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The effect of centralization of care on overall survival in primary urethral cancer

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Abstract

Purpose: Centralization of care to high-volume centers improves outcomes across urologic malignancies, but there exists a paucity of data for low-incidence cancers. Given the rarity of primary urethral cancer (UC) and the need for complex multidisciplinary treatment, we sought to evaluate differences in practice patterns and clinical outcomes across types of treating facilities.

Materials and Methods: We identified all patients diagnosed with UC from 2004 to 2016 in the National Cancer Database. The Kaplan-Meier method was used to evaluate overall survival (OS) and multivariable Cox regression analysis was used to investigate independent predictors of OS. The chi-square test was used to analyze differences in practice patterns.

Results: We identified 6,445 patients with UC. Median overall survival was 40.5 months (interquartile range 38.4−42.6). There was a significant difference in OS based upon facility type, and this difference remained significant on subgroup analysis for squamous cell carcinoma and urothelial carcinoma. Academic centers had superior OS on pairwise comparisons (all $P< 0.05$) and were associated with decreased risk of death, hazard ratio 0.858 (95% confidence interval 0.749−0.983). Academic centers had a significantly greater frequency of neoadjuvant/adjuvant chemotherapy and radiation ($P < 0.001$). Academic centers performed radical surgery in 34.1% of patients compared to 14.5% in community programs ($P < 0.001$), and regional lymphadenectomy in 31.6% of patients compared to 13.2% in community programs ($P < 0.001$).

Conclusion: There exist significant differences in survival for patients with UC based upon treating facility. Variations in practice patterns including multimodal treatment, radical surgery, and regional lymphadenectomy may contribute to the observed differences in clinical outcomes.

Keywords: Urethral neoplasms; Survival analysis; Quality of health care; Guideline adherence

1. Introduction

Centralization of care to high-volume centers has been shown to improve outcomes across urologic malignancies including bladder, prostate, penile, testicular, and renal cancer. However, the literature is sparse regarding the effect of centralization of care for low-incidence urologic cancers [1]. Primary urethral cancer (UC) is a rare urologic cancer, reported to represent <1% of all malignancies. In 2013 the European Association of Urology published guidelines for primary UC, which recommended consideration of regional lymphadenectomy for clinical node-positive patients or those with invasive tumors and further advocated for neoadjuvant chemoradiation in urethral squamous cell carcinoma (SCC) and neoadjuvant chemotherapy in urethral urothelial carcinoma. Given the rarity of this disease and the need for complex multidisciplinary treatment, the guidelines recommend multidisciplinary collaborative care teams including urologists, medical oncologists, and radiation oncologists [2]. Several studies have proposed that all patients with UC be treated at academic centers, though the data supporting this recommendation remains limited [2−4]. We hypothesize that adherence to guidelines would differ among type of treating institution, and that there would be an overall survival benefit to centralization of care to academic centers for patients with primary UC.

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2. Methods

2.1. Cohort, outcome, and variables

The National Cancer Database (NCDB) collects data from over 1,500 Commission on Cancer (CoC)-accredited facilities across the United States, making it an excellent resource for investigating rare malignancies. We identified all patients with primary UC diagnosed at CoC-accredited facilities from 2004 to 2016. We included patients with the 3 predominant histologies, urothelial carcinoma, SCC, and adenocarcinoma; we excluded patients with other rare or variant histologic subtypes.

Our primary outcome was overall survival. Demographic variables included age, race, Hispanic ethnicity, gender, insurance status (uninsured, private insurance, Medicaid, Medicare, "other government," and unknown), and percentage of adults in the patient's home zip code who did not graduate high school (quartiles). Metropolitan versus rural residence used to account for proximity to a metropolitan area. Distance to hospital was reported as the distance in miles from the patient's residence to the reporting hospital. Charlson/Deyo score was calculated based upon ICD-9-CM diagnosis codes, and reported as 0, 1, 2, or ≥3.

