Graduate thesis

NTNU
Norwegian University of Science and Technology
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Department of Clinical and Molecular Medicine

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Analysis of perioperative, postoperative and oncological results after open or robot assisted laparoscopic cystectomy for surgical treatment of bladder cancer

Graduate thesis in Medical School
Supervisor: Carl- Jørgen Arum and Eirik Kjøbli
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Contents

Abstract

Background:

Radical Cystectomy is the gold standard treatment for invasive bladder cancer but is associated with a significant risk for complications of varying severity. Robot Assisted Radical Cystectomy (RARC) was introduced at St. Olavs Hospital in February 2015 with hopes of less complications and a shorter length of stay at the hospital without compromising the oncological quality of the surgery. Our aim is to evaluate the introduction of RARC by comparing perioperative, postoperative, oncological and survival endpoints with the traditional open radical cystectomy (ORC).

Patients and methods:

This is a retrospective study reviewing patients with bladder malignancy whom have undergone treatment for bladder cancer with radical cystectomy (RC) at St. Olavs Hospital between January 2012 and May 2019. The patients' medical records were retrieved from electronic patient records and included in a standardized database. Only patients with biopsy/CTI confirmed T1-T4 or refractory carcinoma in situ were included. A total of 247 patients were included whereof 156 patients were treated with ORC and 91 with RARC. Statistical analyses were generated using SPSS versions 25 and 26.

Results:

156 patients underwent ORC and 91 underwent RARC. Median follow-up was 43 months and 20 months for ORC and RARC respectively. RARC patients had lower median LOS (10 vs 14 days, p=<0.001), lower perioperative blood loss (369ml vs 953ml, p=<0.001) and received fewer blood transfusion (29% vs 50%, p=0.002). Operating time was 18 minutes longer in RARC (253 vs 235 minutes, p=0.034). There were no differences in Clavien I-IV complications, return to OR, readmissions and 12-month stricture rates. Patients in the RARC group more often received extended pelvic lymph node dissection (PLND) (68.1% vs 6.5%) and had a greater lymph node count (16 vs 10, p<0.001). Positive surgical margins (PSM) rate was higher in ORC (9% vs 0%, p=0.001). 2-year overall survival was similar (71.6% vs 76.7%, p=0.643), while 2-year recurrence free survival (RFS) was higher in RARC (83.5% vs 70.1%, p=0.038). 2-year local recurrence rate was 16.2% vs 7.6% (p=0.102) for ORC and RARC respectively. No differences in recurrence patterns were detected.

Conclusion:

This study provides evidence that the introduction of RARC at St. Olavs Hospital has indeed been successful. RARC showed superior results in terms of shorter length of stay (LOS), fewer blood transfusion and better PSM rates, without compromising oncological endpoints. RARC showed promising results on 2-year RFS but several other factors might influence this.

Introduction:

Background:

According to the Norwegian cancer registry, bladder cancer is the most common cancer in the urinary tract(1). In the 2019 report, the incidence of urinary tract cancer in Norway in 2018 was 1748, whereof most were males (1239). The incidence rate has increased 9% since 2009, and this makes urinary tract cancer the 4th most common cancer among Norwegian males, only behind prostate-, lung- and colon cancer. In 2017 393 people died from urinary tract cancer in Norway and the 5- year relative survival following urinary tract cancer in Norway is 78% in males and 70% in females.
Because of entirely different treatment regimes, differentiating between non-muscle invasive and muscle invasive bladder cancer is important. 75-80% of newly diagnosed bladder cancers are non-invasive, and 20-25% are muscle invasive(2). According to Norwegian guidelines, radical cystectomy is recommended for muscle invasive bladder cancer (MIBC) and some cases of high-risk non-muscle invasive bladder cancer(3). According to a study from 15 international academic centres and one from the MAYO clinic 5-year cancer specific survival (CSS) after MIBC treated with radical cystectomy (RC) was 53-68%, and the 5-year overall survival (OS) was 42-58%(4, 5).

St. Olavs Hospital is a tertiary centre for cystectomy performing approximately 50 RC operations annually. In February 2015, robot assisted radical cystectomy (RARC) was introduced at St. Olavs Hospital. Prior to 2015, all cystectomies were performed with open technique. Open radical cystectomy (ORC) has been the gold standard, but is known to be a surgery with high rates of complications (56%) and mortality (3.2%)(6). RARC was introduced with expectations of less complications and shorter length of stay (LOS) at the hospital, and since 2017 most cystectomies have been performed robot assisted except on occasions when the robot or the robot-surgeon has been unavailable or when the patient previously have undergone major abdominal surgery.

There has been a lack of high-quality studies comparing RARC and ORC. The RAZOR study from 2018 was the first large prospective randomised multicentre study to compare oncological endpoints(7). The 2- year progression free survival was non inferior to the ORC group. There were no significant differences in recurrence, cancer free survival and overall survival. Important oncological markers like positive surgical margins and lymph node yields were also not statistically different. The RARC group showed significantly lower estimated blood loss, less transfusions and shorter length of hospital stay (LOS). The operating time was significantly longer in RARC. Neither overall complications or major complications (Clavien 3-5) was significantly different between RARC and ORC. Several other randomised studies and large retrospective cohort studies have also found RARC to be equivalent to ORC when looking at oncological endpoints and survival(8-11).

Gandaglia et al. Found RARC to cause more overall- and low-grade complications than ORC(11). But this was only when including both RARC with extracorporeal urinary diversion (ECUD), that is performing the actual cystectomy with robot and then converting to open technique for the urinary diversion, and RARC with Intracorporeal urinary diversion (ICUD), that is doing the entire operation intraabdominally robotic-assisted. When only looking at RARC with ICUD, the complication rates were similar to those of ORC(11). We believe their results may be affected by ECUD being a less complicated procedure and the surgeons performing ICUD therefore presumably being more experienced. Other studies found less minor complications in RARC(10), mostly due to lower transfusion rates in RARC(10). Several studies also found the complication rates to be similar between RARC and ORC(7, 12-14).

RARC has evidently caused less perioperative bleeding and blood transfusions, but longer operating times(7, 10-14). Another potential benefit of RARC is shorter length of hospital stay (LOS), but the results are divided. Some studies found shorter LOS in RARC than in ORC(7, 10, 11), while others did not identify any differences in LOS(9, 12-14).In the early days of RARC there were some concerns about obtaining a sufficient lymph node count during the PLND(10). A minimum of 9 to 16 lymph nodes have been described in literature to provide better cancer free and overall survival(15-18). Koppie et al. Tried to determine a threshold for lymph node count but found that impossible because survival always increased when the lymph node count increased(19). Lymph node count can also be influenced by the routines of the pathologist(20) and by how the surgeon submits the lymph node specimens; as one package or several packages(21). Literature comparing node count in RARC and ORC have described both similar node counts(7, 12) and node counts in favour of RARC(10) suggesting the non-inferiority of RARC in this regard. In some retrospective studies extended PLND has shown beneficial results on recurrence free survival compared to a more limited PLND(22-24). On the other hand, a prospective randomised study from 2019 by Gschwend et al. failed to describe a significant benefit for extended PLND over standard or limited PLND as they concluded the need of a larger trial(25).

Positive surgical margin (PSM) has been described to be an important predictor for metastatic progression, local recurrence and to increase the risk of cancer specific death(16, 26, 27). Therefore it`s important that RARC can provide the same or lower rates of PSM compared to ORC. Novara et al. accomplished a multicentre study containing 4.400 patients. They found a PSM rate of 6.3% and suggested to use this as a reference when investigating PSM rates in RARC(27). Literature describes a PSM rate from 4.2% to 10%(16, 26). Many studies comparing PSM rates between RARC and ORC describes no significant differences(7, 10-12, 14), although Challacombe et al. found PSM rates in the RARC group to be inferior to ORC in patients with T4 disease(28). Nguyen et al. found less PSM in the RARC group, but that was most likely due to more T4 and less T0/Ta in the ORC group(29). Ahmed et al found a significant difference regarding PSM favouring ICUD compared to ECUD in

RARC(30), though this result may indicate more experienced surgeons in the ICUD group due to ECUD and ICUD not being related to the cystectomy itself.

