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Partial Cystectomy for Pure and Variant Urothelial Carcinoma

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ABSTRACT

Purpose: Evaluation of outcomes for those who undergo partial cystectomy (PC) for the management of select patients with bladder cancer (BC).

Materials and Methods: We performed a retrospective review of consecutive open PCs with lymph node dissection performed by a single surgeon between 2000 and 2018 for BC. Patients were identified via the surgeon's documented case logs. Patients had either a cT2 solitary tumor (N=35), a high-grade (HG) tumor in a diverticulum (N=8), or a HG solitary cT1 lesion concerning for more advanced disease (N=10).

Results: 53 patients had primary urothelial carcinoma (UC), including 18 with variant UC histologies on pre-operative biopsy. Patients had an average of 55 months (range 2-188 months) of follow-up. 37 were male (70%). The median age at the time of PC was 71 years (range 48-90). Pathology specimens at PC revealed 19 as pT0, 9 as pTis-pT1, 6 as pT2 and 19 as pT3. 7 patients died from metastatic BC (1 with pT0 and 6 with pT3 pathology at PC); none had an intravesical recurrence. 12 patients had intravesical recurrences of UC (23%), 11 of whom had a non-MI recurrence managed endoscopically and with intravesical therapies. The 5-year cumulative incidence of BC specific deaths by pathologic stage was: 8% (95% CI 0.4-32.8%) for pT0, 0% for pTis-pT1, 0% for pT2, and 32% (95% CI 12.4-52.9%) for pT3. BC specific death was not significantly changed by the presence of variant UC on pre-operative biopsy.

Conclusion: PC appears to provide oncologically acceptable outcomes in patients who present with solitary UC lesions with pure or variant histologies with tumors amenable to PC.

Keywords: Bladder Cancer; Partial Cystectomy; Cancer Survivor; Surveillance; Urinary Bladder Neoplasms

Introduction

Bladder cancer (BC) is the 6th most commonly diagnosed non-cutaneous malignancy in the United States representing 4.5% of new cancer cases. [1] In 2021, there were an estimated 83,730 new BC cases and 17,200 deaths due to BC.1 Approximately 25% of those new cases were muscle invasive or more advanced. Radical cystectomy (RC) is the gold standard for treating localized muscle invasive BC (MIBC). However, RC is associated with significant immediate morbidity and mortality with an approximate 25.5% readmission rate and 4.8% mortality rate within 90 days after surgery. [2] Long-term complications of RC are also significant, including decreased quality of life (QoL), increased risks of urinary tract infections and decline in renal function. [3]

Bladder preserving therapy for MIBC is favored by some patients because of the risks of complications and decreased QoL after RC. For patients who are unwilling or unable to undergo RC due to significant co-morbidities, the most widely accepted alternative treatment is trimodal therapy (TMT); which includes chemoradiation with maximal transurethral resection of bladder tumors (TURBT). [4] Of those who choose TMT, approximately 20-30% will ultimately undergo RC. [5]

A third option for some patients with MIBC is partial cystectomy (PC). Advantages of PC include complete bladder and nodal staging, the ability for patients to maintain normal voiding without the need for bowel manipulation, and no adverse impact on sexual or renal function.

Regardless of these advantages, PC has remained a controversial procedure due to concerns over oncologic control. However, some retrospective series have suggested that when patients are carefully selected, PC offers acceptable oncologic outcomes.[6,7,8,9] Despite these results, the AUA guidelines do not recommend PC except for those who are medically unfit or unwilling to undergo RC and decline or are not eligible for TMT.[10] Further confounding the matter is that many patients with MIBC are not candidates for PC as trigonal location of a tumor, multiple tumors within the bladder, and the presence of carcinoma *in situ* (CIS) are contraindications. It is also unknown if those with variant histologies have better oncologic outcomes with RC. While there are no randomized trials comparing RC to PC in PC eligible patients, our hypothesis is that carefully selected patients who undergo PC may have at least equivalent oncologic outcomes to those who undergo RC.

This paper retrospectively reviews the clinical outcomes of a consecutive, single-surgeon series of patients who underwent open PC for high-grade (HG) with pure or variant urothelial carcinomas (UCs).

Methods

A protocol for retrospective review of PC cases was approved by the Institutional Review Board at the University of Rochester.

All patients who underwent open PC for UC at the University of Rochester performed by EM as the primary surgeon from December 2000 through May 2018 were reviewed. Patients were excluded from this review if they underwent PC for non-urothelial cancer, particularly urachal adenocarcinomas. Patients in this review who underwent PC were either not medically appropriate for RC or did not want to accept the risks and morbidities associated with RC.

Prior to PC, all patients with cT2 or more advanced tumors were referred to medical oncology and received neoadjuvant chemotherapy (NAC) if deemed medically suitable for chemotherapy.

Patients who underwent PC had either a known or suspected solitary MIBC lesion, or had HG UC within a diverticulum that was not amenable to endoscopic ablation. 'Suspected' cases of MIBC included patients with new onset hydroureteronephrosis and a HG, invasive (at least T1) UC at or near the ipsilateral ureteral orifice.

Prior to PC, all patients underwent a repeat TURBT which included several remote biopsies of normal appearing urothelium to ensure that CIS was not present distant from the solitary lesion. Biopsies were also taken surrounding the solitary lesion to ensure that cancer was not present in the endoscopically normal appearing field surrounding the tumor site. Patients were ineligible for PC if any cancer or CIS was detected distant to the primary lesion.

At the time of PC, care was taken to ensure that the lesion was completely excised. An experienced genitourinary pathologist was requested to be available during the case. After the lesion was excised *en bloc*, with the goal of a 1-2 cm margin, differently colored sutures were placed into each octant of the surgical margin with a matching colored suture placed into the corresponding octant of the surgical specimen to allow for easy margin localization. The specimen was then sent to pathology for frozen sections of the margins. The cystotomy was not closed until negative margins were histologically confirmed.

All patients who underwent PC, also underwent a standard or extended bilateral pelvic lymph node dissection.

All patients had post-operative surveillance with imaging (CT of abdomen and pelvis and chest x-ray or CT every 6 months for 5 years after surgery) and cystoscopy with cytology (every 3 months for 2 years, semiannually for 2 years and then annually thereafter if no recurrence).

