The effect of prior prostate cancer treatment on perioperative and pathological outcomes after cystectomy

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Introduction: *A comprehensive analysis on outcomes in the perioperative and pathological setting in patients with a prior diagnosis of prostate cancer has not been performed. The objective of this study is to describe the effect of prior prostate cancer treatment on perioperative and pathological outcomes after cystectomy.*

Materials and methods: *This was a retrospective review of all male patients who underwent cystectomy at our institution from 01/01/2007-01/01/2020. Patients who were previously diagnosed and treated for prostate cancer were identified and outcomes were assessed.*

Results: *In 525 male patients, 132 (25.1%) had a diagnosis of prostate cancer prior to cystectomy. In the patients with a history of prostate cancer, 59 (46.2%) patients underwent prior radical prostatectomy (RP), 52 (39.4%) underwent some form of radiation therapy and the remaining 21 were managed with other modalities, including 11.4% who were on active surveillance. When comparing perioperative outcomes, there were no significant differences in outcomes. Pathological outcomes revealed that pT4 disease was more common in the RT cohort (19.2%, p = 0.05). In patients with no history of prostate cancer, 151 (40.2%) were found to have incidental prostate cancer at the time of cystectomy. Most (67.5%) patients with incidental prostate cancer had Gleason < 7 disease and only 1.3% developed metastatic prostate cancer on follow up, compared to over 10% of the patients previously treated for prostate cancer (p < 0.05).*

Conclusions: *Patients who underwent prostate cancer treatment prior to cystectomy may be at increased risk for worse perioperative and pathologic outcomes after cystectomy.*

Key Words: bladder cancer, prostate cancer, radiation therapy, prostatectomy

Introduction

Cystectomy is a surgery that is most commonly indicated for high-risk bladder cancer, but can also be performed for other indications including radiation cystitis, end-stage bladder, urinary fistula, refractory urinary symptoms, or for non-bladder malignancies.[1] Because prostate cancer is the most common malignancy in males, it is not uncommon for patients who have undergone cystectomy to have previously received prostate cancer treatment prior to surgery.[2-4]

Some data have suggested more adverse pathological outcomes after cystectomy in patients

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with prior interventions for prostate cancer.[2] These prior interventions can also have an impact on perioperative outcomes, as patients may be at increased risk of complications after surgery.[5] However, a comprehensive analysis on outcomes in the perioperative and pathological setting in patients with a prior diagnosis of prostate cancer has not been done.

In this context, we report our institutional experience on the effect of prostate cancer on cystectomy perioperative and oncological outcomes. This involved assessing patients with a known prostate cancer diagnosis prior to cystectomy, who were actively treated or placed on active surveillance. Outcomes were subsequently evaluated. This study potentially provides additional understanding to surgeons performing cystectomy on patients with prostate cancer.

Materials and methods

Data source

This is a retrospective study that reviewed all male patients who underwent cystectomy at our institution from 01/01/2007-01/01/2020.

Patient selection

After institutional review board approval, we queried our electronic medical record system and identified all patients who underwent cystectomy at our institution from 01/01/2007-01/01/2020. All adult male patients > 18 years of age who underwent cystectomy for any indication were included. Exclusion criteria included female patients.

Variables

Data were collected for the following patient characteristics: demographics (age, body mass index, sex), comorbidities, Eastern Cooperative oncology Group status, Charlson comorbidity index (CCI), bladder cancer clinical stage, indication for surgery, prior surgical history. Prostate cancer-related data was also obtained including prior PSA values, presence of prior prostate cancer, prior prostate cancer stage and Gleason score, and management of previously diagnosed prostate cancer. Pathological information obtained at the time of definitive surgery was also collected.

In addition, perioperative information was collected, which included information on immediate postoperative outcomes such as complications, hospital length of stay (LOS), and hospital readmission. Follow up information was obtained which included the patient's cancer status at the last follow up appointment, cancer recurrence and management, and post-surgical management of prostate cancer.

Statistical analysis

Continuous variables were described using median values with interquartile range. Categorical variables were described as frequency and percentages. Bivariable analysis was performed with Pearson Chi squared test or Fisher exact test, when appropriate. Continuous variables were evaluated with a Kruskal-Wallis test. P values were 2-sided, and $p < .05$ was considered statistically significant. Kaplan-Meier survival plots were generated to evaluate survival outcomes. Bivariable and multivariable Cox regression analyses were performed to identify predictive variables of both overall survival (OS) and bladder cancer recurrence-free survival (RFS). Statistical analyses were conducted with SPSS 25.0 (IBM Corp 2017).