There have been some concerns about more atypical- and local recurrence in RARC. Literature describes a local recurrence rate of 7-22%(31-33). Nguyen et al. Found no significant differences in local recurrence rates(29). Distant recurrence rates were also quite similar. But within distant recurrences, although not significant, it was more common with extra pelvic lymph node metastasis and peritoneal carcinomatosis in the RARC group(29). Bouchner et al. Suggested an increased risk for local recurrence and abdominal recurrence when they combined those into one regional recurrence group(8). Other studies have shown no differences in atypical or local recurrences(7, 10). Port site metastasis have previously been reported in RARC(34, 35), but most recent studies have not supported these findings(7, 10, 29).

In many of the studies mentioned above, the urinary diversion has been done extracorporeally also in the RARC group. ECUD is known to be an easier procedure than ICUD and might indicate lower surgical quality in some cases and ECUD might also be more common in early stages of the learning curve. In addition questions have been raised whether the fact that the urinary diversion is performed open could be hiding some of the potential benefits from RARC(36).

Ahmed et al. compared intracorporal Urinary Diversion (ICUD) and extracorporeal UD (ECUD) after RARC (30). The 30- day and 90-day readmission rates were significantly lower in the ICUD group. The 30 day and 90-day complication rates trended in favour of ICUD over ECUD but was not significant. They proved a 30% less risk of complications in the ICUD group. The mean lymph node yield was significantly higher and the PSM rate was significant lower in IUCD compared to ECUD.

The urinary diversion performed in a radical cystectomy is at risk of developing ureterointestinal anastomosis strictures (UES). UES rates have previously been reported to be 6.5-13%(37-39). Ahmed et al. found a significant association between UES and intracorporeal urinary diversion(30). Anderson et al. described a higher stricture rate in RARC with the UD performed extracorporeally (12.6%) compared to ORC (8.5%), but the difference was not significant(38). The Razor study presented a ureteral stricture rate of 7% in ORC and 9 % in RARC. To our knowledge, no other large RCT or retrospective study have compared stricture rates between ORC and RARC.

Enhanced recovery after surgery (ERAS) protocol was systematically introduced at St. Olavs hospital in January 2018, although some of the elements were introduced to ORC patients prior to 2012. It was introduced with hopes of faster and better postoperative recovery after RC. ERAS includes several elements; prevention of salt and water overload, early postoperative oral nutrition, no nasogastric tube, limited use of opioids, no drains intraoperatively, early mobilization, antibiotic prophylaxis and thromboprophylaxis. All of these elements except more focus on avoiding fluid overload, chewing

gum, weights daily and glucose overload the day prior to surgery were introduced to ORC patients prior to 2012. ERAS has been used in patients undergoing colorectal surgery for more than a decade, providing significantly reduced LOS and complication rates(40). Trials have also investigated if ERAS can provide similar results to RC, and so far, the results are conflicting. Persson et al. did not find a reduced LOS but found a significant reduction in 30- day readmission rates and faster bowel recovery(41). A prospective randomized trial by Karl et al. Also failed to find any benefit in LOS in the ERAS group but stated beforehand that this was due to German citizens expectations not to be discharged from the hospital earlier than usual. They did find a significantly shorter length of stay in intermediary units though(42). A prospective randomized study by S.K Frees et al. found a significant reduction in LOS in the ERAS group (6.1 vs 7.4 days p=0.02) (43). They also found significantly shorter time to first bowel movement and flatulence.

Objective:

Robotic assisted radical cystectomy was introduced at St. Olavs Hospital in 2015. The objective of this study is to evaluate the newly introduced treatment by establishing an ongoing radical cystectomy database to be able to prospectively measure results and effects of changes in treatment and use the retrospective data to compare perioperative, postoperative and oncological outcomes for patients undergoing radical cystectomy between Jan-2012 and May-2019.

Patients and Methods

Study design:

This is a retrospective study reviewing patients with bladder malignancy whom have undergone treatment for bladder cancer with radical cystectomy (RC) at St. Olavs Hospital between January 2012 and May 2019. The patients' medical records were registered and included in a standardized database.

Patients and objective:

All patients treated with RC at St. Olavs Hospital following primary bladder malignancy have been included in the study. This amounts to a total of 247 patients, whereof 156 were treated with open radical cystectomy (ORC). The transition from ORC to robot assisted radical cystectomy (RARC) was established from 2015 to 2016. By 1. January 2017 RARC had become standard treatment. The reasons for ORC to be performed after 2017, has been unavailability of the robot or the robotic trained surgeon, or prior major abdominal surgery. This means that patient selection after 1. January 2017 was not based on patient characteristics except when having undergone prior major abdominal surgery which applied to 2 patients. Patients were followed up according to guidelines from the Norwegian Directorate of Health(44), with a sixty months attempted follow-up. All ORC, except 6 cases, had been performed by one out of two surgeons, whereof one has 20+ years of ORC experience and the other was trained and supervised in ORC by the former, before transitioning to RARC. All RARC-

cases have been performed by one surgeon, whom had five years of training in robot-assisted radical prostatectomy (approx. 500 operations) prior to RARC-training.

Variables:

Collected data includes patient age, gender, BMI, ASA, comorbidity, preoperative diagnostics, perioperative data and postoperative surveillance.

This includes amongst others: Pre and postoperative TNM-stages and WHO-grade, neoadjuvant chemotherapy, pre- and postoperative Hgb, number of transfusions, hospital admission time, Urinary diversion-type, extent of PLND, total lymph-node count, presence of positive margin, complications graded by Clavien Dindo within 30 days, return to operation room within 30 days, readmission, cause of death, time to tumour recurrence, recurrence location, presence of local recurrence and date of last follow up.

Clinical TNM-stage was decided based on both CTI (some MRI) and pathology following TUR-B.
A positive soft tissue surgical margin was defined as presence of tumour at inked areas of soft tissue on the radical cystectomy specimen(27).
Local recurrence was defined by tumour recurrence in the pelvic area below the aortic bifurcation.
Standard pelvic lymph node dissection (PLND) includes lymph nodes in the areas of the internal and external iliac arteries up to the iliac bifurcation, while extended PLND also includes lymph nodes in the areas along the common iliac arteries up to the aortic bifurcation.

Data collection and ethics:

The data was collected from medical records from all hospitals in “Helse midt-Norge”, a region with multiple hospitals, of which St. Olavs Hospital is the tertiary centre and only centre performing RC. The data was registered in a WebCRF-database and extracted to SPSS files.

This study is to ensure the quality of a recently introduced operation method. It is performed on records from patients already treated and provides important information for surgeons to take into consideration for future patient treatment, naming effect of treatment, complications and economical aspects, the former also of great value to the society.

This study was approved by the Regional Ethical Committee (Norwegian abbreviation: REK), reference number 2019/236. Permission from the Norwegian Centre for Research Data (Norwegian abbreviation: NSD) was given to extract the data without patient consent, reference number 154271. The GDPR and Norwegian law demands that patient consent is collected before inclusion in research unless certain conditions apply(45). Health institutions are obligated to ensure the quality of their treatment to be able to give the best possible treatment, and in these occasions NSD may give permission to extract patient data to a database for quality control of health care services without collecting patient consent(46).

The privacy of patients was ensured through keeping a patient identification key separate on a closed and password-protected server area in the hospital's system, while the anonymous database containing study material was stored in an online database with two-step verification. The data in the database will be rendered unidentifiable after 10 years.

Statistical analysis:

Categorical variables were described using percentages and frequencies and analysed using Chi-square test with continuity correction for 2x2 tables. Continuous variables were described using means and medians and analysed using Student's t-test and Mann-Whitney U test (Wilcoxon rank-sum test) depending on the presence of normality in the data. Two-year cancer specific and total survival and two-year progression-free survival was evaluated using Keplan-Meier survival plots with Log Rank (Mantel-Cox) test.

