28]. Just recently in a three-way comparison of ORC, RARC with ECUD and RARC with ICUD, the fully intracorporeal approach demonstrated a further reduction of EBL, LOS, ileus rate, and

Table 4 Multivariable logistic regression for developing postoperative complications stratified for all and high-grade events.

	Any complication				Complications Clavien–Dindo ≥ III			
	OR	95% CI		*P*	OR	95% CI		*P*
		Lower	Upper			Lower	Upper	
Age at surgery								
≥80 vs <80 years	1.1	0.7	1.8	0.6	0.6	0.3	1.1	0.1
Sex								
Female vs male	1.1	0.8	1.5	0.7	0.8	0.5	1.2	0.3
BMI								
≥26 vs <26 kg/m^2	0.8	0.6	1.1	0.11	0.7	0.5	0.98	**0.036**
NAC								
Yes vs no	0.9	0.7	1.3	0.7	1.1	0.8	1.5	0.6
ASA score								
III–IV vs I–II	1.2	0.9	1.5	0.3	1.1	0.8	1.5	0.5
Operating time								
Continuous, per 20 min	1.1	1.04	1.1	**<0.001**	1.05	1.01	1.1	**0.034**
EBL								
Continuous, per 200 mL	1.04	0.9	1.2	0.6	1.1	0.98	1.3	0.1
PLND								
Performed vs not performed	1	0.5	2.2	0.9	1.4	0.5	3.7	0.5
Type of diversion								
Neobladder vs conduit	1.4	0.97	1.9	0.074	0.8	0.5	1.1	0.2

ASA, American Society of Anesthesiologists; BMI, body mass index; EBL, estimated blood loss; NAC, neoadjuvant chemotherapy; OR, odds ratio; PLND, pelvic lymph node dissection. Bold face indicates P < 0.05.

importantly, lower major complication rates, but longer operating time when compared to the other two techniques [29]. The question arises of whether older patients, such as octogenarians, are more likely to benefit from the above-mentioned advantages of RARC with ICUD due to faster recovery [30] or are potentially exposed to higher peri-operative risks due to the longer operating time.

An association of age and complication rates has been reported for ORC but standardized data for octogenarians have been sparse [4]. Donat et al. [5] reported a higher rate of 90-day Clavien–Dindo grade III–V complications in patients aged ≥80 years undergoing ORC (17% vs 13%), but, after adjusting for preoperative variables, no significant difference was detected. For small single-surgeon case series of RARC followed by ECUD in this population, favourable high-grade complication rates ranging between 4% and 15% [17,31,32] have been reported. Only two studies have included octogenarians undergoing RARC with ICUD (n = 63 and n = 14) reporting an overall Clavien–Dindo ≥III rate of 14–26% [15,33]. However, a significant amount of the patient population underwent ECUD, making it impossible to assess the impact of the fully minimally invasive approach without stratification of the results. In the present study, we did not observe an increased rate of high-grade complications associated with ICUD in octogenarians; the 90-day high-grade complication rate was 13% and therefore lower than previously reported rates in representative (n > 25) elderly populations for ORC (17–35.9%) [5,7,34–36], RARC with ECUD (15%) [32], and RARC with ICUD and ECUD (26%) [33], respectively. This beneficial observation may be attributed to the fully minimally invasive approach with ICUD [29].

Notably, the rate was also lower compared to the observed 21% (all) and 20% (ileum conduit) in younger patients in our cohort, respectively. The imbalance of baseline characteristics was addressed in the multivariable logistic regression model; after adjustment for PLND and diversion type, higher age did not show an association with high-grade complications. A possible explanation for the lower high-grade rate in older patients could be the fact that some centres introduced RARC with ICUD first in the younger patients, and included patients aged ≥80 years at a later time point on the learning curve when confidence with the technique had been gained (Fig. S2). Additionally, the lower high-grade complication rate in the elderly might also be attributed to a more conservative approach to postoperative complications suggested by the higher low-grade complication rate in the group. Finally, the operating time was shorter in the patients aged ≥80 years (296 vs 351 min), indicating that those cases were performed by more experienced surgeons. Notably, the overall mean operating time for RARC with ICUD in the present study (346 min) was not longer than those reported for ORC (343 min, population-based registry 'Bladder Base', Sweden). Overall, more than 85% of the patients aged ≥80 years did not experience a high-grade postoperative complication after RARC, which is an encouraging outcome.