Oncologic data included tumor histology, grade, and clinical TNM stage. We chose to utilize clinical staging in order to capture the data upon which practice patterns were based at initial diagnosis; clinical nodal staging has previously been shown to have a high correlation to pathologic staging in UC, and has been advocated to be sufficient to consider multimodal therapy [3]. Treatment data included performance of regional lymphadenectomy, type of surgery (ablative, local excision, simple excision, and radical surgery), any radiation or chemotherapy and neoadjuvant/adjuvant radiation or chemotherapy. As coded in the NCDB, local excision includes polypectomy or excisional biopsy with or without electrocautery, cryoablation, or laser ablation. Simple excision includes simple or partial removal of the primary site.

2.2. Facility type

When patients receive treatment at more than 1 facility, the NCDB uses the best report based upon completeness of coding and recency of patient contact with the facility. The report, however, includes the cumulative treatments administered by any facility. Facility type from the reporting facility includes Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program (which includes NCI-designated comprehensive cancer centers), and Integrated Network Cancer Program. Community Cancer Programs report greater than 100 but fewer than 500 newly diagnosed cancer cases per year. Comprehensive Community Cancer Programs report ≥500 newly diagnosed cancer cases per year.

Academic programs report ≥500 newly diagnosed cancer cases per year and participate in multidisciplinary postgraduate medical education. Integrated Network Cancer Programs does not have a minimum caseload requirement but own or operate a multi-facility network which provides integrated cancer care and comprehensive services. We hypothesize that academic centers and integrated network cancer programs, which are capable of offering comprehensive multidisciplinary care, are more likely to be associated with improved outcomes for this rare malignancy.

3. Analysis

Overall survival for the entire cohort, stratified by facility type, was calculated using the Kaplan-Meier method with log-rank test used for comparisons between groups. Pairwise comparisons were further made to distinguish between each survival curve. Kaplan-Meier subgroup analysis was then performed based upon the 3 most common histologies: SCC, urothelial carcinoma, and adenocarcinoma. We performed multivariable Cox regression analysis to investigate independent predictors of overall survival. The model included age, race, gender, insurance status, metropolitan/rural residence, facility type, Charlson/Deyo score, distance to hospital, tumor histology, grade, and cTNM stage. Missing data were excluded listwise. Multicollinearity was tested using variance inflation factors. Subgroup analysis was performed based upon primary tumor histology. We did not include treatment modality in the model to avoid obscuring the effect of differences in practice patterns across types of treating facilities. We then used chi-square test of independence to analyze the differences in practice patterns across types of facilities including administration of chemotherapy, neoadjuvant/adjuvant chemotherapy, any type of radiation, neoadjuvant/adjuvant radiation, type of surgery (ablative, local excision, simple excision, radical surgery), and regional lymph node dissection. Analyses were performed using SPSS version 20.0.

4. Results

There were 6,476 patients diagnosed with primary UC in centers reporting to the NCDB from 2004 to 2016 who met study inclusion criteria. 31 patients who were coded as clinical T0 were excluded from the analysis, leaving 6,445 in the analytic cohort. 14.4% of patients received treatment at more than 1 facility. Table 1 and Supplementary Table 2 show the baseline demographic and oncologic data for this cohort. Patients treated at academic centers were younger, less comorbid and more racially diverse; patients treated at academic centers also presented with higher tumor grade, clinical T stage, and clinical N stage.

Median overall survival was 40.5 months (interquartile range [IQR] 38.4−42.6 months). There were 3,522 all-cause deaths. There was a significant difference in overall survival based upon type of treating facility, as shown in

Table 1
Demographic and oncologic data for all patients with primary urethral cancer, by facility type