Results

In 525 male patients, 132 (25.1%) had a diagnosis of prostate cancer prior to cystectomy. The patients with a prior treatment for prostate cancer were significantly older (75.0 years vs. 71.0 years, $p < 0.001$), had a higher age-adjusted CCI score (5.0 vs. 3.0, $p < 0.001$) and were more likely to have undergone a prior abdominal surgery (68.2% vs. 56.1%, $p = 0.015$).

In the patients with a history of prostate cancer, 59 (46.2%) underwent prior radical prostatectomy (RP), 52 (39.4%) underwent some form of radiation therapy and the remaining 21 were managed with other modalities, including 15 (11.4%) who were on active surveillance. When comparing perioperative outcomes, Table 1, there were no significant differences between the cohorts, though a rectal injury appeared to be more common in patients who previously underwent a RP (5.1% vs. 1.9% in the RT cohort and 1.0% in patients without a history of prostate cancer, $p = 0.303$).

Pathological outcomes revealed that pT4 disease was more common in the RT cohort (19.2% vs. 1.7% in RP and 8.9% in patients with no prior prostate cancer, $p = 0.050$). The median lymph node count was highest in the group with no prior history of prostate cancer (16.0) and those who were previously on active surveillance (17, $p < 0.001$). In patients who underwent surgery for bladder cancer, the rate of a positive soft tissue margin was highest in patients who underwent radiation therapy, but not statistically significant (7.1% RP, 10% radiation therapy, 3.2% remaining, $p = 0.131$).

TABLE 1. **Perioperative outcomes in all patients as stratified by prior prostate cancer treatment**

	Prostatectomy (n = 59)	Radiation therapy (n = 52)	Active surveillance (n = 15)	Androgen deprivation therapy (n = 4)	Other treatment (n = 2)	No prostate cancer (n = 393)	p value
Median LOS, days (IQR)	6.0 (5.0-8.0)	8.0 (5.0-13.0)	6.0 (4.0-9.0)	7.0	6.5	6.0 (5.0-8.0)	0.642
Median time to flatus (IQR)	3.0 (2.3-4.0)	3.5 (2.0-7.5)	3.0 (2.0-4.0)	4.0	4.5	3.0 (2.0-4.0)	0.892
Complications (%)							
SBO/Ileus	11 (18.6)	14 (26.9)	2 (13.3)	0	1 (50.0)	66 (16.8)	0.335
Transfusion	21 (35.6)	24 (46.2)	5 (33.3)	3 (75.0)	0	163 (41.5)	0.419
Readmission	14 (23.7)	15 (28.8)	3 (20.0)	0	1 (50.0)	89 (22.6)	0.684
DVT	2 (3.4)	3 (5.8)	0	0	1 (50.0)	25 (6.4)	0.109
PE	2 (3.4)	3 (5.8)	0	0	0	16 (4.1)	0.929
Abscess	2 (3.4)	2 (3.8)	0	0	0	8 (2.0)	0.914
Ureteral stricture	5 (8.5)	1 (1.9)	2 (13.3)	0	0	38 (9.7)	0.490
Failure to thrive	8 (13.6)	5 (9.6)	2 (13.3)	0	0	30 (7.6)	0.641
Rectal injury	3 (5.1)	1 (1.9)	0	0	0	4 (1.0)	0.303
Wound infection	5 (8.5)	3 (5.8)	1 (6.7)	0	0	41 (10.4)	0.838
ICU admission	4 (6.8)	4 (7.7)	2 (13.3)	0	0	36 (9.2)	0.923
Lymphocele	0	1 (1.9)	0	0	0	18 (4.6)	0.483
Urinary leak	1 (1.7)	1 (1.9)	0	0	0	25 (6.4)	0.431

LOS = length of stay; IQR = interquartile; SBO = small bowel obstruction; DVT = deep vein thrombosis; PE = pulmonary embolism; ICU = intensive care unit