Our in-depth analysis of early postoperative death revealed that the 90-day ACM rate in patients aged ≥80 years was mainly driven by tumour progression (70%) representing

Fig. 1 Cumulative incidence functions illustrating cancer-specific (CSM), other-cause mortality (OCM), and overall survival (OS; 1 − all-cause mortality) for patients undergoing robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion, stratified by age group (red <80 years, blue ≥80 years) and according to pathological tumour stage (pT) in node-negative patients. Tables include the number of events for CSM and OCM, numbers at risk for OS, and estimates for 1 and 5 years. *P* values derived using Gray's and log-rank tests.

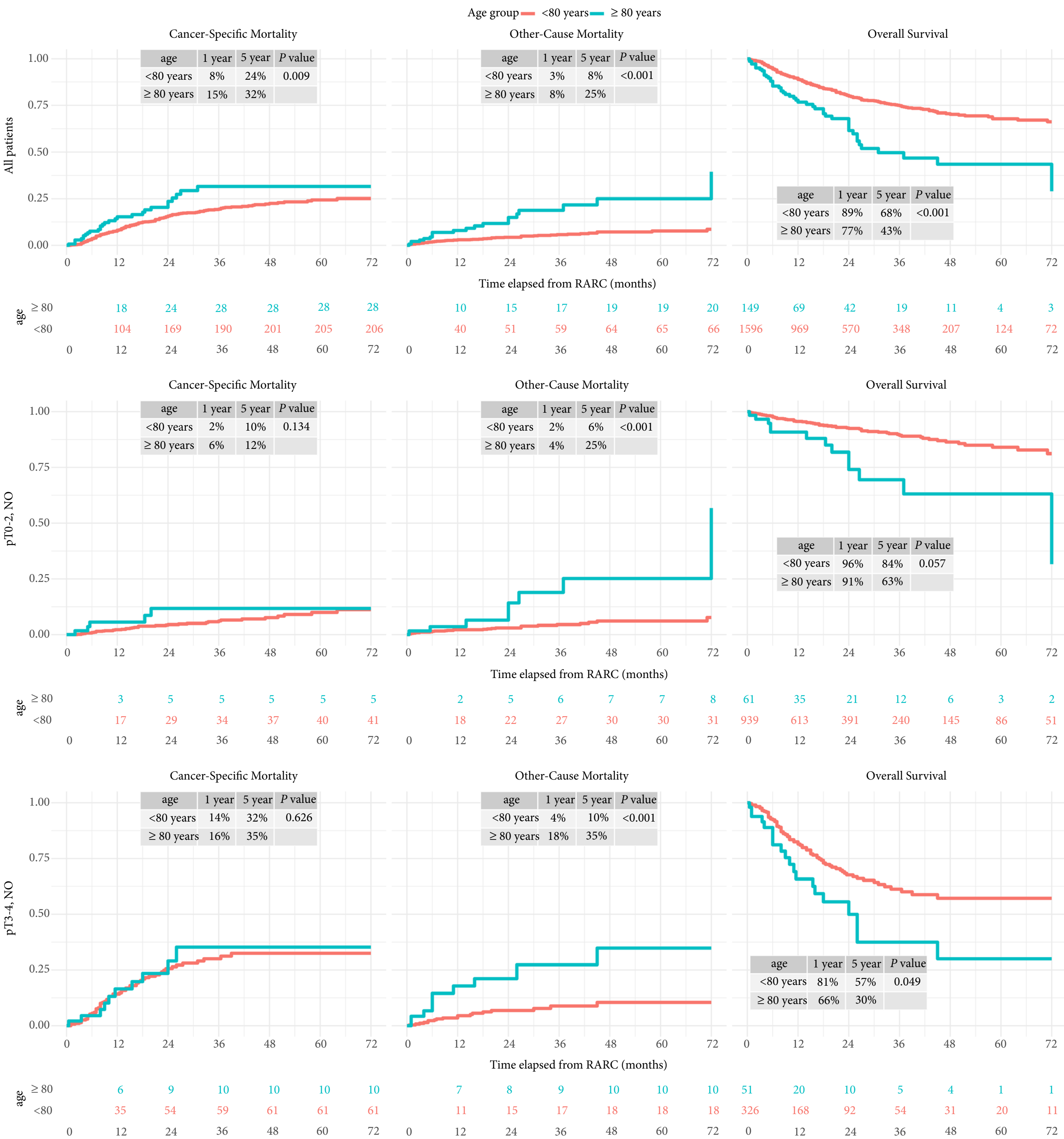

Fig. 2 Cumulative incidence functions illustrating cancer-specific (CSM), other-cause mortality (OCM) and overall survival (OS; 1 – all-cause mortality) for patients undergoing robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion, stratified by age groups (red <80 years, blue ≥80 years) and for node-positive cases and according to the American Society of Anaesthesiologists score. Tables includes the number of events for CSM and OCM, numbers at risk for OS, and estimates for 1 and 5 years. *P* values derived using Gray's and log-rank tests.