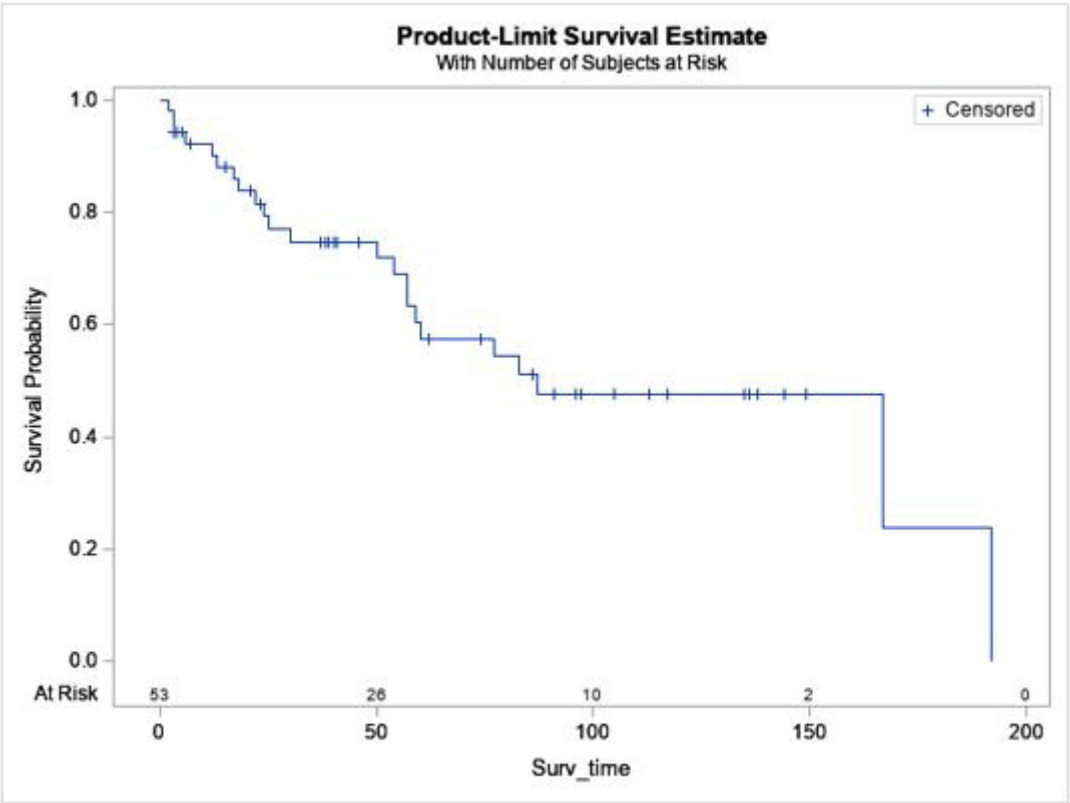
Kaplan-Meier curves were generated for overall survival (OS) and intravesicaThere were 2 patients who underwent salvage cystectomy; both patients had pT1 disease at the time of PC. One patient had a cT2 recurrence and the other had an positive margin on frozen section that was unrecognized at the time of PC.

Variable	Categorical			Continuous	
	N		%	N	Median (range)
Gender	53				
Female	16		30.2		
Male	37		69.8		
Age at PC				53	71 (48-90)
Patients with ASA score available	30		56.6		
ASA score 1-2	8		26.7		
ASA scores > 2	22		73.3		
Length of stay (LOS)				51	5 (2-170)
30-day Readmissions	49				
Yes	4		8.2		
No	45		91.8		
Stage at PC	53				
pT0	19		35.9		
pTis-pT1	9		17.0		
pT2	6		11.3		
pT3	19		35.9		
Clinical stage transition	53				
cT1 prior to PC	16		30.2		
Patient with cT1 prior to PC but pT2 or greater from surgical specimen	7				
cT2 Prior to PC	35		66.0		
Patient with cT2 prior to PC but less than pT2 from surgical specimen (pT0-pT1)	19		54.3		
Patient with cT2 prior to PC but pT0 from surgical specimen	17		48.6		
Neoadjuvant Chemotherapy (NAC) for cT2 disease	8				
pT0	5		62.5		
pTis-pT1	0		0		
pT2	2		25.0		
pT3	1		12.5		
Diverticulectomy	8				

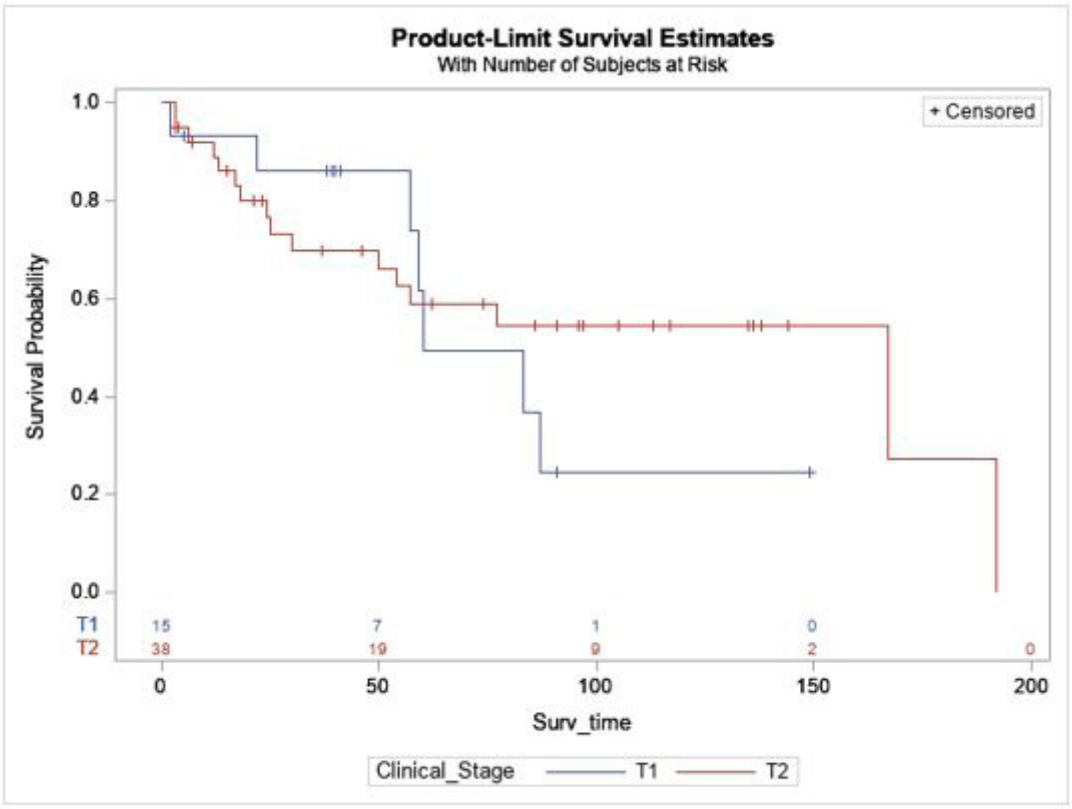
	pT0	0		0		
	pTis-pT1	4		50.0		
	pT2	0		0		
	pT3	4		50.0		
Ureteral Reimplant		25				
	pT0	7		28.0		
	pTis-pT1	3		12.0		
	pT2	4		16.0		
	pT3	11		44.0		
Patients with Variant Histology on Pre-PC TURBT		18				
	pT0	8		44.4		
	pTis-pT1	2		11.1		
	pT2	2		11.1		
	pT3	6		33.3		

Table 1: Demographics of those undergoing PC

Kaplan-Meier estimates of OS rate are illustrated in figure 1. For the entire cohort, 5-year and 10-year OS rates were 58% (95% CI 43.7-73.6%) and 48% (95% CI 30.9-62.8%), respectively (Figure 1A). The 5-year OS rates by clinical stage were: 49.2% (95% CI 16.0-76.1%) for cT1 and 59% (95% CI 39.4-73.9%) for cT2 (Figure 1B). The 5-year OS rates by pathologic stage were: 68% (95% CI 35.7-86.9%) for pT0, 59% (95% CI 18.6-85.0%) for pTis-T1, 100% for pT2, and 39% (95% CI 17.5-60.9%) for pT3 (Figure 1D). OS was not impacted by the presence of variant histologies (Figure 1C).



