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Predictors of Recurrence, and Progression-Free and Overall Survival following Open versus Robotic Radical Cystectomy: Analysis from the RAZOR Trial with a 3-Year Followup

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Abstract

Purpose: The RAZOR (Randomized Open versus Robotic Cystectomy) trial revealed noninferior 2-year progression-free survival for robotic radical cystectomy. This update was performed with extended followup for 3 years to determine potential differences between the approaches. We also report 3-year overall survival and sought to identify factors predicting recurrence, and progression-free and overall survival.

Materials and Methods: We analyzed the per protocol population of 302 patients from the RAZOR study. Cumulative recurrence was estimated using nonbladder cancer death as the competing risk event and the Gray test was applied to assess significance in differences. Progression-free survival and overall survival were estimated by the Kaplan-Meier method and compared with the log rank test. Predictors of outcomes were determined by Cox proportional hazard analysis.

Results: Estimated progression-free survival at 36 months was 68.4% (95% CI 60.1–75.3) and 65.4% (95% CI 56.8–72.7) in the robotic and open groups, respectively ($p=0.600$). At 36 months overall survival was 73.9% (95% CI 65.5–80.5) and 68.5% (95% CI 59.8–75.7) in the robotic and open groups, respectively ($p=0.334$). There was no significant difference in the cumulative incidence rates of recurrence ($p=0.802$). Patient age greater than 70 years, poor performance status and major complications were significant predictors of 36-month progression-free survival. Stage and positive margins were significant predictors of recurrence, and progression-free and overall survival. Surgical approach was not a significant predictor of any outcome.

Conclusions: This analysis showed no difference in recurrence, 3-year progression-free survival or 3-year overall survival for robotic vs open radical cystectomy. It provides important prospective data on the oncologic efficacy of robotic radical cystectomy and high level data for patient counseling.

Keywords

bladder neoplasms; cystectomy; neoplasm recurrence; robotic surgical procedures; mortality

THE RAZOR trial represented the first multicenter, phase 3 study comparing the oncologic outcomes of RARC and ORC for bladder cancer.¹ The 2-year PFS of robotic cystectomy was found to be noninferior to that of open surgery, reassuring the urological community about the safety of the robotic approach. We performed this update to extend the followup of

recurrence and survival outcomes to 3 years because 2 years may have been insufficient to demonstrate important differences between RARC and ORC in this regard.

Radical cystectomy has long been the gold standard for invasive bladder cancer. Surrogates of high quality surgery, including positive margins, lymph node yield and major complications, have been demonstrated to influence oncologic outcomes.² The RAZOR trial revealed no difference between robotic and open cystectomy for any of these parameters, suggesting that high quality cystectomy can be performed by either approach.¹ Other nonsurgical factors, including chemotherapy and patient related factors such as age and performance status, can also impact performance of the surgery and oncologic end points. A major concern about robotic surgery has been an increased incidence of altered patterns of recurrence, such as peritoneal carcinomatosis based on selected early studies.³ This was attributed to the use of pneumoperitoneum and the loss of tactile feedback during robotic surgery, which could result in cutting through the specimen and excessive specimen handling with resultant dissemination or aerosolization of tumor cells.³

The RAZOR trial has provided prospective data revealing no increase in such recurrences after robotic cystectomy.¹ Furthermore, the RAZOR trial provided us with the opportunity to explore the influence of these and other variables known to impact recurrence and survival but which have seldom been studied in the context of a well characterized cohort in a randomized trial. Therefore, we also performed this 3-year analysis of survival outcomes using the RAZOR data to identify other factors associated with intermediate term survival in this population. Thus, the focus of this analysis of the RAZOR data was to report 3-year rates of recurrence, PFS and OS for RARC and ORC, and identify factors associated with these time to event outcomes.