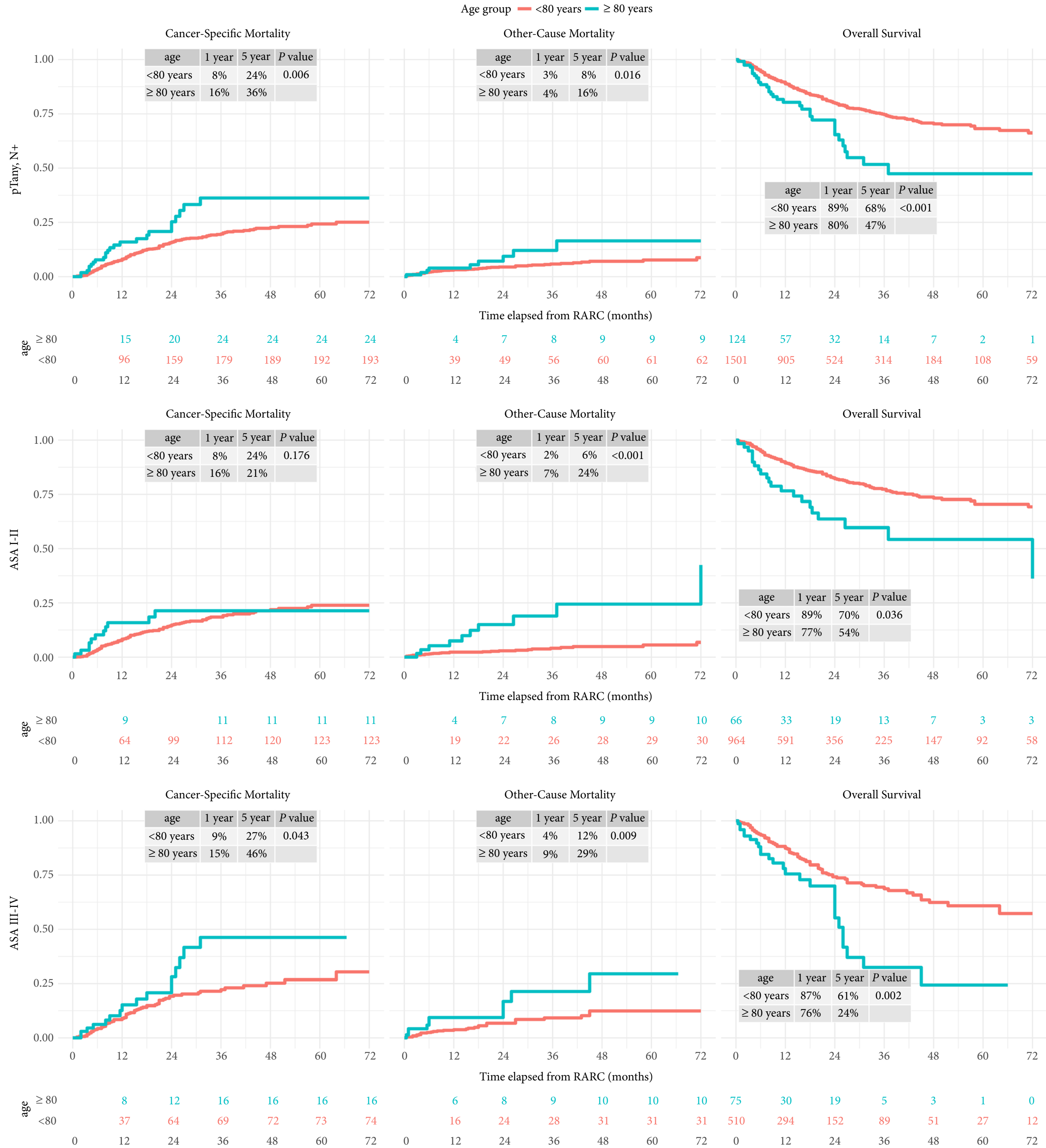

Table 5 Univariable and multivariable Cox regression analysis for cancer-specific, other-cause and all-cause mortality.

Variable	Characteristics	Cancer-specific mortality			Other-cause mortality			All-cause mortality		
		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
A) Univariable										
Age at surgery	≥80 years vs <80 years	1.70	1.2–2.5	**0.007**	4.40	2.7–7.1	**<0.001**	2.30	1.7–3.1	**<0.001**
Sex	female vs male	1.40	1.0–1.8	**0.041**	0.68	0.4–1.2	0.2	1.20	0.9–1.5	0.3
BMI	≥26 vs <26 kg/m^2	0.70	0.5–0.9	**0.008**	0.70	0.4–1.1	0.1	0.70	0.6–0.9	**0.004**
ASA score	III–IV vs I–II	1.30	1.0–1.7	0.073	2.20	1.5–3.3	**<0.001**	1.50	1.2–1.9	**<0.001**
pT stage	pT2 vs pTa/T1/Tis	2.30	1.5–3.5	**<0.001**	1.20	0.7–2.2	0.5	1.70	1.2–2.5	**0.002**
	pT3/T4 vs pTa/T1/Tis	7.50	5.2–10.7	**<0.001**	3.10	2.0–5.0	**<0.001**	5.20	3.9–6.8	**<0.001**
Operating time	continuous, per 20 min	1.00	1.0–1.0	0.8	1.00	0.9–1.0	0.4	0.99	0.9–1.0	0.4
Estimated blood loss	continuous, per 200ml	1.00	0.9–1.1	0.4	1.20	1.1–1.3	**0.004**	1.10	1.0–1.2	**0.038**
pN	pN + vs pN–	4.80	3.7–6.2	**<0.001**	1.90	1.1–3.2	**0.013**	3.50	2.8–4.4	**<0.001**