(A)


Product-Limit Survival Estimates
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Survival Probability
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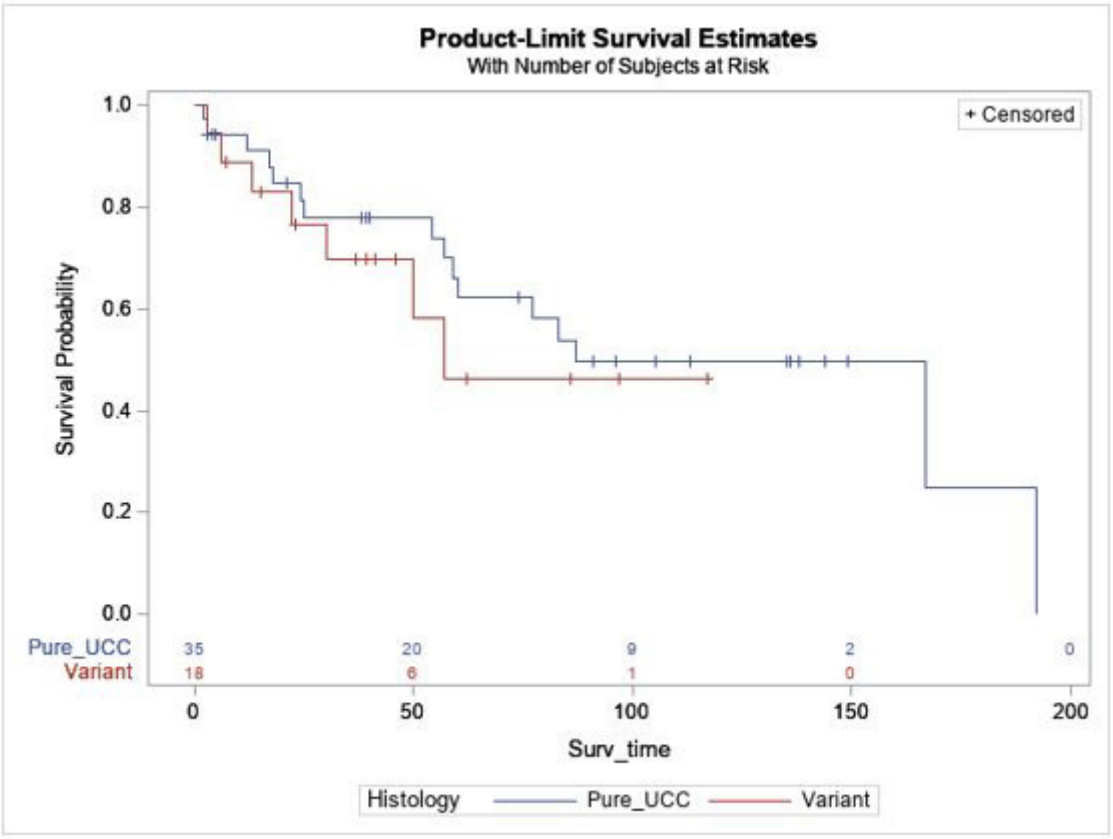
(B)


Product-Limit Survival Estimates
With Number of Subjects at Risk
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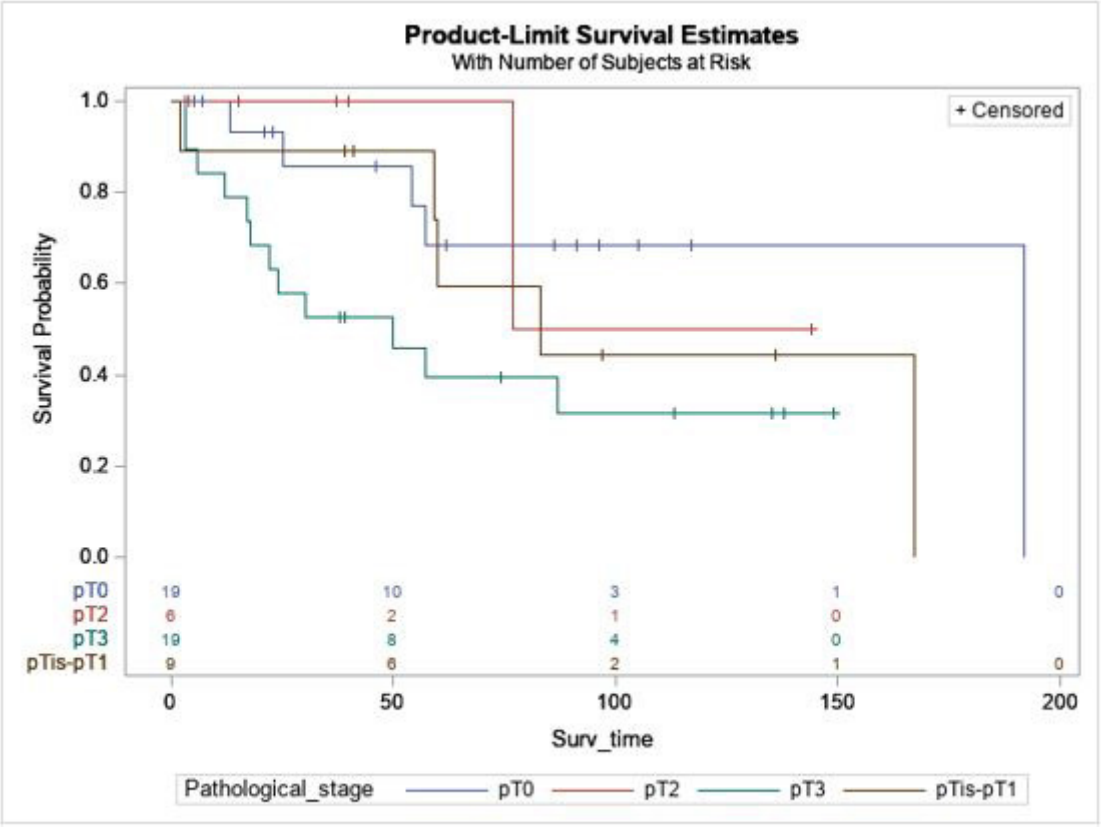
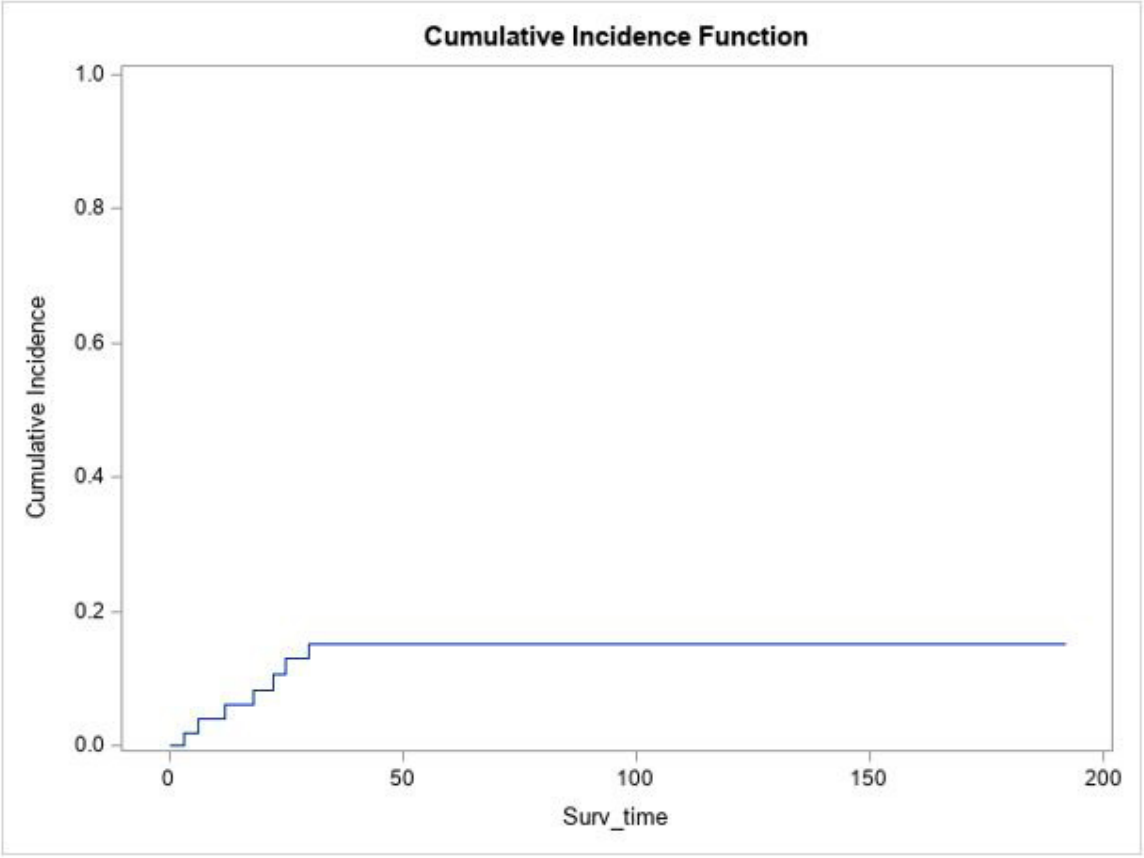


