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Incidence and risk factors for peritoneal carcinomatosis following open radical cystectomy

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Abstract

Objective: To characterize the frequency and risk factors of peritoneal carcinomatosis (PC) in patients undergoing open radical cystectomy (RC).

Methods: We identified 3,285 patients with urothelial carcinoma treated with RC for curative intent between 1980 and 2016. At last follow-up, 72.1% (2,370/3,285) of patients had died, with a median follow-up of 8.6 years (Interquartile Range, (IQR) 3.7, 14.1). PC was defined as any recurrence involving the omentum, small bowel, and mesentery. Overall-specific survival (OSS) and cancer-specific survival (CSS) was evaluated using Kaplan-Meier methodology and log-rank test. Risk factors for mortality and recurrence were performed using Cox proportional hazards regression models.

Results: One hundred and twenty nine (3.9%) patients were diagnosed with PC, while a total of 1,148 (34.9%) patients experienced recurrence at other sites. Median time to PC vs. other-site recurrence was 1.3 (IQR 1.3, 2.3) and 0.9 (IQR 0.5, 2.1) years, respectively (P= 0.04). Only increasing pathologic stage on multivariable analysis was associated with developing PC (pT1 HR 2.51, 95CI 1.14–5.55, P= 0.02; pT2 OR 2.82, 95CI 1.47–5.43, P= 0.002; pT3+ 2.40, 95CI 1.31–4.42, P= 0.005) over other recurrence patterns. Nodal status and tumor margin status were not associated. Patients with PC experienced worse OSS and CSS than other types of recurrence (P< 0.001).

Conclusion: PC was identified in almost 4% of patients undergoing open RC. PC is a rare occurrence after RC and primarily impacts patients with locally advanced disease.

Keywords: Urothelial Carcinoma; Peritoneal Carcinomatosis; Open Cystectomy; Outcomes; Recurrence

Key of Definitions of Abbreviations: PC, Peritoneal Carcinomatosis; RC, Radical Cystectomy; IQR, Interquartile Range; ECOG, Eastern Cooperative Oncology Group; BMI, Body mass index; CIs, Confidence intervals

1. Introduction

In 2019, 80,470 cases of bladder cancer are expected to be diagnosed in the United States [1]. While open radical cystectomy (RC) is the gold standard surgical treatment for nonmetastatic invasive bladder cancer, advances in minimally invasive surgery have spurred increased adoption of robotic RC [2]. However, with the advent of a new surgical technique, comparisons to the established approach are necessary.

Early investigation of open vs. robotic RC has demonstrated comparable results [3–5]. However, with the addition of pneumoperitoneum and multiple port sites, there is increased scrutiny over the frequency of atypical recurrences, particularly peritoneal carcinomatosis (PC) [6–8]. While Nguyen et al. found PC to occur more frequently in their robotic RC group, surgical technique was not a risk factor for developing PC. Nevertheless, the implication of inferior oncologic results has heightened the urological community's awareness of PC following RC given its poor prognosis [9].

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Although there has been significant amount of research into oncologic outcomes following RC, there is a paucity of studies looking at rates of PC in bladder cancer [6,9]. As such, we sought to characterize the frequency and risk factors of PC in open RC patients in our institutional cystectomy registry.

2. Materials and Methods

2.1. Patient Selection

Following Institutional Review Board approval, we queried the Mayo Clinic Cystectomy Registry to identify 3,285 patients treated with open RC for curative intent between 1980 and 2016. Patients with metastatic disease prior to or diagnosed at time of surgery were excluded.

2.2. Clinicopathologic Features

Clinical features included age at surgery, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status at surgery, body mass index at surgery, and history of pelvic radiation. Perioperative features included receipt of blood transfusion. Pathologic features included the primary tumor TNM stage, grade, lymphovascular invasion, and surgical margin status. One genitourinary pathologist (J.C.C.) reviewed the microscopic slides at time of procedure from all specimens without knowledge of patient outcome.

2.3. Peritoneal carcinomatosis

PC was defined as any recurrence, identified surgically or radiographically, involving the omentum, small bowel, and mesentery. Patients with PC and non-PC recurrence were categorized as PC patients. Abdominal recurrences in the liver, pancreas, and spleen were considered metastatic disease, whereas abdominal recurrences involving the rectum and deep pelvis were considered local recurrences. Recurrences not including PC were defined as "other" recurrences for analyses.