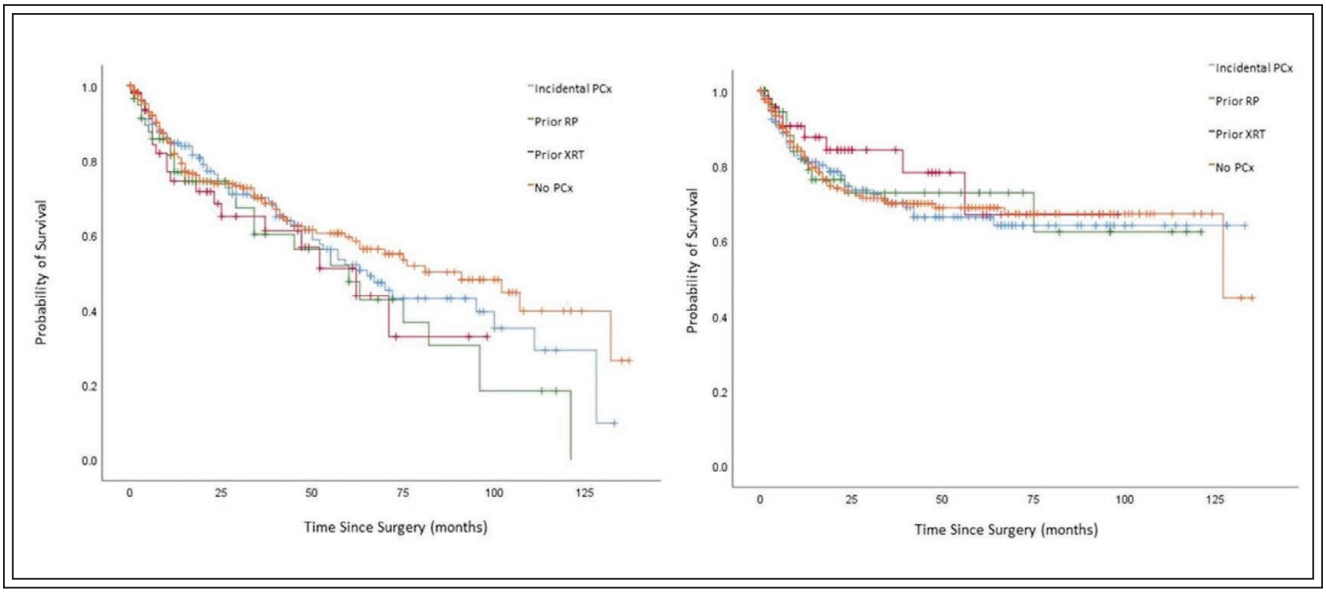

Figure 1. Kaplan Meier estimates. There was no difference (p > 0.05) in overall survival **(left)** and recurrence-free survival **(right)** for bladder cancer patients who had incidental prostate cancer, prior RP, prior XRT and no prostate cancer at any point at median follow up of 64.0, 37.0, 48.5, and 63.5 months, respectively.

TABLE 2. **Characteristics in prostate cancer patients after cystectomy**

	Prostatectomy (n = 59)	Radiation therapy (n = 52)	Active surveillance (n = 15)	Androgen deprivation therapy (n = 4)	Other treatment (n = 2)	No prostate cancer (n = 151)	p value
Median PSA (IQR)							
Preoperative	< 0.01 (0-0.30)	0.51 (0.20-3.10)	5.3 (2.4-7.05)	0.94	0.40	1.90 (0.88-4.50)	< 0.001
Prostate cancer on final pathology (%)	6 (10.2)	12 (23.1)	10 (66.6)	3 (75.0)	2 (100)	100	< 0.001
Gleason score on final pathology (%)							< 0.001
< 7	1 (16.7)	3 (25.0)	6 (60.0)	2 (66.6)	2 (100)	102 (67.5)	
≥ 7	1 (16.7)	8 (66.7)	4 (40.0)	1 (33.3)	0	49 (32.4)	
Not stated	4 (66.7)	1 (8.3)				0	
Prostate cancer at final margin (%)	2 (3.4)	3 (5.8)	2 (13.3)	1 (25.0)	1 (50.0)	7 (4.6)	0.007
Metastatic prostate cancer	7 (11.9)	6 (11.5)	0	0	0	2 (1.3)	0.006
Death from prostate cancer	2 (3.4)	0	0	0	0	1 (0.7)	0.562
Prostate cancer treatment after cystectomy (%)	8 (13.6)	5 (9.6)	0	1 (33.3)	0	2 (1.3)	0.001
Lymph node positive for bladder cancer (%)	11 (18.6)	8 (15.4)	0	1 (33.3)	0	30 (19.9)	0.591

PSA = prostate-specific antigen; IQR = interquartile

In Table 2, the pathological outcome comparisons between all prostate cancer patients is presented and in patients with no history of prostate cancer, 151 (38.4%) were found to have incidental prostate cancer at the time of cystectomy. Most (67.5%) patients with incidental prostate cancer had Gleason < 7 disease and only 1.3% developed metastatic prostate cancer at a median follow up 64 months. In addition, only 0.7% of patients in the incidental prostate cancer cohort required treatment in the form of androgen deprivation therapy +/- chemotherapy due to PSA recurrence which manifested as metastatic disease, versus 13.6%, 9.6% and 33.3% in the patients who previously underwent RP, radiation therapy, and androgen deprivation therapy, respectively (p = 0.001). Additionally, the active surveillance cohort did not experience adverse outcomes from their prostate cancer, as no patients required therapy after prostatectomy and none of these patients experienced metastatic disease or died from prostate cancer.