Complications	Low–grade vs none	0.80	0.6–1.1	0.2	2.20	1.0–5.0	**0.049**	0.97	0.7–1.3	0.8
	High–grade vs none	1.00	0.7–1.4	0.9	4.40	2.0–9.5	**<0.001**	1.30	1.0–1.8	0.077
B) Multivariable										
Age at surgery	≥80 years vs <80 years	1.10	0.7–1.8	0.8	2.60	1.2–5.9	**0.022**	1.30	0.9–2.0	0.2
Sex	female vs male	1.10	0.8–1.6	0.5	0.80	0.3–1.9	0.5	1.10	0.8–1.5	0.6
BMI	≥26 vs <26 kg/m^2	0.80	0.6–1.1	0.2	0.60	0.3–1.1	0.09	0.80	0.6–1.0	0.09
ASA score	III–IV vs I–II	1.20	0.9–1.6	0.3	2.00	1.0–3.8	0.053	1.30	1.0–1.7	0.08
pT stage	pT2 vs pTa/T1/Tis	1.60	1.0–2.8	0.069	1.00	0.4–2.7	0.9	1.50	0.9–2.4	0.09
	pT3/T4 vs pTa/T1/Tis	4.60	3.0–7.2	**<0.001**	2.10	1.0–4.8	0.052	3.80	2.6–5.6	**<0.001**
Operating time	continuous, per 20 min	1.00	1.0–1.0	0.9	0.90	0.9–1.0	0.2	1.00	0.9–1.0	0.3
Estimated blood loss	continuous, per 200 mL	1.00	0.9–1.1	0.6	1.20	0.9–1.6	0.1	1.10	1.0.1.2	0.2
pN	pN + vs pN–	2.70	2.0–3.8	**<0.001**	1.30	0.6–3.2	0.5	2.30	1.7–3.1	**<0.001**
Complications	Low-grade vs none	0.90	0.7–1.3	0.8	1.70	0.7–4.4	0.3	1.00	0.7–1.5	0.8
	High-grade vs none	1.20	0.8–1.8	0.4	5.20	2.2–12.4	**<0.001**	1.60	1.1–2.2	**0.009**