2.4. Mortality

Vital status for patients in our Cystectomy Registry is updated each year. If a patient has died in the previous year, a death certificate is ordered to determine the cause of death. Patients with a visit to our institution for metastatic bladder cancer within 6 months of death were considered to have died from bladder cancer. If the death certificate does not support this, the medical history is reviewed by a urologist to determine cause of death. If a death certificate cannot be obtained, cause of death is verified with the patient's family or local physician. If death certificate reports cancer death but on review of the chart there is no evidence of recurrence, patients are reported as a bladder cancer death, but are not considered a disease recurrence.

2.5. Statistical Methods

Continuous features were summarized with medians, interquartile ranges (IQRs), and ranges; categorical features were summarized with frequency counts and percentages. Overall and cancer-specific survival was estimated using the Kaplan-Meier method with the duration of follow-up calculated from the date of surgery to the date of death or last follow-up. Associations of clinicopathologic features with death from any causes, death from bladder cancer, and cancer recurrence were evaluated using Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals. Age, ECOG status, body mass index, and number of lymph nodes dissected were treated as continuous variables with the remainder treated as categorical variables. Statistical analyses were performed using version 9.4 of the SAS software package (SAS Institute Inc.; Cary, NC). All tests were 2-sided and P values <0.05 were considered statistically significant.

3. Results

Between 1980 and 2016, 3,285 patients underwent open RC for curative intent at our institution. Patient characteristics are reported in Table 1. Recurrence was documented in 1,277 (38.9%) patients, with 129 (3.9%) developing PC. Median time to other recurrence was 11 months (IQR 6–26) while the median time to PC was 16 months after cystectomy (IQR 7–28). At last follow-up, 72.1% (2,370/3,285) of patients had died, with a median follow-up of 8.6 years (IQR 3.7, 14.1). Cancer death occurred in 30.3% of patients (998/3,285).

Factors associated with all cancer recurrences under multivariate analysis include worsening tumor and nodal stage (Table 2). Receipt of neoadjuvant chemotherapy and decision for an incontinent diversion was additionally associated, whereas worsening ECOG status and number of nodes dissected during lymphadenectomy were protective. Subset analysis comparing PC to all other recurrence subtypes found increasing pathologic stage to be the only factor associated with peritoneal recurrence (Table 3). Prior pelvic radiation, lymph node status, use of chemotherapy, or positive tumor margin was not associated with PC.

Overall and cancer-specific mortality are seen in Fig. 1 and 2. At 5 years after cystectomy, patients with no recurrence, nonperitoneal recurrence, and peritoneal recurrence had an overall survival of 76.5%, 41.6, and 10.9%, respectively ($P< 0.001$). Additionally, 5-year cancer specific survival was 88.7%, 30.9%, and 11.3%, respectively ($P< 0.001$).

Risk factors for overall mortality are summarized in Table 4. Factors associated with cancer specific mortality on multivariate analysis include increasing age, worsening

Table 1
Clinical and pathological characteristics of patients undergoing radical cystectomy.