Results

This study contained a total of 247 patients treated with radical cystectomy (RC) in the time period 1. January 2012 to 1. June 2019, whereof 156 underwent ORC and 91 underwent RARC. Median follow-up time was 43 and 20 months respectively. Patient demographics was evenly distributed (Table 1), although patient comorbidity was lower for previous laparotomy and radiation (P = .001 and .006) in the ORC group (Table 2). There were no differences concerning clinical T-stages (p=0,41), but more pre-operative suspect lymph-nodes (P=0,006) in the ORC group. There was also an increased use of neoadjuvant chemotherapy (p=0,03) in the RARC group and a difference in post- op pathological stage (p=0.03), where ORC had more patients with T stage ≥2 and N1. RARC had zero cases with PSM, while ORC had 9%. RARC had significantly more lymph nodes removed (16 vs 10, p= <0.001) and a higher incidence of extended PLND (68.1% vs 6.5%, p<0.001). Histological type and tumour WHO grade were evenly distributed. Type of urinary diversion did not differ significantly, but there was a trend towards more neobladders in RARC (p=0,06)

TABLE 1

Parameter	ORC (n = 156)	RARC (N = 91)	P-Value
Age (years)	71 (64-77)	70 (63-76)	0.58
Female gender	36 (23%)	17 (19%)	0.52*
ASA >2	74 (47%)	34 (37%)	0.16*
Body mass index	25 (23-28)	26 (23-27)	0.34
Type of urinary diversion			0.06
Ileal conduit	136 (87%)	70 (77%)	
Neobladder	19 (12%)	19 (21%)	
Continent reservoir	0 (0%)	2 (2%)	
No diversion* **	1 (1%)	0 (0%)	
Clinical stage			0.41
T0	1 (1%)	0 (0%)	
Ta	2 (1%)	0 (0%)	
T1	35 (22%)	23 (25%)	
T2	69 (44%)	41 (45%)	
T3a	14 (9%)	14 (15%)	
T3b	22 (14%)	7 (8%)	
T4a	11 (7%)	6 (7%)	
T4b	2 (1%)	0 (0%)	
Suspect Lymph Node Pre-op	24 (15%)	3 (3%)	0.006*
Suspect Metastasis Pre-op	11 (6.9%)	7 (7,7%)	1.000*
CIS (carcinoma in situ)	53 (34%)	45(51%)	0.02*
WHO-grade 3	139 (96%)	85 (97%)	1.00*

Neoadjuvant chemotherapy	47 (30%)	42 (46%)	0.02*
Histologic type			0.47
Urothelial carcinoma	139 (90%)	80 (89%)	
Squamous cell carcinoma	9 (6%)	7 (8%)	
Adenocarcinoma	1 (1%)	2 (2%)	
Small cell carcinoma	5 (3%)	1 (1%)	
Post-op pathologic stage			0.03
T0	44 (28%)	36 (40%)	
Ta	2 (1%)	2 (2%)	
T1	12 (8%)	15 (17%)	
T2	32 (21%)	7 (8%)	
T3a	15 (10%)	7 (8%)	
T3b	32 (21%)	12 (13%)	
T4a	18 (12%)	12 (13%)	
T4b	1 (1%)	0 (0%)	
Post-op N-stage**			0.009
N0	111 (71%)	82 (90%)	
N1	36 (25%)	9 (10%)	
Post-op CIS (carcinoma in situ)	45 (29%)	25 (28%)	0.90*
Soft tissue positive margin	13 (9%)	0 (0%)	0.01*
Lymph nodes removed (n)	10 (7-14)	16 (11-21)	<0.001
PLND Groups			<0.001
Limited	10 (7%)	0 (0%)	
Standard	133 (87%)	29 (32%)	
Extended	10 (67%)	62 (68%)	

*Continuous variables are stated as medians (interquartile range), categorical variables as n (% within group). *Continuity corrected. **9 patients were NX in ORC group. ***Earlier bilateral nephrectomy*

One patient with pT0 was treated with RC due to CIS-recurrence after pT1 treated with BCG, while also having prostate cancer Gleason score 7. Two patients with pTa were treated with RC, one due to earlier unilateral nefro-ureterectomy following high grade urothelial cancer, and the last one due to macroscopic relapsing pTa cancer and an earlier bilateral nephrectomy following a renal carcinoma.

TABLE 2 (Comorbidity)

Parameter	ORC (n = 156)	RARC (n = 91)	P-value*
Prostate cancer	12 (8%)	5 (6%)	0.691
Angina	7 (5%)	2 (2%)	0.566
Myocardial infarction	25 (16%)	6 (7%)	0.050
Heart failure	6 (4%)	2 (2%)	0.739
COPD	10 (6%)	6 (7%)	1.000
Kidney failure	8 (5%)	6 (7%)	0.85

Diabetes	12 (8%)	9 (10%)	0.72
Hypertension	55 (35%)	21 (23%)	0.06
Hypothyroidism	8 (5%)	2 (2%)	0.43
Previous laparotomy	41 (26%)	7 (8%)	0.001
Cerebral insult	13 (8%)	5 (6%)	0.57
Arrhythmia	18 (12%)	10 (11%)	1.0
IBD	0	0	
Arthritis	2 (1%)	4 (4%)	0.27
Other cancer diseases	26 (17%)	8 (9%)	0.12
Coronary diseases	8 (5%)	0	0.07
Previous radiation	15 (10%)	0	0.006

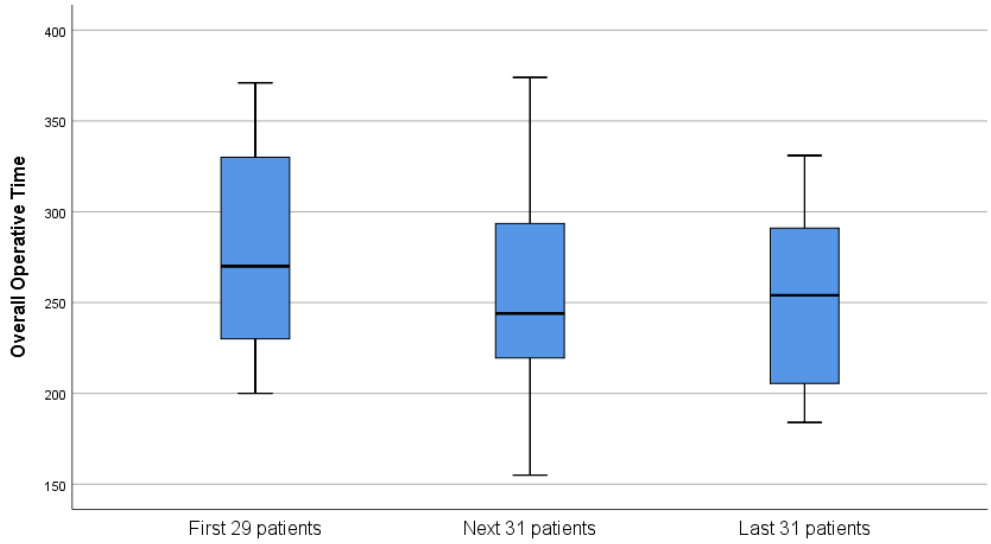
**Continuity corrected*

TABLE 3 (Operating time)

Parameter	**ORC (n = 156)**	**RARC LC* (n = 29)**	**RARC PLC**(n = 62)**	**P-value**
Operation time (minutes)	235 (224)	279 (270)	253 (246)	<0.001
Operation time (minutes)	235 (224)		253 (246)	0.034

*Values stated as mean (median). *LC = patients operated within learning curve. **PLC = Patients operated Post learning curve.*

FIG. 1



Overall operative time in RARC patients in and after the learning curve with medians.