METHODS

The RAZOR trial was a multicenter, open label, randomized, phase 3, noninferiority trial comparing RARC and ORC to treat bladder cancer. Patients were enrolled at a total of 15 participating institutions in the United States after Institutional Review Board approval was received at each site. Patients were centrally randomly assigned 1:1 via a web based system to receive ORC or RARC. Intraoperative protocols such as pneumoperitoneum pressure and insufflation devices as well as perioperative management were applied according to the institutional protocol. Complete methodology, including inclusion criteria as well as oncologic, perioperative and pathological outcomes, have been reported previously.¹ The primary end point of the study was 2-year PFS.

The study end points were time to recurrence, PFS and OS as defined from the date of surgery. After surgery patients were followed for bladder cancer progression or death from any cause every 3 to 6 months with planned followup visits at 3, 12, 24 and 36 months. Disease recurrence was determined based on radiographic or pathological evidence of disease or death from disease according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria. Local recurrence was defined as any recurrence within the pelvis and lymph node dissection boundaries, and distant metastasis was defined as cancer outside this template. Disease recurrence and death from any cause were considered events

for the progression-free survival end point. Event-free patients were censored at the date of last contact. The analysis set was the per protocol population of 302 patients in the RAZOR study.

Cumulative recurrence rates were estimated using competing risk methods with nonbladder cancer death as the competing risk event.⁴ Time to the first event (recurrence or nonbladder cancer death) was defined as the date of surgery to the date of the documented first event with event-free patients censored at the date of last contact. The Gray test was used to assess the significance of differences in the estimated cumulative incidence of recurrence curves.⁵ Estimated SHRs with the corresponding 95% CI and p value were calculated by fitting Fine and Gray subdistribution hazard models to evaluate unadjusted and adjusted effects of key variables on the risk of recurrence with nonbladder cancer death considered the competing risk.⁶

PFS and OS curves were estimated using the Kaplan-Meier method and compared by the log rank test. For the group comparison of 36-month PFS and OS rates we used the chi-square test based on the $\log(-\log(\cdot))$ transformation of the corresponding rates. PFS and OS predictors were assessed using the Cox proportional hazard model with results summarized as the HR with the corresponding 95% CI and as the p value.⁷ The Cox models included a shared frailty term (mixed modeling analysis) with cluster specific random effects to account for institutional differences.⁸ The proportional hazard assumption was assessed as reasonable based on graphic and numerical methods implemented in SAS®.

The initial set of potential predictors of the 3 outcomes were surgical group (robotic or open), urinary diversion procedure, chemotherapy use, patient age, gender, BMI, baseline ECOG Performance Status, intraoperative blood loss, perioperative blood transfusion, lymphadenectomy extent, pathological stage, surgical margin status and surgical complications at 90 days. To better understand the effect of chemotherapy we also fit a multivariate model in a subset of 234 patients with cT2 or greater, or pT2 or greater disease and who received platinum based chemotherapy. We also excluded 4 patients from analysis who did not receive platinum based chemotherapy.

Based on univariable analysis results and considering the number of observed events per variable category we selected a subset of common variables for multivariable analyses. The final multivariable models included surgical group, chemotherapy and additional variables at $p < 0.05$. Gender, BMI, urinary diversion procedure and lymphadenectomy extent were tested for inclusion in the multivariable models individually and jointly. However, they were excluded because they were not statistically significant predictors of any of the 3 outcomes ($p > 0.05$). Data analysis was performed in SAS®, version 9.4.

RESULTS

At 36 months PFS was comparable in the 2 groups ($p=0.756$). The estimated progression-free rate at 36 months was 68.4% (95% CI 60.1–75.3) in the robotic group and 65.4% (95% CI 56.8–72.7) in the open group ($p=0.600$, fig. 1, A). Similarly, 36-month OS was

comparable in the 2 groups ($p=0.432$). The HR was 73.9% (95% CI 65.5–80.5) in the robotic group and 68.5% (95% CI 59.8–75.7) in the open group ($p=0.334$, fig. 1, B).