	No Recurrence (N = 2008)	Nonperitoneal (N = 1148)	Peritoneal (N = 129)	*P* value
Age at surgery median (IQR)	68.7 (62.0, 75.4)	68.7 (61.3, 74.7)	65.9 (60.4, 73.3)	0.174
Sex Male	1631 (81.2%)	935 (81.4%)	102 (79.1%)	0.8068
ECOG performance status (N = 1963:1133: 127)				0.0029
0	1568 (79.9%)	899 (79.3%)	107 (84.3%)	
1	289 (14.7%)	183 (16.2%)	13 (10.2%)	
2	80 (4.1%)	44 (3.9%)	5(3.9%)	
3	24 (1.2%)	5 (0.4%)	0 (0.0%)	
4	2 (0.1%)	2 (0.2%)	2 (1.6%)	
Smoking history Yes	1556 (77.5%)	902 (78.6%)	96 (74.4%)	0.5082
BMI median (IQR) (N = 1965:1132:129)	27.3 (24.6, 30.4)	27.1 (24.4, 30.0)	26.9 (24.3, 30.6)	0.4816
Prior pelvic radiation for cancer	52 (2.6%)	35 (3.0%)	3 (2.3%)	0.7174
Diversion				0.0072
Continent diversion	503 (25.0%)	236 (20.6%)	24 (18.6%)	
Incontinent diversion	1505 (75.0%)	912 (79.4%)	105 (81.4%)	
Pathologic stage				<0.0001
pTa/Tis/T0	885 (44.1%)	312 (27.2%)	16 (12.4%)	
pT1	224 (11.2%)	93 (8.1%)	12 (9.3%)	
pT2	338 (16.8%)	196 (17.1%)	29 (22.5%)	
pT3+	561 (27.9%)	547 (47.6%)	72 (55.8%)	
Neo adj chemo	146 (7.3%)	120 (10.5%)	20 (15.5%)	0.0002
Adjuvant chemo	152 (7.6%)	158 (13.8%)	20 (15.5%)	<0.0001
Node stage				<0.0001
NX	189(9.4%)	115 (10.0%)	15 (11.6%)	
N0	1586(79.0%)	760 (66.2%)	80 (62.0%)	
N1	94(4.7%)	111 (9.7%)	9 (7.0%)	
N2	97(4.8%)	112 (9.8%)	16 (12.4%)	
N3	42(2.1%)	50 (4.4%)	9 (7.0%)	
# of lymph nodes Mean (SD)	15.3(11.3)	14.2 (11.2)	14.7 (11.9)	0.016
Blood transfusion	1192(59.4%)	724 (63.1%)	81 (62.8%)	0.1092
OR time (total minutes) mean (SD) (N = 1449:868:98)	307.3(96.8)	310.9 (88.4)	294.7 (71.6)	0.1513
Time to Last FU (years) Median (IQR)	6.8 (2.2-12.9)	2.2 (1.0, 4.9)	1.8 (0.9, 2.9)	<0.0001
WHO primary tumor grade (N = 1190,864,114)				0.0698
Low	372(31.3%)	234 (27.1%)	39 (34.2%)	
High	818(68.7%)	630 (72.9%)	75 (65.8%)	
Lymphovascular Invasion	262(13.0%)	266 (23.2%)	38 (29.5%)	<0.0001
Positive tumor margin	31(1.5%)	33 (2.9%)	7 (5.4%)	0.0016
Time to recurrence (y)		0.9 (0.5, 2.1)	1.3 (0.6, 2.3)	<0.0001
Overall mortality	1202 (59.9%)	1039 (90.5%)	129 (100.0%)	<0.0001
Cancer specific mortality	225 (11.2%)	874 (76.1%)	124 (96.1%)	<0.0001

ECOG status, pathologic tumor and lymph node stage, lymphovascular invasion, perioperative blood transfusion, receipt of neoadjuvant chemotherapy, and cancer recurrence (Table 4). Development of PC was associated with cancer specific mortality with a hazard ratio of 11.4 ($P< 0.0001$) (Table 5). Receipt of adjuvant chemotherapy and prior pelvic radiation was protective.

4. Discussion

Open radical cystectomy is the gold standard for treatment of muscle invasive bladder cancer. However, as urologists adopt minimally invasive techniques, ensuring comparable outcomes is necessary. Recently, there has been increasing discussion on whether pneumoperitoneum and the surgical technique of minimally invasive surgery may increase rates of PC [6,7]. While outcomes following open RC have been extensively reported, little has been studied on rates of PC [7,9–11]. Herein we report our recurrence outcomes following open RC in a tertiary referral center.

Historical reports on PC in patients with urothelial carcinoma of the bladder have been limited to those presenting with metastases following heterogeneous treatment modalities [10,11]. To our knowledge, reports on rates of PC following open RC are limited to within the last few years. Moschini et al. reported their experience with recurrences following open RC in patients treated from 1992 to 2012. Of their 1,110 patients treated during the study period, only 7 patients (0.6%) developed PC without any other recurrence. Although they did not further describe those patients with multiple metastases, an additional 124 (11%)

Table 2
Multivariate risk factors for urothelial recurrence following radical cystectomy.