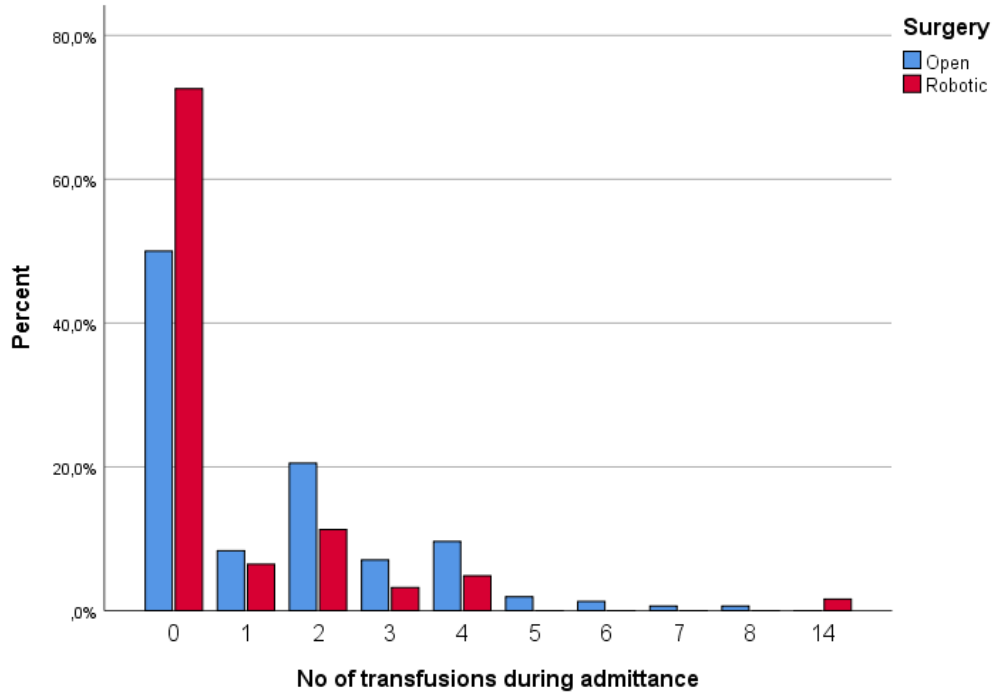
TABLE 4

Parameter	ORC (n = 156)	RARC (n = 91)	P-value
Blood loss (ml)	953 (820)	369 (300)	<0.001
Received any transfusion	78 (50%)	26 (29%)	0.002*
Hb difference	2.3 (2.5)	1.9 (1.9)	0.049

*Continuous variables stated as mean (median). Categorical variables stated as n (% within group). *Continuity corrected*

Operating time in RARC dropped by 26min after the learning period, but still represented a longer operating time than in ORC (253 vs 235, p=0.034). ORC patients suffered a higher blood loss (953ml vs 369ml, p<0.001) and received more blood transfusion (50% vs 29%, p=0.002) than RARC. In addition, the difference between pre-op and 3-5 days post-op Hb was slightly higher in ORC (2.3 vs 1.9, p=0.049).

FIG. 2



Percentage of patients within groups receiving given number of transfusions.

TABLE 5

Parameter	ORC (n = 156)	RARC (n = 91)	P-value*
Length of hospital stay	14 (14,39)	10 (11,65**)	<0.001
Return to or <30 days	12 (8%)	11 (12%)	0.36
Readmission <30 days	13 (8%)	10 (11%)	0.64
Readmission total	35 (22%)	26 (29%)	0.33
12 month stricture rate**	10/155 (7%)	5/76 (7%)	1.00

*Continuous variables stated as median (5% trimmed mean). Categorical variables stated as n (% within group). *Continuity corrected **Patients with >12 months possible follow-up counting both urethral and ureter anastomosis strictures.*

TABLE 6

Parameter	RARC first n=29	RARC next n=31	RARC last n=31	P-value
12 MONTH stricture RATE*	4 (14%)	0 (0%)	1/17 (6%)	0.092
Clavien 2	18 (62%)	12 (39%)	12 (39%)	0.114
Clavien 2 including perioperative transfusions	19 (66%)	14 (45%)	14 (45%)	0.194
Clavien 3	3 (10%)	3 (10%)	5 (16%)	0.695
Clavien 4	0 (0%)	1 (3%)	0 (0%)	0.376

**Patients with >12 months possible follow-up counting both urethral and ureter anastomosis strictures.*

Patients in RARC group had a shorter length of stay at the hospital (10 vs 14, p<0.001). Although not significant, RARC tended to provide more return to OR within 30 days (12% vs 8%) and more readmissions in total and within 30 days post-op (29% vs 22% and 11% vs 8%). An equal share of patients experienced anastomosis stricture in both groups (7% vs 7%).

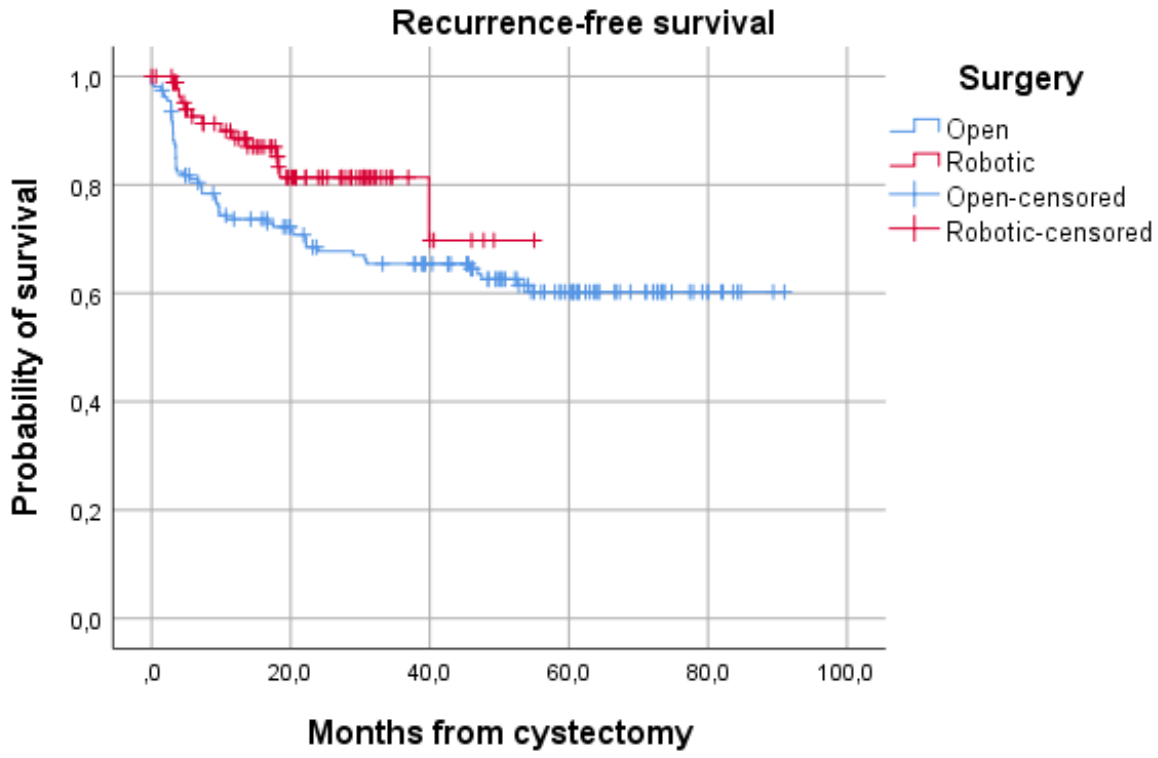
TABLE 7

Parameter	ORC (n = 156)	RARC (n = 91)	P-value*
Clavien 2	58 (37%)	42 (46%)	0.21
Clavien 2 including perioperative transfusions	103 (66%)	47 (52%)	0.04
Clavien 3	17 (11%)	11 (12%)	0.94
Clavien 4	2 (1%)	1 (1%)	1.00
Clavien total including perioperative transfusions	108 (69,2%)	52 (57,1%)	0.075