Table 1 shows that there was a total of 49 progression events in the robotic group and 50 in the open group. There was no significant difference between the 2 groups in local or distant recurrences, or bladder cancer or noncancer deaths. When restricted to the 78 recurrences (39 per surgery group), the median time to recurrence was 10.2 months in the robotic group vs 6.3 months in the open group (supplementary table, <https://www.jurology.com>).

Figure 2 shows the cumulative incidence of recurrence with noncancer deaths as a competing risk. There was no significant difference in the cumulative incidence rates of recurrence in the open group vs the robotic group ($p=0.802$). However, pathological stage and positive surgical margins significantly affected the cumulative incidence of recurrence (each $p < 0.0001$). Of the 14 patients with local and distant recurrences 12 presented with simultaneous local and distant recurrences, suggesting a disseminated pattern of metastases. In the other 2 patients (1 per group) local recurrence developed prior to metastatic disease. The patient in the robotic arm had local recurrence at 6 months, followed by liver metastasis and death at 2 years. The patient in the open arm had local recurrence at 12 months, followed by disseminated metastases and death at 2 years.

Table 2 shows the univariable analysis. Age, performance status, blood transfusion, pathological stage, margins status and 90-day complications were significant predictors of PFS and OS. Chemotherapy and the extent of lymphadenectomy were not predictors of PFS or OS. Adjuvant therapy was associated with an increased risk of recurrence on univariable analysis. An ileal conduit was associated with significantly worse OS but not with recurrence or PFS on univariable analysis.

Multivariable analysis was done to determine potential predictors of recurrence (considering nonbladder cancer deaths), PFS and OS (table 3). Age greater than 70 years, poor ECOG Performance Status (2–3) and major complications (Clavien grade III or greater) were significant predictors of worse PFS and OS. Higher pathological stage and positive margins were also significant predictors of recurrence, PFS and OS. The surgical approach (robotic or open), blood transfusion and chemotherapy were not significant predictors of any outcome on multivariable analysis.

DISCUSSION

The RAZOR trial proved the noninferiority of RARC to ORC with respect to 2-year PFS. The 2-year PFS HR was 72.3% (95% CI 64.3–78.8) in the robotic cystectomy group and 71.6% (95% CI 63.6–78.2) in the open cystectomy group (difference 0.7%, 95% CI -9.6–10.9 noninferiority $p=0.001$).¹ There were also significant advantages to RARC in estimated blood loss, the blood transfusion rate and length of stay.¹ In the current study we report 3-year PFS, which did not differ between the 2 approaches at this extended followup. The 3-year PFS HR was 68.4% (95% CI 60.1–75.3) in the robotic group and 65.4% (95% CI 56.8–72.7) in the open group ($p=0.756$). There was no difference in 3-year overall survival between the approaches. Our study further provides a comparison of the types and predictors

of recurrence after robotic and open cystectomy in the RAZOR trial. Importantly, we found no difference between the 2 groups in local or distant recurrence, or bladder cancer or noncancer death.

Previous studies of RARC and ORC have shown similar survival outcomes. Stein et al reported 68% 5-year RFS and 66% OS in 1,054 patients treated with ORC.⁹ As expected, survival worsened with increasing pathological T stage and lymph node positive disease. They further observed that most deaths related to bladder cancer occurred within 3 years of surgery with a median time to recurrence of 12 months and with 86% of cases recurring within 3 years. Median time to recurrence in our study was 6.3 months in the open group and 10.2 months in the robotic group. While overall perioperative chemotherapy rates were similar in our 2 groups, adjuvant therapy was more common in the robotic group (16.8% vs 11.3%, $p=0.176$) while neoadjuvant therapy was less common (27.5% vs 36.7%, $p=0.09$). This may account for some of the difference in time to recurrence.