Variable	*P* value	HR	95% of HR	
Age at surgery*	0.052	0.99	0.98	1.00
ECOG performance status*	0.035	0.87	0.76	0.99
Smoker ever	0.41	1.08	0.90	1.29
BMI*	0.79	1.00	0.98	1.01
Diversion				
Continent	Reference			
Incontinent	0.031	1.24	1.02	1.50
Pathologic stage				
pTa/Tis/T0	Reference			
pT1	0.099	1.25	0.96	1.64
pT2	<0.0001	1.67	1.34	2.08
pT3+	<0.0001	2.39	1.96	2.92
Nodal stage				
pN0	Reference			
pN1	0.0007	1.70	1.26	2.31
pN2	0.006	1.56	1.14	2.13
pN3	0.019	1.72	1.09	2.70
pNX	0.93	1.01	0.77	1.34
Neoadjuvant chemotherapy	0.0006	1.58	1.22	2.04
Adjuvant chemotherapy	0.37	1.13	0.86	1.49
Number of total lymph nodes dissected*	0.004	0.99	0.98	1.00
Lymphovascular Invasion	0.12	1.18	0.96	1.46
Positive tumor margin	0.86	1.04	0.64	1.71
Blood transfusion	0.45	1.06	0.91	1.24
Prior pelvic radiation	0.64	1.11	0.71	1.75

* Hazards ratio and CI represent a 1-unit increase in the feature listed.

Table 3
Multivariate risk factors for peritoneal recurrence compared to other recurrence subtypes (subgroup analysis).

Variable	P value	HR	95% of HR	
Age at surgery*	0.15	0.99	0.97	1.00
ECOG performance status*	0.67	0.93	0.66	1.31
Smoker ever	0.28	0.79	0.51	1.21
BMI*	0.91	1.00	0.96	1.04
Diversion				
Continent	Reference			
Incontinent	0.36	1.28	0.76	2.13
Pathologic stage				
pTa/Tis/T0	Reference			
pT1	0.026	2.46	1.11	5.42
pT2	0.001	2.91	1.52	5.59
pT3+	0.003	2.50	1.36	4.58
Nodal stage				
pN0	Reference			
pN1	0.27	0.66	0.31	1.38
pN2	0.88	1.05	0.55	2.03
pN3	0.61	1.25	0.54	2.89
pNX	0.45	1.30	0.66	2.54
Neoadjuvant chemotherapy	0.19	1.43	0.84	2.44
Adjuvant chemotherapy	0.75	0.91	0.50	1.64
Number of total lymph nodes dissected*	0.80	1.00	0.98	1.02
Lymphovascular invasion	0.70	1.09	0.70	1.70
Positive tumor margin	0.24	1.69	0.70	4.07
Blood transfusion	0.52	0.89	0.59	1.31
Prior pelvic radiation	0.57	0.70	0.20	2.40