**Continuity corrected*

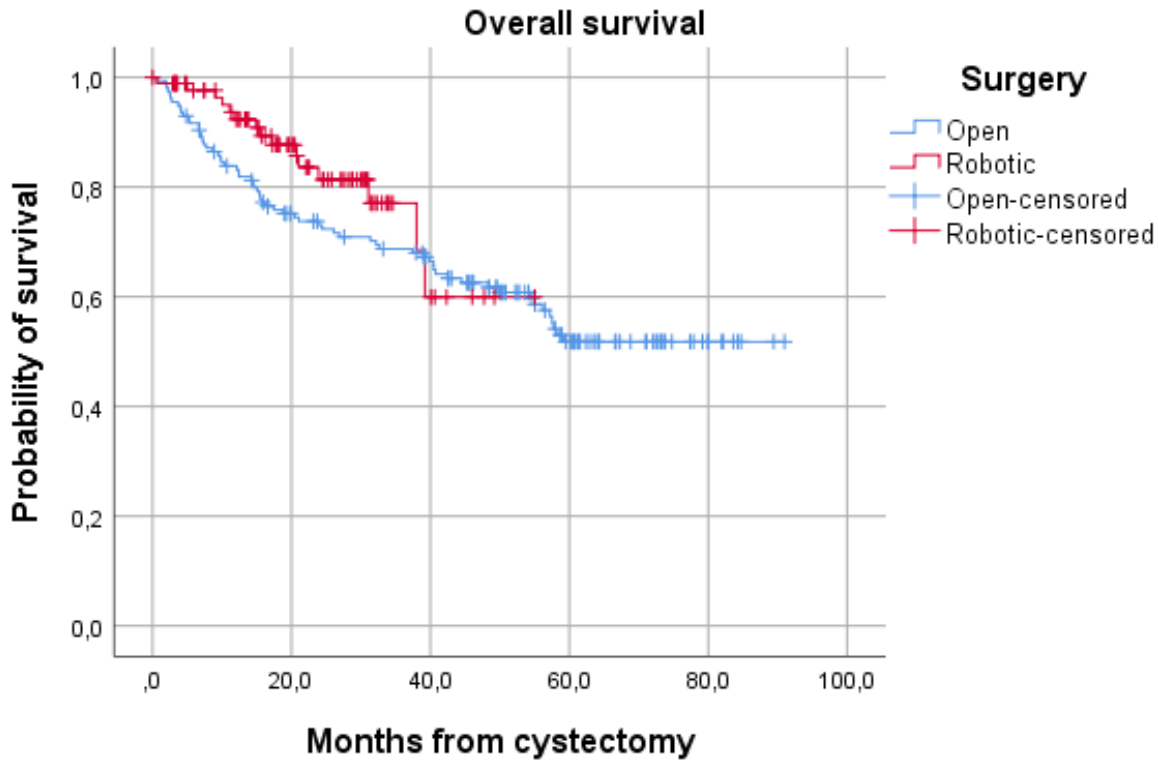
When including perioperative transfusions, ORC provided more Clavien 2 complications (66% vs 47%, p= 0.04). No differences were detected in serious complications (clavien 3-4). Although not significant, more patients suffered from any kind of complication in the ORC group (69,2% vs 57,1%, p=0.075).

FIG. 3



Log Rank (Mantel-Cox): 0.020

FIG. 4



Log Rank (Mantel-Cox): 0.156

FIG. 5

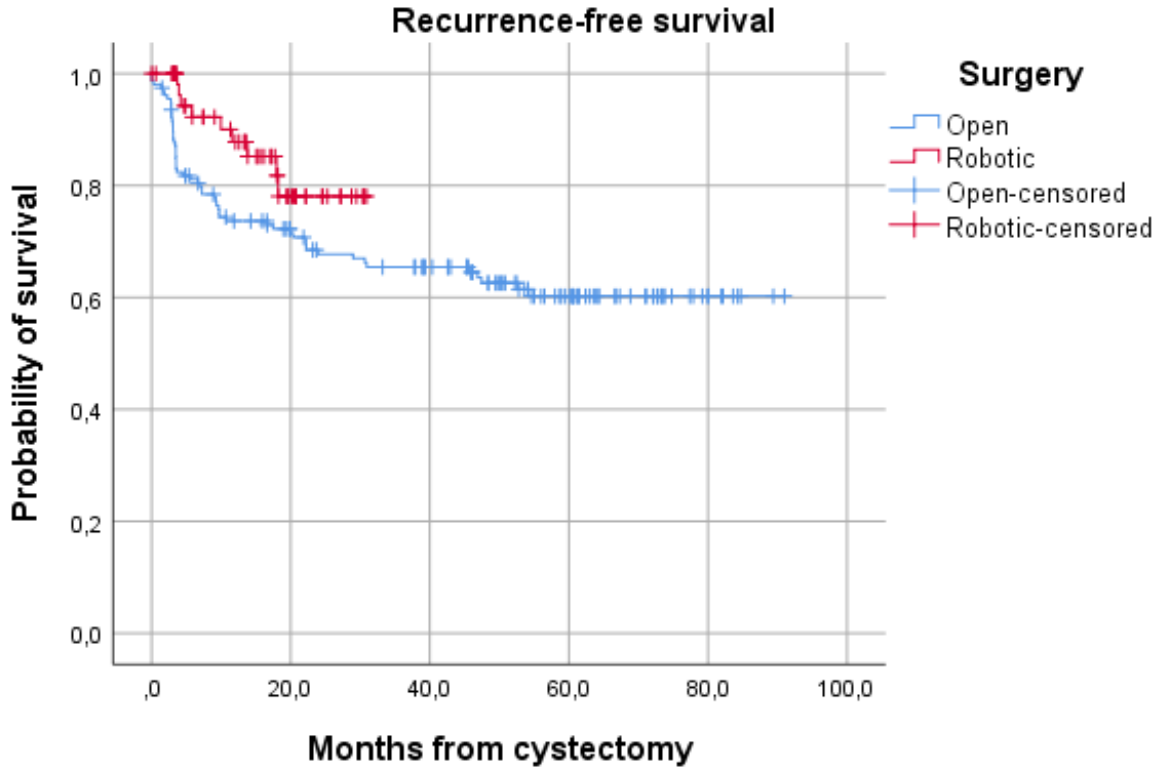


Table shows probability of survival with patients treated within learning curve excluded. Log Rank (Mantel-Cox): 0.071

FIG 6.

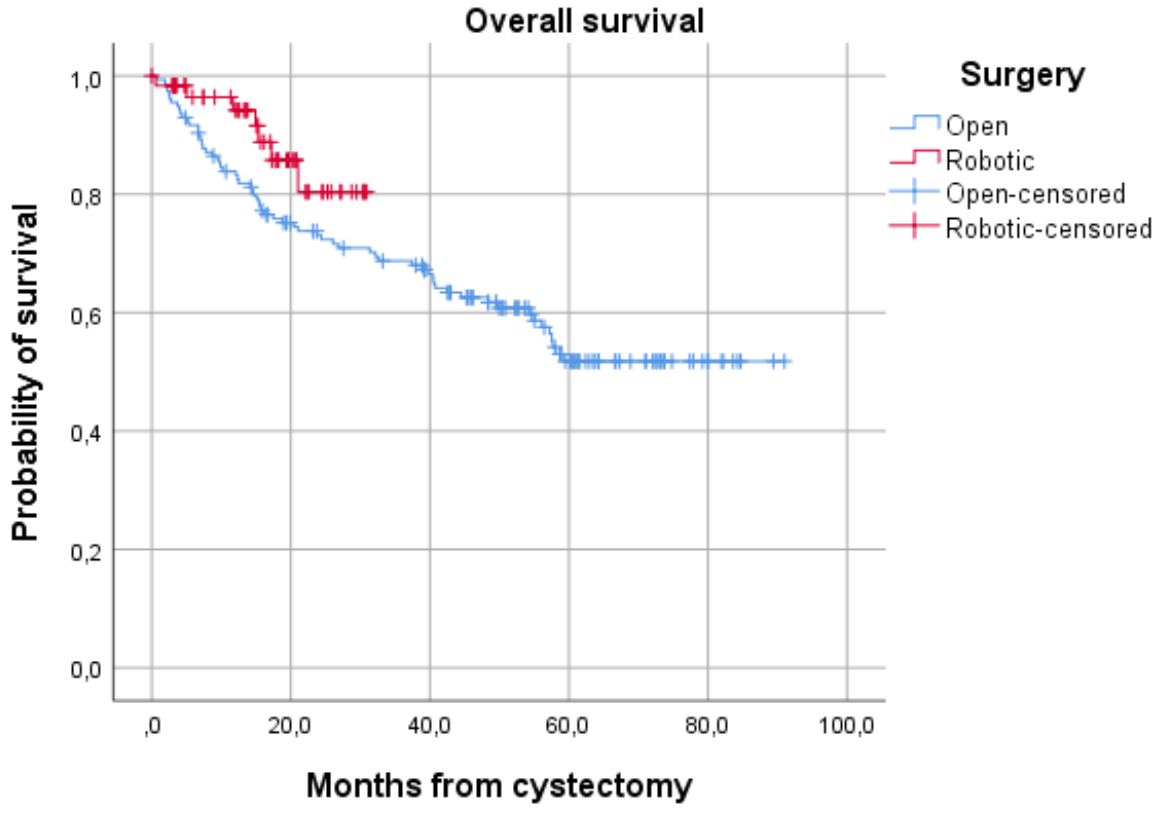


Table shows probability of survival with patients treated within learning curve excluded. Log Rank (Mantel-Cox): 0.116

When comparing all RARC and ORC patients, there is an increased RFS(p=0,020) for patients treated with RARC. When excluding patients within learning curve, the difference is no longer significant.