ASA, American Society of Anaesthesiologists; BMI, body mass index; HR, hazard ratio; PLND, pelvic lymph node dissection. Bold face indicates P < 0.05.

poor patient selection and that the non-cancer-related mortality rate was low (2.3%, in the context of age and the aggressive nature of the disease) and comparable to that of younger patients (1.8%; $P = 0.7$). This observation is consistent with the established tendency to defer RC in older individuals until all alternatives have been exhausted [37] and an earlier treatment of this population could potentially reduce this early cancer-driven mortality rate. Ultimately, a comparison with contemporary open series in octogenarians revealed a potential benefit of the RARC approach; our 30-day and 90-day ACM rate of 2.8% and 7.5% was constantly lower than the reported rates of 5.8–7.7% and 13–18%, respectively [7–9,38].

The survival analysis revealed that CSM drives the overall mortality rates irrespective of patient age. This was more obvious for the first year after RARC with an observed CSM for patients aged <80 years and patients aged ≥80 years of 8% and 15% compared to an OCM of 3% and 8%, respectively. Although this difference was still significant after 5 years for the younger patients (24% CSM and 8% OCM), in patients aged ≥80 years, it decreased to 32% (CSM) and 25% (OCM). These findings have significant implications for therapeutic decisions in this contemporary cohort of elderly patients; an estimated 12-month OCM rate of <10% is a strong argument for curative treatment considering the reported 12-month CSM rate of nearly 60% for untreated MIBC [6] and 12-month OS of <45% with symptom improvement of only 53% for palliative radiation therapy in stage I–II bladder cancer [39]. Additionally, our observed 5-year OS rate of 43% in patients aged ≥80 years treated by RARC with ICUD is consistently higher than reported rates for ORC (27% [7] and 23% [9]), RARC with ECUD (35% [32]), and RARC with ICUD and ECUD (28% [33]), which may be partly attributed to patient selection and increasing life expectancy, but also a lower 90-day mortality in the present cohort. Finally, in the multivariate Cox regression analysis, high-grade complications remained an independent predictor of ACM, highlighting its clinical relevance in the context of the observed lower rate in our RARC cohort compared to ORC and RARC with ECUD cohorts.