Survival outcomes for four groups were also obtained: no history of prostate cancer, prior RP treatment, prior RT treatment, incidental prostate cancer. Neither overall nor bladder cancer recurrence-free survival, Figure 1a and 1b, differed between the cohorts. A Cox-proportional hazards model, Table 3, demonstrated that age, variant histology, comorbidity index, advanced bladder cancer stage, positive soft tissue margin, bladder cancer recurrence, node positivity, poor performance status were associated with increased risk of death. The only prostate cancer-related variable that was associated with poor survival was the development of metastatic prostate cancer and this was confirmed on multivariable analysis (HR 2.153, 95% CI 1.091-2.212, p = 0.046).

Discussion

In the present study, prior treatment of prostate cancer was not associated with adverse perioperative

TABLE 3. **Cox regression analysis for overall survival**

	Univariate analysis		Multivariable analysis	
Variable	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.040 (1.023-1.057)	< 0.001	1.027 (1.006-1.048)	0.012
CCI	1.213 (1.112-1.324)	< 0.001	1.141 (1.014-1.285)	0.029
Neoadjuvant chemotherapy	0.963 (0.713-1.301)	0.807		
Final stage pT3+	3.247 (2.458-4.291)	< 0.001	1.741 (1.229-2.465)	0.002
Preoperative variant histology	1.074 (0.757-1.525)	0.688		
Postoperative variant histology	1.714 (1.248-2.345)	0.001	1.162 (0.823-1.641)	0.394
Positive soft tissue margin	7.079 (4.266-11.746)	< 0.001	2.975 (1.721-5.143)	< 0.001
Bladder cancer recurrence	4.001 (3.014-5.311)	< 0.001	2.903 (2.116-3.983)	< 0.001
Prostate cancer at margin	1.334 (0.657-2.709)	0.426		
Lymph node count	0.986 (0.971-1.001)	0.072	0.984 (0.967-1.003)	0.093
Node positive	2.974 (2.210-4.003)	< 0.001	1.553 (1.091-2.212)	0.015
Metastatic prostate cancer	2.111 (1.079-4.128)	0.029	2.153 (1.014-4.570)	0.046
ECOG > 1	1.639 (1.030-2.608)	0.037	1.474 (0.910-2.388)	0.115
Prior prostatectomy	1.409 (0.960-2.068)	0.080		
Prior radiation therapy	1.264 (0.787-2.032)	0.333		
Prior prostate cancer treatment	1.306 (0.941-1.813)	0.110	0.874 (0.572-1.336)	0.534
Incidental prostate cancer	0.980 (0.732-1.313)	0.894	0.965 (0.702-1.327)	0.826
Smoker	1.231 (0.70-1.741)	0.241		
Preoperative Gleason 7 and greater	1.162 (0.632-2.136)	0.630	0928 (0.452-1.906)	0.830

outcomes. We observed an association between pT4 disease and prior radiation therapy for prostate cancer. With the exception of development of metastatic prostate cancer, no prostate cancer pathological variables were associated with overall survival outcomes, confirming that though prior treatment for prostate cancer may make the operation more difficult, survival outcomes after cystectomy are more dependent on non-prostate cancer related variables.

Incidental prostate cancer at the time of cystectomy is not an uncommon entity, as reported rates have been as high as 60%.[6-8] There has been sparse evidence that these cases of incidental prostate cancer could have clinical implications. Gakis et al reviewed 822 male patients who underwent cystectomy across three institutions and sought to assess the clinical significance of incidental prostate cancer. The study found 43.8% of patients with incidental prostate cancer, 14.2% of whom had clinically significant disease by the Epstein criteria. Patients with clinically significant prostate cancer had a significantly lower 5 year OS than those with insignificant and no prostate cancer (33.3% vs. 51.3% vs. 51.5%, respectively, p = 0.05). Clinically significant prostate cancer, however, was not independently associated with survival on multivariable analysis.[8] Similarly in our study, 38.4% of patients were found to have incidental prostate cancer. Thirty-two percent of these cases had Gleason 7 or greater disease. Two patients developed metastatic prostate cancer during follow up and only one of those deaths were due to prostate cancer. This supports the literature that the clinical significance of incidental prostate cancer at time of cystectomy is minimal.