TABLE 8

Parameter	ORC	RARC	P-value*
2- year overall survival**	71.6% (101/141)	76.7% (33/43)	0.643
2- year recurrence free survival***	70.1% (108/154)	83.5 (66/79)	0.038
2- year local recurrence***	16.2% (25/154)	7.6% (6/79)	0.102
Local recurrence****	20.1% (31/154)	6.7% (6/90)	0.008
Tumor recurrence****	35.9% (56/154)	15.4% (14/91)	0.001

Continuity Corrected **Patients with >24 months possible follow-up and median patient follow-up time was 44 and 30 months for ORC and RARC respectively ***Patients with >5 months possible follow-up and median follow-up time was 43 and 21 months for ORC and RARC respectively ** All patients regardless of follow-up time*

Median time to death in the ORC group was 15,4 months, median time to recurrence in the ORC group was 5,0 months and median time to local recurrence in the ORC group was 3,6 months.

TABLE 9

Recurrence*	ORC (n=145)	RARC (n=44)	P-value**
Axial/ pelvic skeleton	26 (17.9%)	3 (6.8%)	0.120
Liver	21 (14.5%)	3 (6.8%)	0.281
Lung	18 (12.4%)	4 (9.1%)	0.739
Brain	4 (2.8%)	1 (2.3%)	1.0
Carcinomatosis	10 (6.9%)	2 (4.5%)	0.836
Port site metastasis		0 (0%)	
Distant lymph node	23 (15.9%)	5 (11.4%)	0.622

*Patients <24mnd follow-up excluded *All sites of recurrence during follow-up **Continuity Corrected*

Discussion

In this study, we sought to investigate the oncologic results and complications of the recently introduced RARC-treatment to the old standard ORC at St. Olavs Hospital. Median patient follow-up was 20 and 43 months for RARC and ORC respectively.

An advantage of RARC compared to ORC is the amount of blood-loss during operations and the decreased usage of transfusions(7, 10-14). Most studies only report perioperative blood loss and numbers of transfusions. In this study we also present the difference in pre-op and post-op Hgb, this provides extra evidence to meet the contentions that recorded perioperative blood loss might be slightly underestimated because of potential bleeding after the robot is undocked following the decreased abdominal pressure. In accordance with previous literature we found less perioperative bleeding and fewer blood transfusions in the RARC group. The difference in Hgb drop between ORC and RARC was 0,4 g/dl (p=0.049), barely significant in favour of RARC, and less than expected considering the difference in perioperative bleeding (953ml vs 368ml). Fluid restriction was systematically introduced with ERAS on RARC patients after 2018 suggesting that patients prior to 2018 might experience a larger Hb-drop secondary to dilution. On the other hand, taking into consideration that the amount of transfusions in the ORC group is higher, this further supports the consensus on less perioperative bleeding in RARC. According to Moschini et al., perioperative transfusions may increase all disease recurrence, cancer specific mortality and overall mortality(47) which should result in RARC having less of these. Yet so far, no studies have shown increased RFS, cancer specific survival or overall survival in favour of RARC and thereby brings Moschini et al's conclusion into question.

A disadvantage reported by all known studies are the increased operation time in RARC. This corresponds with our results, although our study shows the possibility of doing high quality RARC in a comparably short time. Studies show a time span of RARC operation time from 252-456, whereof only Nix et al. reported less than 300 minutes (7, 9, 12, 13, 48). In this study the mean OR-time was 253 minutes when counting out the learning curve, and the mean difference between ORC and RARC was only 18 minutes. Operative time in RARC decreased from a mean of 279 (median 270) for the first 29 patients to 256 (median 244) minutes for the next 31 patients to 250 (median 254) minutes for the last 31 patients. Important to note, is that among the middle 31 RARC patients and all ORC patients there were 10% and 12% neobladders and among the last 31 RARC patients there were 32% neobladders. The mean operative time for patients receiving neobladders in our material was on average 77 minutes longer than for patients receiving Bricker-bladders. The mean operative time in the last 31 RARC patients group when excluding patients receiving Studer-bladder was 229 minutes (median 218), suggesting that the gap between ORC and RARC operative time could be closed in future patients. Cheng et al. have suggested that a 30-minute increase in operative time across all

surgeries may increase complication likelihood by 14%(49). RARC could therefore potentially have resulted in more complications in our patients, as also suggested by Gandaglia et al. who described more overall- and low-grade complications in RARC(11). On the other hand, our study and most other studies on ORC vs RARC show no difference regarding complications(7, 12-14). It seems the minimally invasive benefits of RARC might outweigh the effect of increased operative time. When including perioperative transfusions, we described a lower Clavien 2 complication rate for RARC vs ORC by 52% vs 66% (p=0.04) respectively, while Clavien 3-4 was evenly distributed. This difference in clavien 2 complications is in line with the results from Faraj et al. (61.6 vs 75.9%) (10). Due to variable reporting of Clavien Dindo 1 complications, they were not included in the analysis.

To our knowledge, few studies comparing RARC and ORC have described 30-days readmission or return to operating room (OR) rates. Our analysis showed no significant difference between ORC and RARC (8 vs 11% respectively, p=0.64). The rate of readmissions might still be a little higher in the RARC group and it is possibly due to the adoption of ERAS. After the implementation of ERAS, patients are supposed to be discharged at an earlier time(43) and thereby a consequence could be more readmissions. A retrospective study by Ahmed et al. suggested a difference in 30-days readmission rate for patients treated with RARC with ICUD vs ECUD of 5 vs 13% respectively(30). The 30- day readmission rate in our material for RARC was 11%, which is a little high compared to 5% described in Ahmed K et al. for ICUD, but our numbers for RARC include 30% learning curve patients that might influence the numbers negatively. For returns to operation room within 30 days, our numbers were also fairly equal (8 vs 12% for ORC vs RARC respectively, p=0.36).

Total stricture rates for the anastomosis between the ureters and bowel segment (UES) and between the bowel segment and the urethra in neobladders at 12 months were also similar, both at 7%, between ORC and RARC in our study. Parekh et al. reported anastomotic strictures at 7 vs 9% for ORC vs RARC respectively(7). A study by Ahmed Y. et al. found a stricture rate at 16% for ICUD, stating that ICUD provided higher odds for UES(39), but our results speak against this. Something interesting to note, is the decrease in strictures after the learning curve. 4 of the first 29 patients got strictures at 12 months, but only one of the next 48 got strictures, suggesting that the stricture rate might be lower than 7% in the future.

The randomised RAZOR trial described a decreased LOS for the RARC group compared to ORC of 6 vs 7 days (p=0.02)(7). Faraj et al. supported this difference in LOS when they described 5 days in RARC and 7 days in ORC (p=<0.01)(10). Contrary to this, Bochner et al. found similar results of 8 days in both groups(7, 12). Our results of a median LOS at 14 vs 10 days (p<0.001) for ORC and RARC respectively, speaks of a great advantage of RARC in this regard. Compared to the above-mentioned studies from USA our LOS is high, while it`s low compared to an European retrospective study from two high referral centres by Gandaglia et al. They described LOS to be 13 days in RARC

and 20 days in ORC (p=<0.001)(11). LOS is probably influenced by national guidelines, clinical traditions, long or short travel distance for patients, ERAS, comorbidity and preoperative ASA score. The 4 days of reduced LOS in this study is a big advantage for RARC but could be influenced by several factors. ORC had 10% more patients with preoperative ASA >2, which can lead to longer LOS after surgery(50). ERAS was more systematically adhered to at St. Olavs Hospital as of January 2018 and has been described by Frees et al. to reduce LOS(43). Since most of the RCs performed after January 2018 are robot assisted, the RARC group could take more advantage of ERAS compared to ORC. As discussed earlier there was no differences in severe complications between ORC and RARC, but a significant higher estimated blood loss and higher transfusion rates in ORC, which has been described to increase LOS by Baumgartner et al(51). This could partly explain shorter LOS in RARC, but postoperative ileus is described to be a more prominent factor for prolonged LOS(51). This study detected no significant difference in ileus rates between ORC and RARC (7.1% vs 3.3% p=0.344), suggesting that less ileus cannot describe shorter LOS in RARC.