Herr et al noted 54% 5-year post-cystectomy survival in the SWOG (Southwest Oncology Group) 8710 population and determined that age, stage, lymph node yield and negative margins were significant predictors of improved survival after cystectomy.² Retrospective robotic cystectomy studies from the IRCC (International Robotic Cystectomy Consortium) and other high volume centers revealed similar long-term survival results.⁹⁻¹⁷ In addition to age, stage and worsening performance status, positive margins and major complications were significant predictors of PFS and OS on multivariable analysis in this study. Similar predictors of survival were also found in the robotic literature and in prior studies.^{11,12,16-19} The surgical approach (open or robotic), the extent of lymphadenectomy (standard vs extended) and perioperative chemotherapy were not significant predictors of PFS or OS. Blood transfusion has been associated with worse oncologic outcomes but it was not a significant predictor of PFS or OS on multivariate analysis in this study. These data offer high quality evidence from a randomized study to support the similarity of oncologic outcomes of the 2 approaches.

One of the early oncologic concerns raised about minimally invasive surgery in general was the risk of peritoneal seeding due to pneumoperitoneum. Specific to the robotic system, it was also thought that the lack of tactile feedback may increase the risk of positive margins, especially in locally advanced disease cases, and potentially lead to a higher incidence of local recurrence. Indeed, Nguyen et al reported a higher incidence of peritoneal carcinomatosis and extrapelvic lymph node recurrence for RARC than for ORC.³ In a subsequent larger study the same group concluded that tumor biology and not the surgical approach was responsible for these atypical recurrences.¹⁹

Our study did not show a significant difference in the cumulative incidence, type or location of recurrence after cystectomy between the 2 approaches. The overall recurrence rate at 3 years in this study was 26% in the robotic group and 26.3% in the open group. As expected, pathological stage and surgical margins were significant predictors of recurrence. This is similar to findings in other studies of open and robotic cystectomy.^{9,11,14,17} Nguyen et al reported 69% 3-year recurrence-free survival in a series of 310 RARCs.¹⁹ Significant predictors of recurrence were stage, margin status, lymphovascular invasion, an estimated

glomerular filtration rate less than 60 ml/minute/1.73 m² and blood transfusion.¹⁹ Raza et al reported 67% 5-year recurrence-free survival from the IRCC and found that stage, positive margins, adjuvant chemotherapy and variant histology were predictors of recurrence.¹² A long-term study from the Cleveland Clinic showed 54% 10-year RFS for 121 minimally invasive radical cystectomies.¹³ Data from the RAZOR trial are similar to those reported in these nonrandomized studies.

Some limitations of our analysis must be acknowledged. The RAZOR trial was powered to prove the noninferiority of 2-year PFS for robotic vs open cystectomy. However, we report other oncologic outcomes, including recurrence rates and overall survival. All oncologic outcomes were comparable in the 2 groups, providing high quality, prospective evidence of the oncologic efficacy of robotic cystectomy. Whether chemotherapy was performed was left to physician discretion at individual sites since it was not part of the protocol.

CONCLUSIONS

This analysis from the RAZOR trial shows no difference in the cumulative incidence of recurrence, 3-year PFS or 3-year OS for RARC and ORC, reinforcing the oncologic equivalence of the 2 approaches. It provides prospective data on which physicians can base a discussion with patients before selecting a surgical approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

BMI	body mass index
ECOG	Eastern Cooperative Oncology Group
ORC	open radical cystectomy
OS	overall survival
PFS	progression-free survival
RARC	robotic radical cystectomy
RAZOR	Randomized Open versus Robotic Cystectomy
SHR	subdistribution HR