(D)

Figure 1: Kaplan-Meier estimates of overall survival of the entire cohort (A), by clinical stage (B), by presence of variant histology, and by pathologic stage (D). No statistically significant differences in OS were found between groups in figure B (p=0.08), figure C (p=0.52) or figure D (p=0.63) using log-rank tests

While one should be circumspect about extrapolating beyond the last observed event, cumulative incidence of BC specific death is illustrated in figure 2. The latest observed BC specific death happened at month 30. The Kaplan-Meier estimate (Figure 2A) shows that the estimated cumulative incidence of BC specific death of the entire cohort at that point is 15% (95% CI 6.5-26.7%). As there were no observed BC specific deaths from month 30 to the end of follow-up (192 months), we use 15% to estimate the BC specific death rates at year 5 (60 months) and year 10 (120 months) due to the right-continuity of the cumulative incidence function (CIF). We used the same idea to estimate the CIF at year 5 of each clinical and pathological stage. Ongoing observation will reveal if this continues to be the case. The 5-year cumulative incidence of BC specific deaths by clinical stage was: 7% (95% CI 0.4-28.7%) for cT1 and 19% (95% CI 7.4-34.2%) for cT2 (Figure 2B). The 5-year cumulative incidence of BC specific deaths by pathologic stage was: 8% (95% CI 0.4-32.8%) for pT0, 0% for pTis-pT1, 0% for pT2, and 32% (95% CI 12.4-52.9%) for pT3 (Figure 2D). BC specific death was not impacted by the presence of variant histologies (Figure 2C).

The rates of intravesical recurrences were evaluated in the entire cohort and broken down by stage at PC in figure 3. The 5- and 10-year rates of patients free of intravesical recurrence for the entire cohort was 88% (95% CI 71.7-95.5%) and 60% (95% CI 35.7-77.1%), respectively (Figure 3A). Figure 3B shows the 5-year intravesical recurrence-free rates by stage at PC were: 100% with pT0 (95% CI 100-100%), 80% with pTis-pT1 (95% CI 20.4-96.9%), 50% with pT2 (95% CI 5.8-84.5%), and 83% with pT3 (95% CI 45.1-95.5%). Only 1 recurrence was cT2.