A review by Morii(52) found RARC to be more expensive than ORC, particularly in centres with low patient volume. The most expensive factors were operating and LOS-related costs. With the lower hospital admission time, fewer transfusions and small difference in operation time, this should reduce the additional cost of RARC compared to ORC substantially.

Hospital economy is always an important factor to consider when introducing a new treatment like RARC. To create an anticipation of what to expect at St. Olavs Hospital (SOH) we have looked at a thorough cost analysis from Bristol Urological institute (UK) written by Bansal et al.(53). They found RARC to be 18.9% more expensive than ORC. The average cost per case of RARC and ORC was 12 449£ and 10 474£ respectively. Included in these numbers from Bansal et al. are hospital LOS, operating room costs, equipment costs, blood transfusions, complications and re- admissions. Operation time (OT), LOS and case volume were identified as the most important factors to lower the price in RARC. Their analysis suggested that RARC would become cheaper than ORC if the OT was under 156 minutes or if the LOS was under 4 days in the RARC group, which of course is to ambitious, even though reductions are possible. The OT at St. Olavs Hospital was 253 minutes in the RARC group after the learning curve which is higher than the OT of 235 minutes in the ORC group, but when considering the amount of Studer-bladders in the last 31 RARC patients is three times that of ORC and the middle 31 RARC patients, the numbers are more equal when only counting Bricker-bladder patients. The mean OT of the last 31 RARC patients when excluding Studer-bladder patients was 229 minutes and the mean OT for ORC patients receiving Bricker-bladder was 226 minutes. This suggests that the operating room costs of RARC might be similar to those of ORC in future patients.

TABLE 10

Variable	RARC, £	ORC, £	RARC/ORC
Hospital LOS	3749.00	4894.77	0.77
Operating room cost	4815.52	3496.44	1.38
Equipment cost	3638.88	1514.39	2.40
Blood transfusion	22.15	88.85	0.25
Complications	136.95	172.49	0.79
Re-admissions	87.37	307.60	0.28
Total	12 449.87	10 474.54	1.19

Table 10 is retrieved from Bansal et al. and shows all elements included in the total costs. They based their hospital LOS costs on a mean of 8.76 days in RARC and 12.50 days in ORC. We found a slightly higher median LOS of 10 days in RARC and 14 days in ORC, which might increase the costs in both groups, but the difference of 4 days is similar and should provide a similar difference of costs in favour of RARC also at St. Olavs Hospital.

Operating room costs consists of fees to the surgeon and nursing staff, allocated costs and total OT. Bansal et al. assumed an OT of 264 minutes in RARC and 192 minutes in ORC, which gave a difference of 72 minutes in OT. At St. Olavs Hospital the difference in OT was only 18 minutes (253 min in RARC and 235 min in ORC). Therefore, it is plausible to assume that the difference in operating room costs at St. Olavs Hospital will decrease.

Equipment costs reported by Bansal et al. is 2.4 times more expensive in RARC than ORC. This is heavily influenced by Intuitive Surgical Inc`s market monopoly on robotic equipment, but the possibility exists of pricing of disposable equipment being reduced with increased competition between robot-equipment suppliers. Bansal et al. assumed the robotic equipment to have a lifetime of 10 years, and that 400 surgeries were performed by the robot annually – which is the same number as at St. Olavs Hospital. Approx. 50 of these were RARC, similar to the RARC-volume at St. Olavs hospital. The equipment costs will increase in a Hospital with lesser volume of robotic procedures, therefore it`s essential to keep the robotic surgery volume as high as possible to keep the costs as low as possible.

A weakness of Bansal et al. study is that when they calculated costs for complications, they added 2 days of LOS for clavien 2, 3 days for clavien 3 and 4 days for clavien 4 complications. This method will miss cases that needed costly reoperations, ICU care and radiological interventions. At St. Olavs Hospital there was no significant differences in high grade complications or reoperations, ensuring that the costs are equal on this regard. Transfusion rates were significantly higher in ORC than RARC at St. Olavs Hospital. Bansal et al. calculated the costs of transfusion on a base model that 2 units of SAG were given 30.9% of ORC and 9.7% of RARC, which gave a 66£ cost advantage for RARC. At St. Olavs we found a lesser difference between ORC and RARC at 20.5% and 13.2% respectively. Therefore, the cost advantage of RARC on this topic will be lesser at St. Olavs Hospital compared to

Bansal et al`s study. It is also important to bear in mind that the transfusion costs play a minor role to the total cost (0.84% of the total price of ORC in Bansal et.al). 90-day re-admission rates in Bansal et al. were 5.4% in RARC and 19.1% in ORC, providing a significant cost reduction in RARC. But also, on this topic it`s important to bear in mind that it composed a rather small part of the total costs (2.9% in ORC). The readmission rates in our study did not differ significantly, thus we expect the costs to be equal between RARC and ORC in that regard. What might save some costs in RARC at St. Olavs Hospital, is that RARC-patients are not observed in the ICU the first day, contrary to ORC patients.

Bansal et al. did not include long term re-admission or returns to OR, for example for anastomosis strictures. We found an interesting trend towards less strictures in the RARC group after excluding the 29 first learning cases of RARC. In the next 30 patients RARC had 0 strictures, and in the last 30 patients RARC had 1 stricture (3%). Compared to the 7% stricture rate in ORC, this could potentially save some long-term costs in the RARC group. In total it seems as if the reduced LOS in RARC balances out the potential extra 18 minutes OT in our study, while also making the equipment cost difference smaller. There is probably still a difference due to higher equipment costs in RARC, but we believe the difference is smaller than in this study by Bansal et al.

The costs from Bristol urological Institute only gives us a rough idea on what we can expect at St. Olavs Hospital. We used the numbers from Bansal et al. because it`s from a European hospital, and we assume that they are more comparable to Norwegian costs than numbers from American studies.

In our display of survival by Keplan Meier curves including all RARC patients, there is a significant increased RFS for RARC (p=0.02). 2-year OS for patients with >2-year follow-up was 71.6 vs 76.7% for ORC and RARC respectively (p=0.643). The RFS for patients >5 months follow-up was 70.1 vs 83.5% for ORC and RARC respectively (p= 0.038).We chose to do the RFS and OS-analysis at two years, as we had shorter follow-up in the RARC group, and according to Sonpavde et al. “disease-free survival rates at 2 and 3 years correlate with and are potential intermediate surrogates for 5-year overall survival in patients treated with radical cystectomy for muscle invasive bladder cancer regardless of adjuvant chemotherapy.”(54). In this study by Sonpavde et al., median time to recurrence was between 10 and 13.8 months. In our study, median time to recurrence was 5 months, possibly due to CTI at first follow-up, which Sonpavde et al. only did at physician discretion. The median follow-up for RARC patients in our RFS-analysis was 21 months and should therefore contain a substantial amount of the recurrences that would have appeared within 24 months, also since 90% of 24-months recurrences in the ORC group happened within 21 months. We acknowledge that these numbers aren’t a perfect representation, but we believe them to be the best display of our results until follow-up time will have increased in a few years from now. Both 2-year RFS and 2-year OS included 29 patients from the learning curve of the RARC surgeon. The beneficial RFS results in RARC, although only significant in the Kaplan Meier curve, is most likely partly due to selection bias in patients from the

learning curve of RARC. Patients with less comorbidity and less extensive bladder cancer were selected in the early days of RARC at St. Olavs Hospital, resulting in more patients with organ confined cancer and less lymph node metastasis in the post-operative pathology report despite the obvious inexperience of the surgeon at this time. The amount of organ confined cancer and number of lymph node metastasis are two variables important for RFS or OS and can influence our results in benefit of RARC(32). There was also an increased usage of neoadjuvant chemotherapy in RARC, 30 vs 46% for ORC and RARC respectively, probably resulting in a difference in post-operative T0 of 28% vs 40% for ORC and RARC respectively, which contributes to better OS and RFS in RARC. According to a review by Vale et al., platinum combination based neoadjuvant chemotherapy might give a 9% absolute increase in RFS, and a 5% absolute increase in OS(55). Kaplan Mayer curves based on only RARC patients after learning curve shows no significant difference between ORC and RARC, and thereby supports previous oncological findings(7-11).