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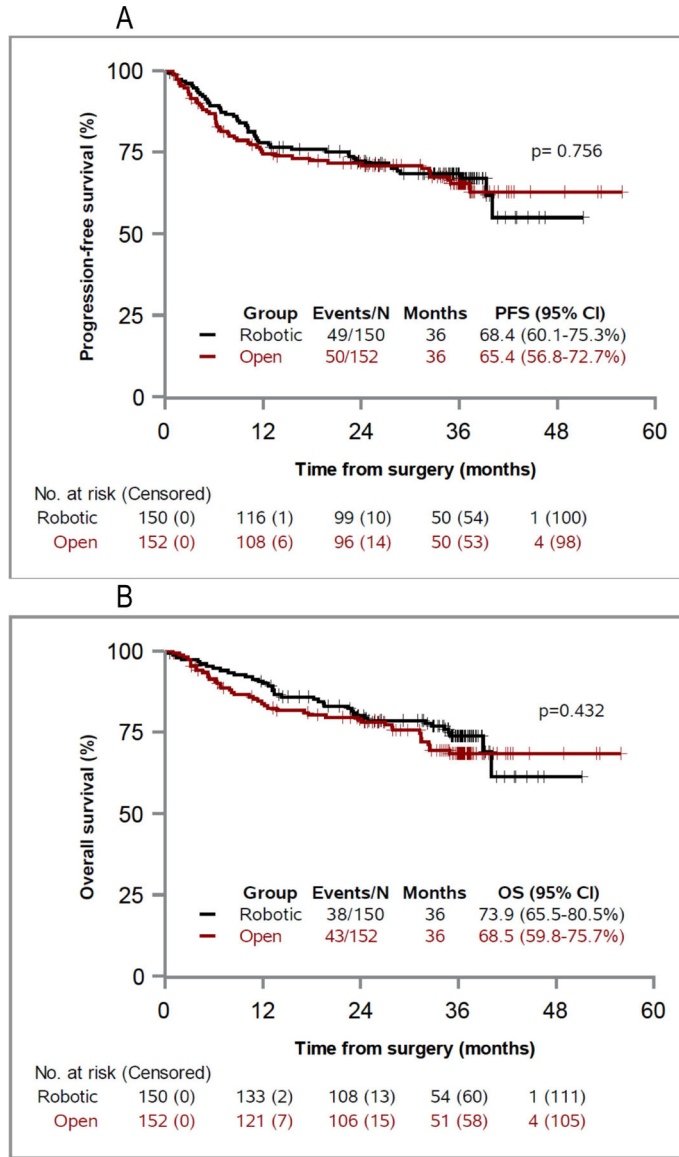


Figure 1. Progression-free survival (A) and overall survival (B) by surgical groups.
 † Tick marker for censored observations.

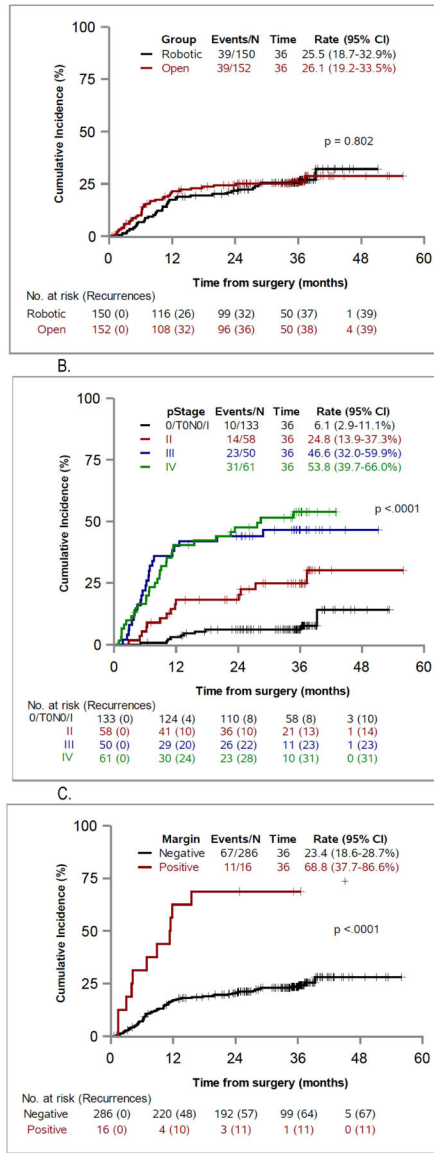


Figure 2. Cumulative incidence of recurrence, taking into account non-cancer death as a competing risk, by surgical group (A), pathological stage (B) and surgical margin (C).

† Tick marker for censored observations.