Cumulative Incidence Function
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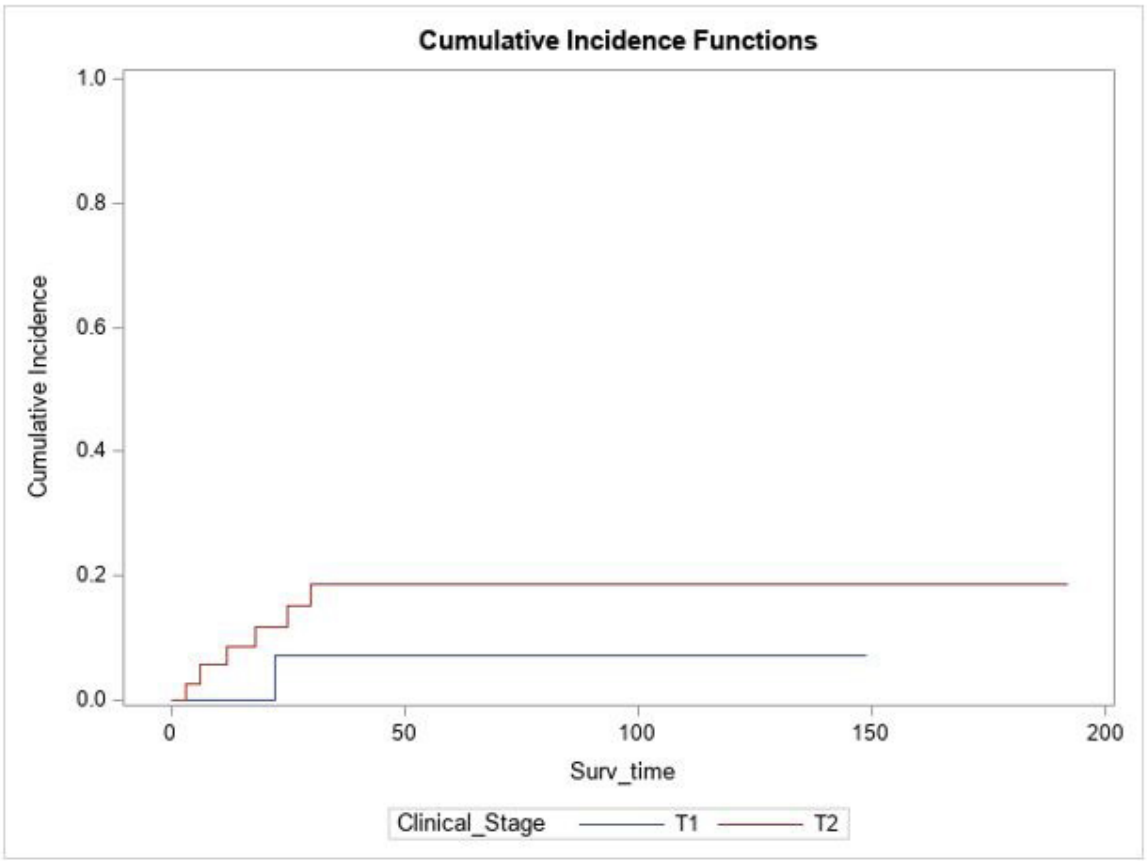
Cumulative Incidence Functions
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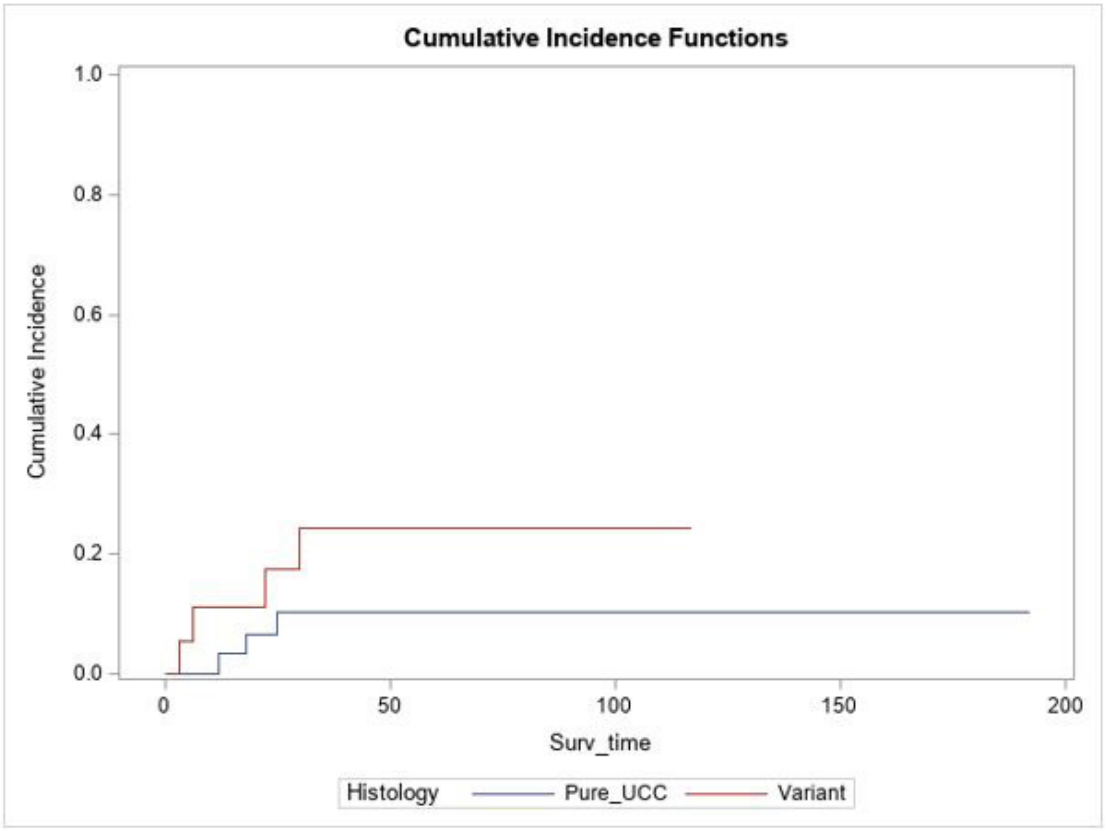