In some retrospective studies extended PLND has shown beneficial results on RFS and local tumour control compared to a more limited PLND(22-24). Ideally when comparing ORC and RARC, the extent of the PLND should be equally distributed between the groups. In our study there was a significant skewness towards more extended PLND in RARC, and more standard PLND in ORC. Still, the effect of this difference is disputable, as the only prospective randomised study performed found no significant difference in favour of Extended vs Standard PLND. As expected because of more extended PLND, the lymph node count in RARC was significantly higher than in ORC (16 vs 10). But the results of both groups are well within the minimum of 9-16 lymph nodes described in literature(15-18). A new surgical method called en-bloc was introduced after the initial learning period of RARC. The idea behind en-bloc is to remove the bladder specimen and all lymph nodes in one continuous specimen. This technique was first described in surgery for colon cancer(56), and provided a significant reduction in local recurrence rates(57). An ongoing study at St. Olavs hospital is investigating if en-bloc also can provide less local recurrence in bladder cancer. If they succeed to bring evidence in favour of en-bloc, it will influence the interpretation of our RFS and Local recurrence results, because of a severe skewness towards more en-bloc in the RARC group.

In our study the RARC group experienced fewer local recurrences (LR) at two years compared to the ORC group, although the difference was not significant (7.6% vs 16.2%, p=0.102). According to Sabir et al., the median time to local recurrence is 15 months(31), while median follow-up for RARC patients in this analysis was 21 months. In our material, median time to LR in the ORC group was 3.6 months, probably this short due to CTI at first follow-up. LR in RARC could therefore increase with longer follow-up, but not by much, and should still provide a possible improvement over ORC. As mentioned earlier, there is a possibility that the higher incidence of extended PLND, neoadjuvant chemotherapy and en-bloc along with lower PSM rates in the RARC group is responsible for the difference in LR.

PSM has been described to be an important predictor for metastatic progression, local recurrence and to increase the risk of cancer specific death (16, 26, 27). The PSM rate in RARC was 0% compared to the 9% in ORC (p=0,01). Neither Faraj nor Parekh et al. found any difference in PSM(7, 10), contrary to our results. This exceptionally low PSM rate probably contributes to the low LR in RARC. The low PSM rate in RARC might be influenced by patient selection bias in the learning period, providing more T0 and organ confined cancer in the post-op pathology. Locally advanced cancer and lymph node metastasis are important risk factor for PSM(26). Higher incidence of these two risk factors in the ORC group can explain some of the difference in PSM rates. Still, the percentage of T4a cancer is the same in the two groups.

Concerns have been raised regarding atypical recurrences in RARC(34, 35), but in line with other studies(7, 8, 10), our population reported no port site metastasis, and patterns of recurrence were similar between both groups (Table 9).

This study has its limitations. It is a retrospective study and initial patients selected for RARC were subject to selection bias, that is the 29 patients treated with RARC in 2015-2016. After 2017 the only reason for ORC to be performed is unavailability of the robot, and therefore patients treated after the start of 2017 should have minimal selection bias. In the ORC-group there were 3 surgeons performing RC, one only 6 times, while in the RARC group all were performed by one surgeon. More surgeons in each group might have provided more generalizable results. Four patients were lost to follow-up: One moved abroad, one moved follow-up to another region and two were lost to follow-up for unknown reasons.

There are few patients with sufficiently long follow-up in the RARC group (79 with >5 months and 43 with >24 months possible follow-up) and more patients with longer follow-up would have provided more reliable analysis. For this reason, we could not provide long term oncological results, but our data will contribute to this analysis in the future.

In this study we did not assess Quality of life, long term readmissions following e.g. hernias and leakage or sexual functions after surgery, all factors arguably more important for the patients than e.g. LOS or numbers of transfusions. Differences in factors affecting quality of life should also be taken into consideration when evaluating a new treatment, and the results from this study cannot be the whole basis of evaluation by itself.

Conclusion:

Results following the transition from ORC to RARC seems favourable to RARC, but it is difficult to determine which factors contributes the most, the surgery itself, patient selection, en-bloc or the frequency of neoadjuvant chemotherapy. Regardless of this, the study provides evidence of non-inferiority of RARC regarding oncological and survival endpoints. There is also evidence of less perioperative transfusions, a shorter length of stay in RARC and only a minor difference in operative time. The last two are two of the most important factors in operation cost and thereby the RARC operation seems to be only slightly more expensive than ORC due to higher equipment costs.

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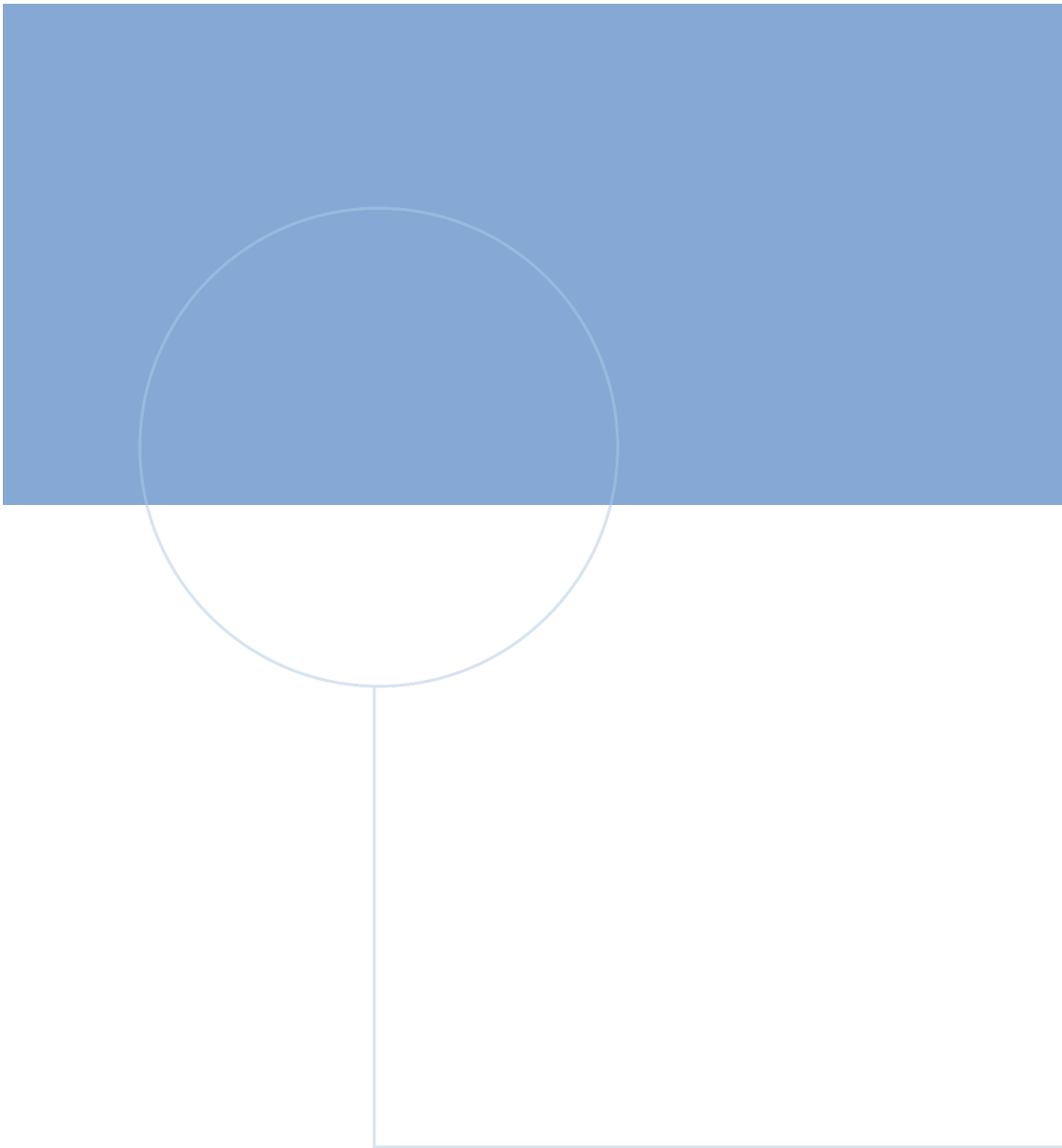

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