Table 1.
Deaths and disease recurrence following cystectomy

(Per-protocol population)

Characteristic	Robotic Cystectomy (N=150) n (%)	Open Cystectomy (N=152) n (%)	P
Total events for OS	38 (25.3)	43 (28.3)	0.432 ^a
Death from bladder cancer	28 (18.7)	32 (21.3)	
Non-bladder cancer death	10 (6.7)	11 (7.2)	
Total events for PFS	49 (32.7)	50 (32.9)	0.756 ^a
Any recurrence	39 (26.0)	39 (26.3)	
Non-bladder cancer death	10 (6.7)	11 (7.2)	
Recurrence, alive at last contact	11 (7.3)	7 (4.6)	
Pure local recurrence: Total	6 (4.0)	4 (2.6)	0.541 ^b
Cystectomy bed ¹	6 (4.0)	2 (1.3)	
Pelvic lymphadenectomy template	0	1	
Abdominal wall/Port site	0	1	
Distant recurrence (with or without local): Total	33 (22.0)	35 (23.0)	0.605 ^b
Lung	8	10	
Liver	6	7	
Bone	9	10	
Extrapelvic lymph nodes	9	9	
Peritoneal carcinomatosis	2	1	
Adrenal	2	1	
Colon	-	3	
Small Intestine	1	-	
Kidney	1	-	
Brain	-	1	
Not specified	4		
Secondary Urothelial Ca: Total	1 (0.6)	3 (2.0)	
Upper urinary tract	1	2	
Urethra	0	1	
Censored observations: Total	101 (67.3)	102 (67.1)	
Censored within first 2 years	10 (6.7)	14 (9.2)	
Under follow-up	9	8	
Lost-to-follow-up	1	6	

^aP value from log-rank test for OS and for PFS.

^bP value from Gray's test for local recurrence and for distant recurrence taking into account as competing risks the other site of recurrence and non-bladder cancer death.

Table 2.

Univariable analysis of recurrence, progression-free survival (PFS) and overall survival (OS)

Variable	Total patients (n=302)	Recurrences (n=78)	Non-bladder cancer deaths (n=21)	Total deaths (n=81)	Recurrence [#] SHR (95%CI)	P	PFS [§] HR (95%CI)	P	OS [§] HR (95%CI)	P
Group										
Open	152	39	11	38	1 (Reference)		1 (Reference)		1 (Reference)	
Robotic	150	39	10	43	0.95 (0.61, 1.47)	0.805	0.94 (0.63, 1.39)	0.756	0.84 (0.54, 1.30)	0.432
Urinary diversion procedure										
Neobladder/Continent cut. Res.	67	16	0	11	1 (Reference)		1 (Reference)		1 (Reference)	
Ileal conduit	235	62	21	70	1.16 (0.67, 2.00)	0.591	1.65 (0.97, 2.82)	0.067	2.06 (1.09, 3.89)	0.026
Chemotherapy [¶]										
None	113	32	12	20	1 (Reference)		1 (Reference)		1 (Reference)	
Neoadjuvant only	83	19	4	17	0.78 (0.45, 1.38)	0.396	0.67 (0.40, 1.10)	0.115	0.59 (0.33, 1.06)	0.075
Adjuvant +/- Neoadjuvant	38	21	-	15	2.50 (1.42, 4.40)	0.002	1.66 (0.99, 2.80)	0.056	1.38 (0.77, 2.45)	0.274
Other	68	6	5	10	0.26 (0.11, 0.62)	0.002	0.33 (0.17, 0.65)	0.001	0.37 (0.18, 0.74)	0.005
ECOG PS										
0-1	294	76	18	76	1 (Reference)		1 (Reference)		1 (Reference)	
2-3	8	2	3	5	1.01 (0.24, 4.34)	0.989	2.86 (1.16, 7.04)	0.022	3.44 (1.39, 8.53)	0.008
Age in years										
70	172	41	5	35	1 (Reference)		1 (Reference)		1 (Reference)	
>70	130	37	16	46	1.19 (0.76, 1.85)	0.445	1.61 (1.09, 2.39)	0.018	1.87 (1.20, 2.90)	0.005
Sex										
Men	254	63	18	15	1 (Reference)		1 (Reference)		1 (Reference)	
Women	48	15	3	66	1.42 (0.80, 2.51)	0.229	1.33 (0.80, 2.23)	0.268	1.38 (0.79, 2.42)	0.258
BMI (kg/m ²)										
<25	77	21	5	22	1 (Reference)		1 (Reference)		1 (Reference)	
25-29.9	124	30	10	32	0.79 (0.45, 1.38)	0.405	0.86 (0.53, 1.42)	0.560	0.80 (0.46, 1.37)	0.413