On a separate note, patients who previously received treatment for prostate cancer are especially of interest due to the possible increased incidence of adverse outcomes at the time of surgery. For instance, Schuster et al reviewed 458 patients who underwent cystectomy, including 29 who had previously received definitive treatment for prostate cancer (12 prior RP, 17 prior RT) and found that the patients who previously

underwent definitive treatment for prostate cancer were at increased risk of developing complications compared to the remainder of the cohort (55% vs. 33%).[5] Though the present study revealed a higher frequency of rectal injury in the patients who underwent prior RT, this was not statistically significant, possibly secondary to the small sample size available for analysis.

In regards to pathological outcomes, prior studies have suggested that patients who received prior RT were found to have extravesical disease in 60% of cases, compared to 33% in the prior RP cohort, suggesting that prior RT may be associated with a greater risk of developing more advanced disease.[5] This was also suggested in a review of 34 patients who underwent radical cystectomy with a prior history of radiation therapy, where 54% presented with locally advanced disease.[2] In addition, Yee et al reviewed outcomes in 144 patients diagnosed with bladder cancer who had either previously undergone some form of radiation therapy vs. no radiation. The study found that in patients who were previously irradiated, there was a higher incidence of high-grade disease ($p = 0.001$) and a higher rate of non-organ confined disease at the time of cystectomy, though this was not statistically significant.[9] In our study, we found that the patients with a prior history of radiation therapy had the highest incidence of pT4 disease (19.2% vs. 1.7% in the prior RP cohort and 8.9% in the cohort with no history of prostate cancer, $p = 0.050$). No other pathologic differences were seen between cohorts. Additionally, we found no difference in long term overall survival or recurrence-free intervals between the cohorts.

Another concept to consider in patients with prior treatment of prostate cancer is the implication of the previously treated prostate cancer disease on prostate cancer oncological outcomes. This was explored in a retrospective review of 78 patients who underwent radical cystectomy with a history of prior radiotherapy. The median time from radiation therapy and radical cystectomy was 77 months. Residual gradable prostate cancer was found in 45% of patients, where 69% were Gleason 7 or greater. There were also 5 patients with positive prostate cancer surgical margins and 3 patients with positive lymph nodes containing prostate cancer. Despite this, no patients died of prostate cancer, though the overall follow up was not presented.[4] In our study, 23.1% of patients in the RT cohort and 10.2% in the prior RP cohort were found to have prostate cancer on the final pathology. Of these cases, 66.7% in the RT group were Gleason 7 or greater vs. only 1 (16.7%) in the prior RP group ($p < 0.001$). Seven patients (11.9%) developed metastatic prostate cancer in the prior RP and six (11.5%) in RT cohort and two patients in the RP cohort eventually died of prostate cancer. This confirms that patients with a history of previously treated prostate cancer who undergo cystectomy may still experience adverse oncological outcomes related to the prostate cancer when residual disease remains.

The present study has its limitations. First, this is a retrospective study that involved patients who underwent cystectomy by at least five surgeons in a time frame of around 12 years. Second, because many patients received their treatment for prostate cancer at variable time intervals prior to cystectomy and many were performed at outside institutions, there was limited information available about the prostate cancer pathology, treatment details, PSA trends. Additionally, because a significant amount of patients (25%) in the prostate cancer cohort underwent cystectomy for benign indications, this may have likely impacted survival outcomes, as these patients did not have a prior diagnosis of bladder cancer. This could have contributed to the lack of survival differences between cohorts, despite a higher frequency of pT4 patients in the RT cohort. Despite these limitations, we were able to report a comprehensive analysis of patients undergoing cystectomy at our institution and the relationship of prostate cancer with perioperative and survival outcomes. Perhaps larger, multi institutional reviews such as meta-analyses can shed additional light on these questions regarding outcomes after prostate cancer treatment in patients who undergo cystectomy.

Conclusions

Prostate cancer is a common diagnosis that is seen around the time of cystectomy. Patients who underwent definitive prostate cancer treatment prior to cystectomy may be at higher risk for worse perioperative outcomes, though we found no statistical differences demonstrating this in our study. In addition, more adverse pathological outcomes may be present in patients who received prior RT. Survival in patients who undergo cystectomy for bladder cancer, however, is dictated mostly by the underlying bladder cancer diagnosis. □

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