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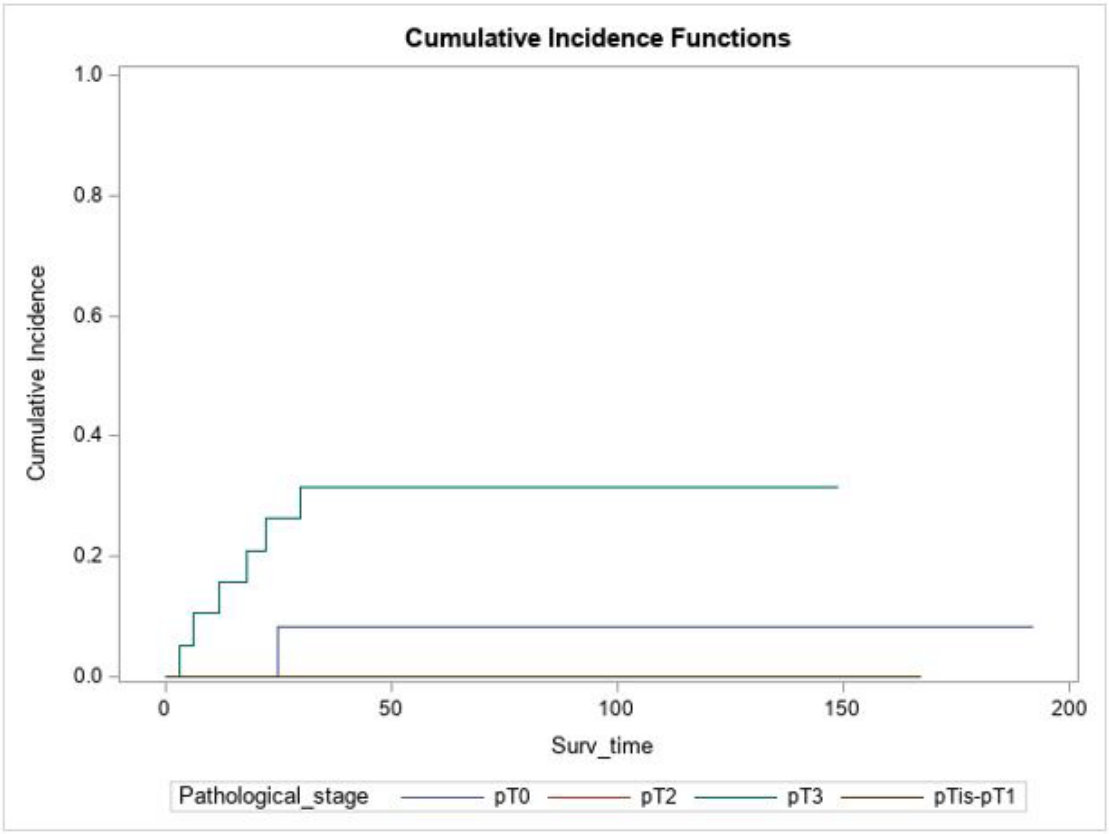
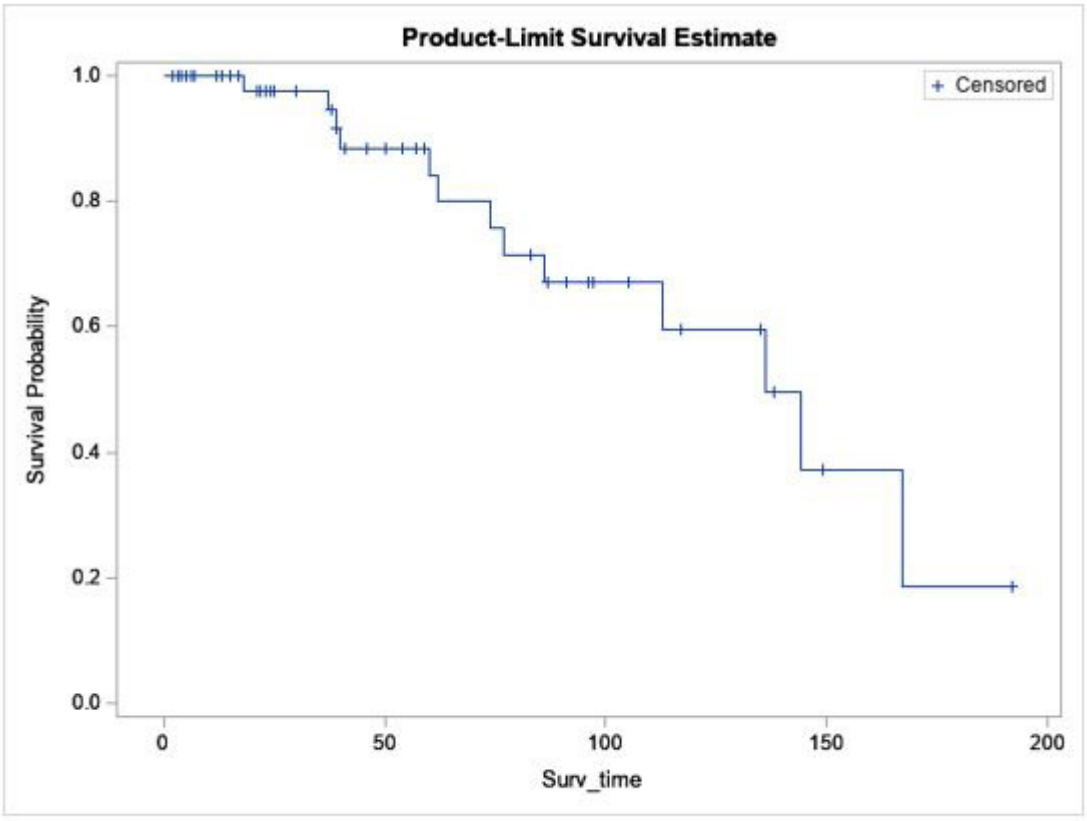
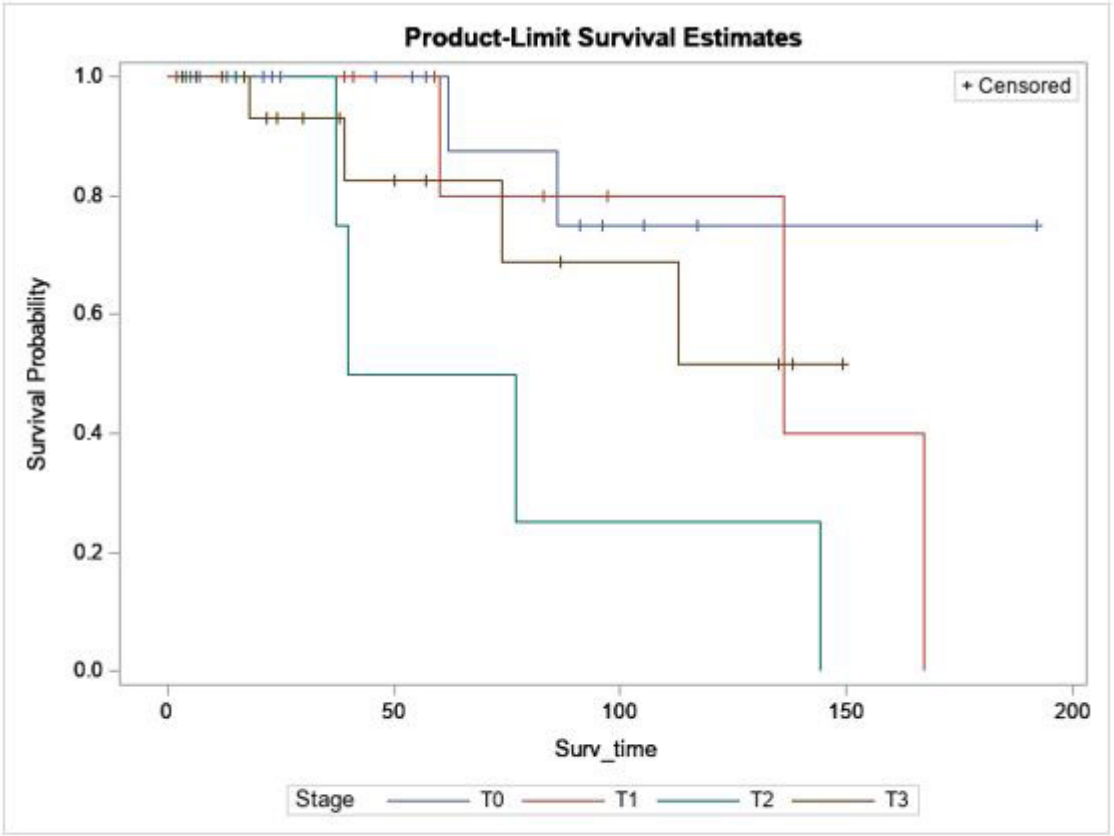


(D)

Figure 2: Cumulative incidence of deaths due to bladder cancer of the entire cohort (A), by clinical stage (B), by presence of variant histology, and by pathologic stage (D). No statistically significant differences in the cumulative incidence of deaths due to bladder cancer were found between groups in figure B (p=0.31) or figure C (p=0.07) using Gary's tests, or figure D (p=0.21) using log-rank tests



(A)



(B)

Figure 3: Kaplan-Meier estimates of intravesical recurrence free survival of the entire cohort (A) and by stage at PC (B). No statistically significant difference was identified in intravesical recurrence free survival between groups in figure B (p=0.09) using a log-rank test

Change in glomerular filtration rate (GFR) was plotted and shown in Figure 4. There were 31 patients with pre-operative and at least 1 post-operative GFR in our records. The most recent GFR was then subtracted from the pre-operative GFR. The coefficient of determination was 0.0035 showing that PC did not have a significant impact on GFR over time.