Variable	Total patients (n=302)	Recurrences (n=78)	Non-bladder cancer deaths (n=21)	Total deaths (n=81)	Recurrence [#] SHR (95%CI)	P	PFS [§] HR (95%CI)	P	OS [§] HR (95%CI)	P
30	101	27	6	27	0.93 (0.52, 1.65)	0.795	0.91 (0.54, 1.52)	0.718	0.85 (0.48, 1.49)	0.573
Intraoperative blood loss										
500 ml increase					1.06 (0.87, 1.28)	0.566	1.18 (0.99, 1.41)	0.055	1.26 (1.05, 1.51)	0.014
Blood transfusion										
No	202	50	9	45	1 (Reference)		1 (Reference)		1 (Reference)	
Yes	100	28	12	36	1.22 (0.77, 1.94)	0.388	1.57 (1.05, 2.34)	0.029	1.83 (1.18, 2.84)	0.007
Lymph nodes dissection										
Standard (1 not done)	141	38	14	44	1 (Reference)		1 (Reference)			
Extended	161	40	7	37	0.96 (0.61, 1.48)	0.838	0.78 (0.53, 1.16)	0.229	0.72 (0.47, 1.12)	0.150
Pathological stage										
0/T0N0, I	133	10	10	15	1 (Reference)		1 (Reference)		1 (Reference)	
II	58	14	3	13	3.72 (1.69, 8.21)	0.001	2.35 (1.23, 4.50)	0.009	2.37 (1.13, 4.99)	0.023
III	50	23	1	21	8.46 (4.03, 17.79)	<.0001	4.38 (2.42, 7.94)	<.0001	4.73 (2.44, 9.19)	<.0001
IV	61	31	7	32	9.54 (4.74, 19.17)	<.0001	6.28 (3.65, 10.81)	<.0001	6.66 (3.60, 12.33)	<.0001
Surgical margin status										
Negative	286	67	19	70	1 (Reference)		1 (Reference)		1 (Reference)	
Bladder/Urethral Positive	16	11	2	11	4.49 (2.35, 8.58)	<.0001	5.04 (2.80, 9.10)	<.0001	4.74 (2.50, 9.00)	<.0001
Complications within 90 days										
Grades 0-II	235	60	12	57	1 (Reference)		1 (Reference)		1 (Reference)	
Grades III-V	67	18	9	24	1.12 (0.66, 1.90)	0.672	1.56 (1.00, 2.43)	0.048	1.77 (1.10, 2.86)	0.019

Abbreviation: ECOG Eastern Cooperative Oncology Group Performance Status. SHR: subdistribution hazard ratio. HR: hazard ratio. CI: confidence interval P: two-sided p-value. NA: not applicable.

[#] Univariable Fine-Gray subdistribution hazards model for cumulative incidence of recurrence, with non-bladder cancer death as competing risk.

[§] Univariable Cox proportional hazards model for PFS and OS.

[&] The first three categories under chemotherapy include a total of 234 patients with clinical or pathological stage T2 or above. Of these, 121 received platinum-based chemotherapy (83 neoadjuvant, 31 adjuvant, and 7 both).

The "Other" category includes 68 patients as follows: 57 of stage T1 who did not received chemotherapy, 7 of stage T1 who received chemotherapy, and 4 who received non-platinum-based chemotherapy.

Table 3.