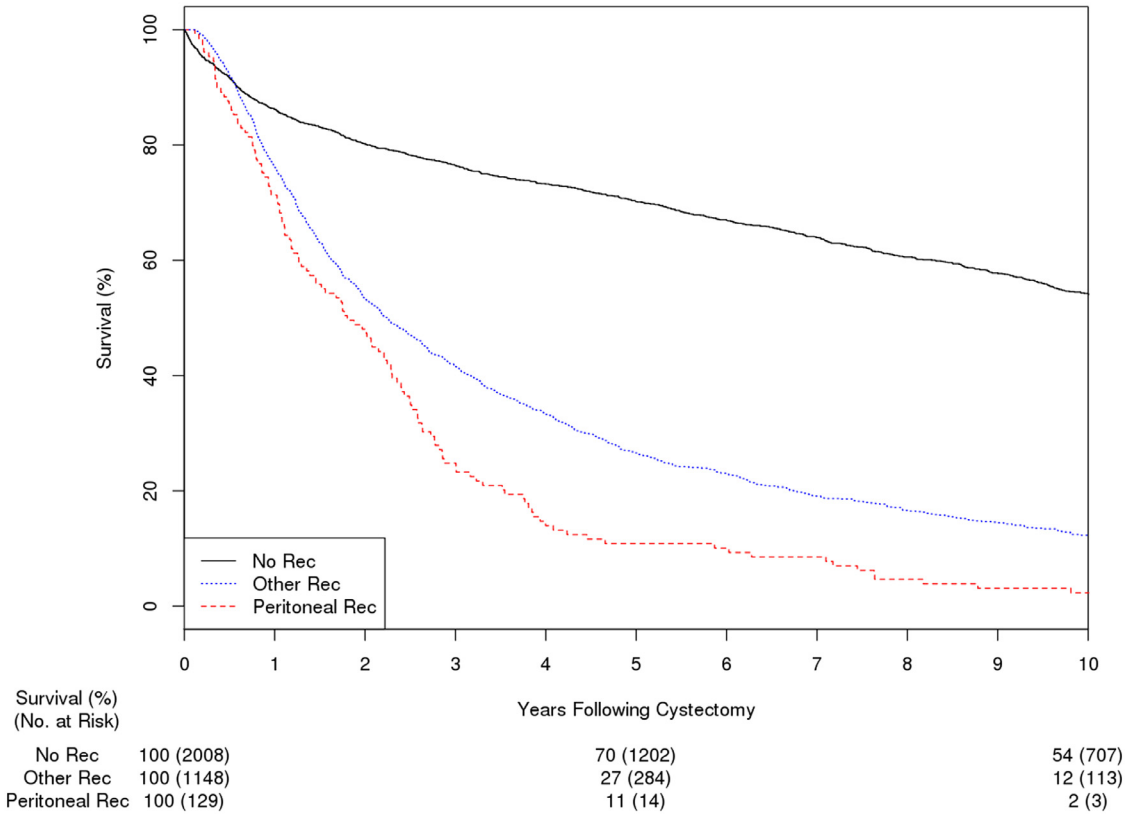
* Hazards ratio and CI represent a 1-unit increase in the feature listed.

had multiple recurrences with a median follow-up of 7.5 years [9]. Nguyen et al. compared recurrence patterns of robotic vs. open RC and demonstrated PC to occur in 3.4% (9/263) and 1.7% (2/120) respectively with a median follow-up of 2.5 years [7]. Additionally, new studies of robotic RC outcomes report PC rates ranging from 0.7% to 5.5% with median follow-ups of 2 to 3.5 years [7,12–14]. Our experience with open RC from 1980 to 2016 demonstrated a 3.9% rate of PC. While our rate of PC is higher than those seen in the open RC studies by Moschini and Nguyen, we present the largest report on PC following open RC with the longest median follow-up of 8.6 years.

Rates of overall tumor recurrence following RC have been reported between 21% and 44% [15,16]. In our study, 38.9% developed a recurrence at a median time of 11 months. Risk factors for cancer recurrence included increasing pathologic tumor and nodal staging, receipt of neoadjuvant chemotherapy and use of an incontinent diversion. While neoadjuvant chemotherapy has been shown to improve disease survival and diversion technique should intuitively not affect recurrence risk, these variables highlight that there is some treatment selection bias that remains unaccounted for [17].