To assess the clinical value of ASA score in patients aged ≥80 years for outcome after RARC, we included it in the survival analyses. Notably, a higher ASA score had only a small impact on OCM in the first year after RARC (7% for ASA scores I–II and 9% for ASA scores III–IV; Fig. 2). This remained unchanged even after 5 years (24% and 29%). Notably, the estimated 5-year CSM rate was significantly higher in patients with ASA scores III–IV (46%) compared to those with ASA scores I–II (21%), indicating that elderly patients with higher ASA scores are more likely to undergo surgery if they harbour advanced tumours.

A limitation of the present study consists in the surgical selection bias. Elderly RC patients may be in a better health condition than age-matched controls, which may affect OCM rates. However, more than half of this population had an

ASA score of III–IV, reflecting a contemporary patient cohort in clinical practice. Since this was a multicentre retrospective study, the surgical technique and peri-operative care was not standardized, representing possible confounders with regard to mortality rates. Results of this study may not be generalizable to all centres as this patient cohort underwent surgery in high-volume centres. Elderly patients were more likely to not be considered at the beginning of the learning curve, with a potential negative impact on outcome in the control group. However, most centres included patients aged ≥80 years very soon after the beginning of the observation period and the very large number of younger patients included subsequently may compensate for this selection bias. Furthermore, no data on readmission rates and quality of life, especially relevant to the elderly group, were available. Finally, the median follow-up time of 18 months is rather short for longer survival estimates. Nevertheless, combined with a minimum follow-up of 90 days for 86% of the patients, the assessments of the peri-operative and 1-year mortality remain robust.

In conclusion, the present study represents the first multicentre analysis of morbidity and mortality in patients aged ≥80 years with bladder cancer undergoing RARC with ICUD. The minimally invasive approach is associated with a tolerable high-grade complication rate in well-selected elderly patients. The postoperative 90-day mortality in patients aged ≥80 years is largely driven by cancer progression and the non-cancer-related rate is equivalent to that of younger patients. However, an increased OCM rate in the elderly group (patients aged ≥80 years) after the first year has to be taken into account. These results will support clinicians and patients taking difficult therapeutic decisions when balancing cancer-related vs treatment-related risks and benefits.

Conflicts of Interest

Dr. Decaestecker reports personal fees from Intuitive Surgical, personal fees from MSD, outside the submitted work; Dr. Collins reports grants from Medtronic, personal fees from Medtronic, personal fees from Intuitive Surgical, personal fees from CMR Surgical, outside the submitted work; Other authors declare no conflicts of interest.

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Correspondence: Ashkan Mortezavi, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, 17177 Stockholm, Sweden.

e-mail: Ashkan.Mortezavi@ki.se

Abbreviations: ACM, all-cause mortality; ASA, American Society of Anaesthesiologists; BMI, body mass index; CSM, cancer-specific mortality; EBL, estimated blood loss; ECUD, extracorporeal urinary diversion; HR, hazard ratio; ICUD, intracorporeal urinary diversion; LOS, length of hospital stay; MIBC, carcinoma invading bladder muscle; NAC, neoadjuvant chemotherapy; OCM, other-cause mortality; OR, odds ratio; OS, overall survival; ORC, open radical cystectomy; PLND, pelvic lymph node dissection; RARC, radical cystectomy; RC, radical cystectomy.

Supporting Information

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

Fig. S1. Patient selection process. ECUD, extracorporeal urinary diversion; ICUD, intracorporeal urinary diversion; RARC, robot-assisted laparoscopic radical cystectomy; y, years.
Fig. S2. Visualization of RARC cases per year and centre, classified by each age group (blue: <80 years, red: ≥ years).
Table S1. Quality criteria for accurate and comprehensive reporting of surgical outcomes recommended by the European Association of Urological (EAU) Guidelines on reporting and grading of complications.