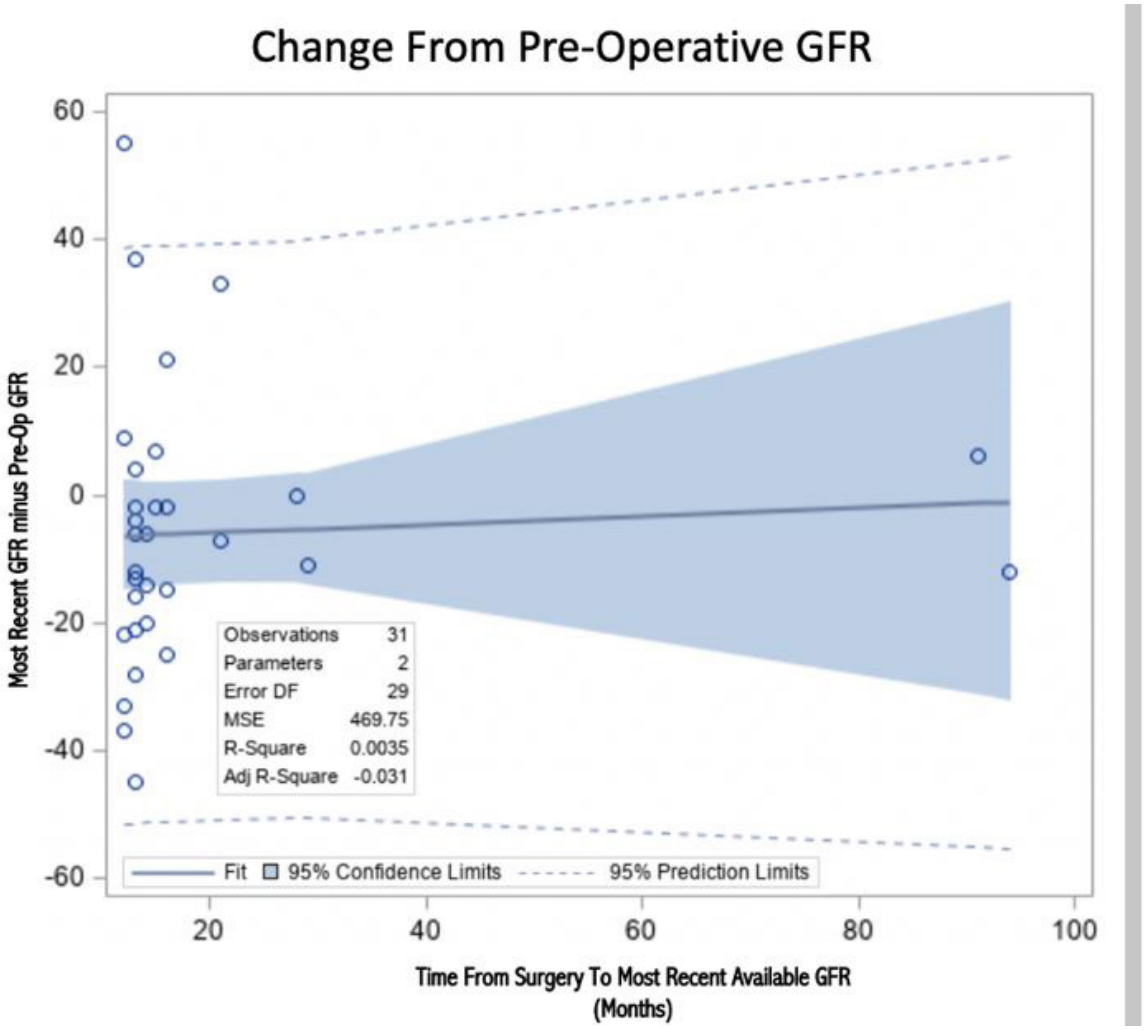


Figure 4: Scatter plot of change in GFR after PC with each point representing a patient's most recently available GFR subtracted from the pre-op GRF

Discussion

Our results indicate that PC appears to be a viable option for patients with a confirmed solitary MIBC lesion or those with invasive HGUC lesions that are concerning for muscle invasion. Importantly, pathologic stage at PC, OS and cumulative incidence of BC specific death did not seem to be impacted by the presence of variant histologies. Abdollah *et al.* published SEER data on pathologic stage specific survival of patients undergoing RC with lymph node dissection for UC.11 The overall 5-year and 10-year survivals of those undergoing RC was 47% (95% CI 46-48%) and 34% (95% CI 33-36%), respectively. Their cohort's 5-year BC specific survival (CSS) by stage at RC was: 89% (95% CI 83.4-94.7%) for pTa/is, 86% (95% CI 82.8-88.7%) for pT1, 75% (95% CI 73.4-77.0%) for pT2, and 47% (95% CI 46.9-49.5%) for pT3. Compared to the data reported by Abdollah *et al.*, our OS and cumulative incidence of BC specific death by pathologic stage outcomes are comparable or better (Table 2). Due to competing risks of mortality, we calculated a cumulative incidence of death for those who underwent PC and calculated cancer specific mortality from the CSS reported by Abdollah *et al* [11] shown in Table 2. However, it should be noted that the PC and RC groups may not be similar since those undergoing RC are more likely to have CIS present throughout the bladder, present with larger tumors, and can have multifocal tumors. These factors also would make propensity matching impractical and propensity matched results would likely not add much to our conclusions.

Stage at Cystectomy	PC 5–year cumulative incidence of BC specific death	RC 5-year stage specific mortality reported by Abdollah *et al.*
pT0	8.44% (CI 0.42-32.76%)	NA
pTa/is	0%	11.1% (CI 5.3-16.6%)
pT1	0%	14.3% (CI 11.3-17.2%)
pT2	0%	24.8% (CI 23.0-26.6%)
pT3	31.58% (CI 12.39-52.93%)	53.1% (CI 50.5-55.5%)

Table 2: Comparison of cancer specific mortality estimates by stage who underwent RC reported by Abdollah *et al.* to cumulative incidence of bladder cancer specific death who underwent PC

There was 1 patient in our series who died from metastatic UC who had pT0, N0 disease at the time of PC. Prior to PC, the patient had cT2 disease and received NAC. This patient did not have a local recurrence but was found to have new retroperitoneal lymphadenopathy on routine follow-up imaging. A retroperitoneal lymph node biopsy showed metastatic micropapillary UC. Thus, it is likely that this patient would have succumbed to the disease even if he/she had undergone RC.