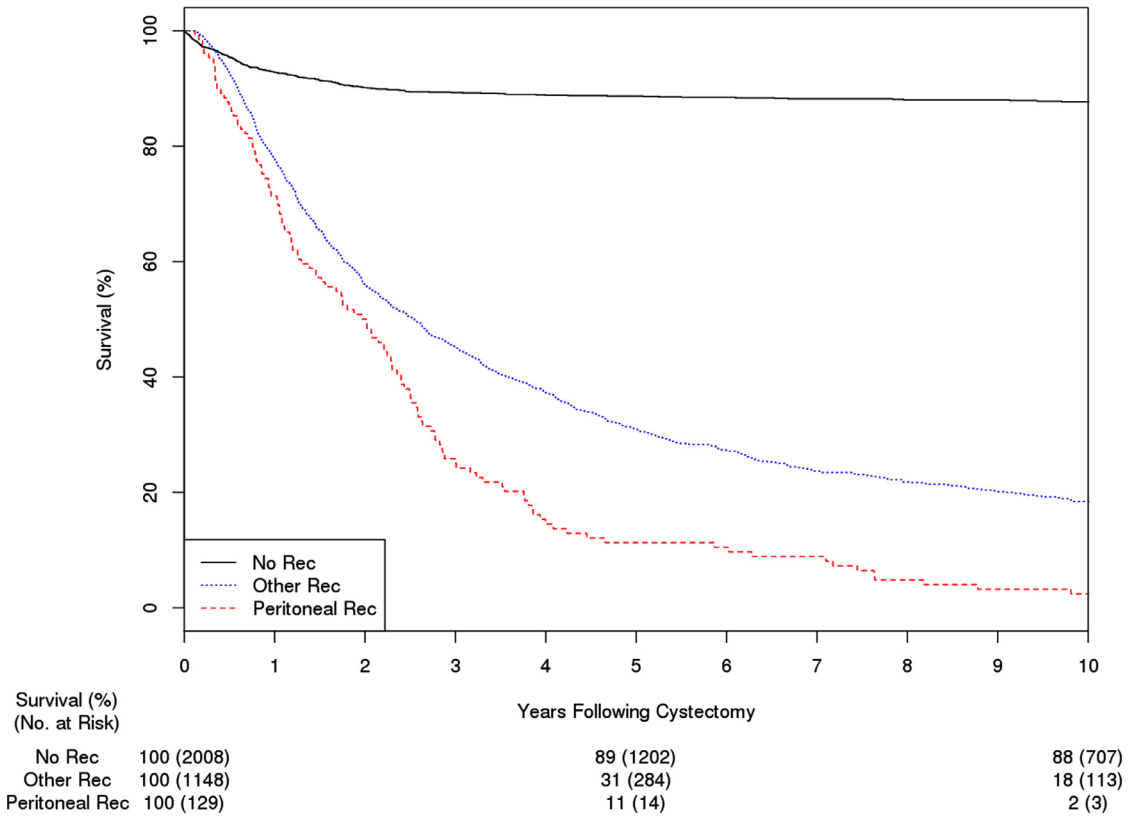
In contrast, increasing number of nodes dissected during lymphadenectomy and worsening ECOG status was protective. These findings are similar to those seen in previous reports and highlight the importance of an adequate node dissection during lymphadenectomy [6,15,18,19]. Previous studies have demonstrated that poor comorbidity status leads to an increased risk of perioperative and all-cause mortality [20]. As such, in our patients, poor ECOG status was found to be protective of disease recurrence likely due to the patients' increased risk of death from other causes prior to metastasis." Interestingly, positive tumor margins were not associated with recurrence in our multivariate analysis. This likely is the result of a relatively small number of patients found with positive margins (71/3,285 or 2.1%) along with some colinearity found with increasing tumor stage.

In our subset analysis, we sought to evaluate risk factors for developing PC over other recurrence patterns. When controlling for clinicopathologic features, only increasing tumor stage was statistically significant. Neither positive nodal status nor positive margins was associated with development of PC. Nguyen et al. reported similar findings when studying features associated with distant and atypical (PC and extrapelvic lymph node) metastases [6]. They reported that pathologic stage, presence of lymphovascular invasion, chronic kidney disease, and perioperative blood transfusion were associated. Additionally, previous abdominopelvic surgery was protective. OR time, as a surrogate for pneumoperitoneum



Survival (%) (No. at Risk)			
No Rec	100 (2008)	70 (1202)	54 (707)
Other Rec	100 (1148)	27 (284)	12 (113)
Peritoneal Rec	100 (129)	11 (14)	2 (3)

Fig. 1. Overall survival stratified by recurrence pattern following open radical cystectomy.



Survival (%) (No. at Risk)			
No Rec	100 (2008)	89 (1202)	88 (707)
Other Rec	100 (1148)	31 (284)	18 (113)
Peritoneal Rec	100 (129)	11 (14)	2 (3)

Fig. 2. Cancer specific survival stratified by recurrence pattern following open radical cystectomy.

Table 4
Multivariate risk factors for overall mortality following radical cystectomy.