Multivariable analysis for recurrence, progression-free survival and overall survival

Prognostic Factor	Recurrence [#]		Progression-free survival ^{\$}		Overall survival ^{\$}	
	SHR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Surgery group						
Open	1 (Reference)		1 (Reference)		1 (Reference)	
Robotic	0.80 (0.49, 1.31)	0.374	0.74 (0.48, 1.13)	0.161	0.68 (0.43, 1.08)	0.105
Blood transfusion						
No	1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.05 (0.64, 1.72)	0.837	1.17 (0.75, 1.82)	0.484	1.36 (0.83, 2.21)	0.219
Chemotherapy ^{&}						
None	1 (Reference)		1 (Reference)		1 (Reference)	
Neoadjuvant only	1.15 (0.64, 2.07)	0.646	1.02 (0.59, 1.78)	0.936	0.97 (0.52, 1.82)	0.918
Adjuvant +/- Neoadjuvant	1.34 (0.63, 2.85)	0.451	0.83 (0.43, 1.59)	0.574	0.74 (0.37, 1.47)	0.388
Other	0.82 (0.29, 2.29)	0.705	0.76 (0.34, 1.70)	0.510	1.00 (0.42, 2.37)	0.995
Age in years						
70	--		1 (Reference)		1 (Reference)	
>70	--		1.62 (1.06, 2.76)	0.027	1.99 (1.22, 3.25)	0.006
ECOG performance status						
0-1	--		1 (Reference)		1 (Reference)	
2-3	--		3.32 (1.22, 9.08)	0.019	3.67 (1.33, 10.15)	0.012
Pathologic stage ^a						
NRD, 0a/0is, I	1 (Reference)		1 (Reference)		1 (Reference)	
II	3.19 (1.28, 7.97)	0.013	2.30 (1.09, 4.84)	0.028	2.70 (1.14, 6.44)	0.025
III	7.10 (2.87, 17.61)	<.0001	3.67 (1.84, 7.31)	0.0002	4.36 (1.97, 9.62)	0.0003
IV	7.11 (2.63, 19.23)	0.0001	5.80 (2.90, 11.59)	<.0001	7.21 (3.27, 15.87)	<.0001
Surgical margin status						
Negative	1 (Reference)		1 (Reference)		1 (Reference)	
Bladder/Urethral Positive	2.66 (1.32, 5.37)	0.006	3.41 (1.77, 6.56)	0.0002	3.43 (1.71, 6.90)	0.0005
Surgical complication within 90 days						
Grades 0-II	--		1 (Reference)		1 (Reference)	
Grades III-V	--		1.71 (1.06, 2.76)	0.027	1.84 (1.10, 3.09)	0.021
Institution (random effects):						
	--		NA	0.152	NA	0.180

Abbreviation: ECOG Eastern Cooperative Oncology Group Performance Status. SHR: sub-distribution hazard ratio. HR: hazard ratio. CI: confidence interval P: two-sided p-value. NA: not applicable.

[&]The first three categories under chemotherapy include a total of 234 patients with clinical or pathological stage T2 or above. Of these, 121 received platinum-based chemotherapy (83 neoadjuvant, 31 adjuvant, and 7 both). The "Other" category includes 68 patients as follows: 57 of stage T1 who did not received chemotherapy, 7 of stage T1 who received chemotherapy, and 4 who received non-platinum-based chemotherapy.

[#]Multivariable Fine-Gray subdistribution hazards model for cumulative incidence of recurrence, with non-bladder cancer death as competing risk.

^{\$}Multivariable shared-frailty Cox proportional hazards model for progression-free survival and overall survival, including shared frailty site-specific terms as random effects following a gamma distribution to account for institutional differences.

Note: The final multivariate model included arm, intraoperative blood loss, chemotherapy, and additional variables with $p < 0.05$. Type of urinary diversion procedure (which was a significant predictor of OS on univariate analysis) was tested for inclusion in the multivariable models, individually and jointly, but was finally excluded as it was not a statistically significant predictor of any of the three outcomes ($p > 0.05$).

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