While 16 patients underwent PC with evidence of only cT1 disease, 44% had pT2 disease or greater. Furthermore, 6 (38%) of the patients who were cT1 were pT3. There were 2 additional 'unstaged' cancers in diverticula which were pT3 disease at PC. Of these 18 patients with cT1 or unstaged disease, 8 had cancer in a diverticulum. This points to the importance of using clinical judgement to drive decision making as using only information from a biopsy may understage patients. PC allowed these patients to have definitive therapy for UC but avoided the morbidity which often accompanies RC. Mortality based on clinical stage also provides important information. OS not affected by clinical stage (Figure 1B), however there is a clear (although not statistically significant) separation of the groups when looking at cancer specific mortality based on clinical stage (Figure 2B) and pathological stage (Figure 2D). CSS is likely improved for those with cT1 BC as fewer patients in the cT1 group had pT3 cancer at PC.

Recently, increased emphasis has been placed not just on length of survival, but the quality of life (QoL) of cancer patients after attempted curative intervention. Reported data on QoL metrics after RC have been inconsistent and there is no clear benefit of continent versus incontinent urinary diversions in terms of QoL. [12] Hedgepeth *et al.* evaluated QoL of BC patients after RC compared to those managed by TURBT using the Body Image Scale (BIS). [13] In the RC group, 139 and 85 patients underwent creation of a neobladder or ileal conduit, respectively. While there was not a clear benefit of diversion with neobladder or ileal conduit, both groups had worse BIS scores compared to those managed cystoscopically. Mak *et al.* compared QoL metrics using multiple validated instruments on 109 patients who underwent RC and 64 treated with TMT for MIBC. [14] The authors found a significantly better overall QoL with higher physical, role, social, emotional, cognitive, bowel and sexual function of those who underwent TMT compared to RC. Ebbing *et al.* looked at QoL outcomes in BC patients after PC.7 Of the cohort of 27 patients who underwent PC, 12 had the European Organization for the Research and Treatment of Cancer QLQ-C30 survey administered to them between 2.8 and 7.7 years post-operatively. These responses were compared to an historic set of 58 patients who had undergone RC at the same institution and the authors found that those who underwent PC or ileal neobladder had better QoL metrics compared to those with ileal conduit. This evidence suggests that continent voiding and absence of a stoma tends to lead to a higher QoL. Clements *et al.* used a variety of surveys to look at QoL outcomes of 206 patients who had a continent diversion and 205 patients who underwent incontinent diversion after RC. [15] Those with continent diversions had significantly better outcomes in the domains of physical, urinary and sexual function. However, those with incontinence diversion had significantly better social functioning for unclear reasons. However, those undergoing continent diversion had a mean age of 10 years younger than those undergoing incontinent diversion.

Because the 5- and 10-year intravesical recurrence free survival rate in our series was 88% (95% CI 71.7-95.5%) and 60% (95% CI 35.7-77.1%), respectively, we would recommend that cystoscopic surveillance continue indefinitely. Furthermore, we would recommend a very low threshold for immediate cystoscopy to evaluate any concerning symptoms such as new onset irritative voiding or gross hematuria.

Only 2 patients underwent salvage cystectomy; 1 for a positive margin at PC and 1 for recurrent cT2 disease. Neither of these patients ultimately died from UC. Thus, the salvage cystectomy rate in this study was 3.8%, much lower than the 20-30% rate often quoted for those undergoing radiation therapy. [5,16] However, it is difficult to make direct comparisons between PC and other bladder sparing therapies due to the lack of pathologic staging with the latter treatment. For instance, Herr published a commentary discussing preventable cancer deaths of patients who underwent either radical TUR or PC for organ confined solitary MIBC less than 5cm wide with a complete clinical response to NAC. [17] Herr analyzed the radical TUR and PC groups together and found a 5% "excess" mortality rate compared with similar patients undergoing RC. However, it is possible that some patients undergoing radical TUR had greater than T2 disease or nodal spread at the time of surgery; important prognostic features that were unknown because pathologic staging did not occur. Moreover, our study shows that of those with cT2 disease 37% of those who received NAC and 56% of those who did not receive NAC, did not have their cancer completely eradicated by TURBT and re-TURBT. Lastly, our study clearly shows that clinical staging can underestimate pathologic stage and that those with pT3 disease have worse oncologic outcomes.

Often, RC is associated with a decline in renal function over time. [18] However, we were unable to find any decline in renal function with respect to time from PC, including many patients who underwent ureteral reimplantation at the time of PC. No patient in this case series required dialysis.

Lastly, studies such as ours remain relevant as the role of PC remains in debate. For instance, Bagheri *et al.* recently published a study showing that RC and PC have comparable total costs with those undergoing PC having worse CSS. However, this study lacks granularity of patient characteristics and clinical details as it used a SEER database to identify patients undergoing RC and PC. For instance, the authors note similar CSS for patients undergoing PC for cT2 tumors compared with those undergoing RC, but worse CSS for those with cT3 and cT4 tumors undergoing PC. In our series no patients had cT3 or cT4 cancers. Also, in Bagheri's *et al.* study only 23% of patients undergoing PC underwent a LND, there was a 24% 30-day readmission rate for those who underwent PC and 22% of those undergoing PC required skilled nursing facilities at discharge. [19] These clinical details suggest that in their study's population, PC may have often been performed for palliative reasons with at least several patients having medical comorbidities prohibiting RC.

Limitations to this study include its retrospective design and small sample size. Selection bias is also a concern given that those who are eligible to undergo PC may have a more oncologically favorable prognosis. However it is important to point out that we looked at outcomes based on stage at PC with 36% of our cohort having pT3 disease. Furthermore, we did not have all data points as some patients followed up from long distances, all labs from remote sites were not always available to us and a few of the archived records were not complete. However, even if patients were followed by urologists not in our system, we had records on the vast majority of the patients.

Strengths of our study include that this was a single surgeon consecutive case series with long term follow-up. Importantly, we demonstrate that stage at PC is an important determinant of oncologic outcomes. Also, all patients in our study had negative margins at frozen section for UC (despite 1 patient having final pathology with a positive margin) which has been shown to have a better oncologic prognosis. [20] Our study also only includes patients undergoing PC for UC with curative intent.

In conclusion, the results from our study provide additional evidence that PC provides meaningful oncologic control of MIBC lesions. While many patients had intravesical UC recurrences, recurrence of MIBC lesions was rare; consistent with previous retrospective studies on PC. These results further support PC as a viable option for those with solitary UC lesions with known or suspected T2 disease who are ineligible or unwilling to undergo RC.

Previously Presented at

Northeastern Section of the American Urologic Association Virtual 72nd Annual Meeting, October, 2020.

Disclaimers/Conflict of Interest: None

Ethics statement: This was a retrospective study and did not require informed consent of the participants. The study was approved by the University of Rochester IRB under STUDY 00000837: Cystectomy Database.

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