Variable	P value	HR	95% CI of HR	
Age at surgery*	<0.0001	1.04	1.03	1.04
ECOG performance status*	<0.0001	1.38	1.30	1.47
Smoker ever	<0.0001	1.26	1.14	1.40
BMI*	0.77	1.00	0.99	1.01
Diversion				
Continent	Reference			
Incontinent	0.15	1.10	0.97	1.23
Pathologic stage				
pTa/Tis/T0	Reference			
pT1	0.18	1.11	0.95	1.29
pT2	<0.0001	1.41	1.24	1.60
pT3+	<0.0001	2.18	1.95	2.43
Nodal stage				
pN0	Reference			
pN1	0.003	1.30	1.09	1.54
pN2	<0.0001	1.84	1.56	2.19
pN3	<0.0001	2.52	1.94	3.26
pNX	<0.0001	1.52	1.31	1.77
Neoadjuvant chemotherapy	<0.0001	1.52	1.31	1.76
Adjuvant chemotherapy	0.0005	0.75	0.64	0.88
Number of total lymph nodes dissected*	0.059	1.00	0.99	1.000
Lymphovascular invasion	0.046	1.12	1.00	1.26
Positive tumor margin	0.18	1.19	0.92	1.53
Blood transfusion	<.0001	1.27	1.16	1.38
Prior pelvic radiation	0.41	0.91	0.73	1.14
Recurrence				
None	Reference			
Nonperitoneal	<0.0001	2.66	2.43	2.91
Peritoneal	<0.0001	3.75	3.09	4.54

* Odds ratio and CI represent a 1-unit increase in the feature listed.

Table 5
Multivariate risk factors for cancer specific mortality following radical cystectomy.

Variable	*P* value	HR	95% CI of HR	
Age at surgery*	<0.0001	1.01	1.01	1.02
ECOG performance status*	<0.0001	1.25	1.14	1.36
Smoker ever	0.19	1.10	0.95	1.26
BMI*	0.28	0.99	0.98	1.00
Diversion				
Continent	Reference			
Incontinent	0.14	1.13	0.96	1.32
Pathologic stage				
pTa/Tis/T0	Reference			
pT1	0.49	1.09	0.85	1.41
pT2	<0.0001	1.79	1.48	2.17
pT3+	<0.0001	3.11	2.64	3.68
Nodal stage				
pN0	Reference			
pN1	0.043	1.24	1.01	1.54
pN2	<0.0001	1.85	1.51	2.26
pN3	<0.0001	2.25	1.68	3.01
pNX	<0.0001	1.67	1.36	2.04
Neoadjuvant chemotherapy	<0.0001	1.77	1.48	2.10
Adjuvant chemotherapy	0.007	0.77	0.64	0.93
Number of total lymph nodes dissected*	0.44	1.00	0.99	1.00
Lymphovascular invasion	0.017	1.19	1.03	1.37
Positive tumor margin	0.28	1.18	0.88	1.58
Blood transfusion	0.0001	1.28	1.13	1.44
Prior pelvic radiation	0.003	0.56	0.38	0.82
Recurrence				
None	Reference			
Nonperitoneal	<0.0001	8.74	7.50	10.18
Peritoneal	<0.0001	11.43	9.06	14.42

* Odds ratio and CI represent a 1-unit increase in the feature listed.

exposure was not associated with distant or atypical metastases.

Overall and cancer specific survival was found to be significantly worse in patients with PC. While the majority (76.1%) of patients with all other forms of cancer recurrence die secondary to their malignancy, development of PC is a particularly ominous oncologic sign with a 5-year cancer specific survival of 10.9%. While this finding is consistent with natural progression of PC, we present the only report on survival in patients with PC following open RC.

There are multiple limitations to our study. First, this is a retrospective study at a tertiary referral center, and therefore the outcomes may not be applicable to all patients. In addition, many of the patients treated at our facility undergo transurethral resection by outside providers, and therefore we lack the ability to track potential bladder perforations. Although this likely represents a rare event, previous reports have implicated both intravesical and extravesical perforations as potential risk factors for disease spread [21]. Nevertheless, we believe our findings further our understanding of cancer recurrence following RC.

5. Conclusions

PC was identified in almost 4% of patients undergoing open RC. While PC is a rare occurrence after RC, patients with locally advanced disease are at an increased risk of developing this recurrence pattern with a poor prognosis.

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