	Community	CCCP	Academic	INCP	Total	*P* value
N	484	2,210	2,923	828	6,445	
Median age (IQR)	74 (65−81)	75 (66−82)	69 (60−77)	73 (63−81)	72 (62−80)	<0.001
Race						
White	419 (86.6%)	1,935 (87.6%)	2,280 (78.0%)	673 (81.3%)	5,307 (82.3%)	<0.001
Black	46 (9.5%)	217 (9.8%)	529 (18.1%)	126 (15.2%)	918 (14.2%)	
Asian/Pacific Islander	11 (1.3%)	27 (1.2%)	52 (1.8%)	11 (1.3%)	101 (1.6%)	
Other/unknown	8 (1.7%)	31 (1.4%)	62 (2.1%)	18 (2.2%)	119 (1.8%)	
Hispanic ethnicity	25 (5.2%)	66 (3.0%)	121 (4.1%)	28 (3.4%)	240 (3.7%)	0.05
Gender						<0.001
Male	366 (75.6%)	1,681 (76.1%)	2,003 (68.5%)	591 (71.4%)	4,641 (72.0%)	
Female	118 (24.4%)	529 (23.9%	920 (31.5%)	237 (28.6%)	1,804 (28.0%)	
Insurance status						
Uninsured	7 (1.4%)	23 (1.0%)	72 (2.5%)	14 (1.7%)	116 (1.8%)	<0.001
Private	106 (5.8%)	550 (24.9%)	937 (32.1%)	222 (26.8%)	1,815 (28.2%)	
Medicaid	26 (5.4%)	46 (2.1%)	144 (4.9%)	30 (3.6%)	246 (3.8%)	
Medicare	333 (68.8%)	1,538 (69.6%)	1,586 (54.3%)	536 (64.7%)	3,993 (62.0%)	
Other government	5 (1.0%)	23 (1.0%)	39 (1.3%)	10 (13.0%)	77 (1.2%)	
Unknown	7 (1.4%)	30 (1.4%)	145 (5.0%)	16 (1.9%)	198 (3.1%)	
% without HS degree						
≥21%	90 (18.6%)	361 (16.5%)	510 (17.5%)	118 (14.3%)	1,079 (16.8%)	<0.001
13.0-20.9%	131 (27.1%)	576 (26.3%)	764 (26.3%)	185 (22.4%)	1,656 (25.8%)	
7.0-12.9%	182 (37.7%)	770 (35.1%)	888 (30.5%)	305 (36.9%)	2,145 (33.5%)	
<7.0%	80 (16.6%)	487 (22.2%)	747 (25.7%)	218 (26.4%)	1532 (23.9%)	
Urban/rural						
Metropolitan	400 (84.0%)	2,002 (93.0%)	2,706 (95.0%)	786 (99.0%)	5,894 (94.0%)	<0.001
Rural	76 (16.0%)	150 (7.0%)	141 (5.0%)	8 (1.0%)	375 (6.0%)	
Charlson/Deyo Score						
0	337 (69.6%)	1,577 (71.4%)	2,245 (76.8%)	570 (68.8%)	4,729 (73.4%)	<0.001
1	100 (20.7%)	444 (20.1%)	501 (17.1%)	184 (22.2%)	1,229 (19.1%)	
2	32 (6.6%)	137 (6.2%)	116 (4.0%)	58 (7.0%)	343 (5.3%)	
≥3	15 (3.1%)	52 (2.4%)	61 (2.1%)	16 (1.9%)	144 (2.2%)	
Median distance to hospital, miles (IQR)	7.3 (3.0−15.3)	8.4 (3.8-19.2)	18.8 (6.9-59.6)	8.0 (4.0−15.0)	11.1 (4.6−31.3)	<0.001
Histology						
SCC	90 (18.6%)	435 (19.7%)	733 (25.1%)	149 (18.0%)	1,407 (21.8%)	<0.001
Urothelial	336 (69.4%)	1,501 (67.9%)	1,673 (57.2%)	535 (64.6%)	4,045 (62.8%)	
Adenocarcinoma	58 (12.0%)	274 (12.4%)	517 (17.7%)	144 (17.4%)	993 (15.4%)	
Grade						
I	52 (10.7%)	217 (9.8%)	175 (6.0%)	61 (7.4%)	505 (7.8%)	<0.001
II	94 (19.4%)	358 (16.2%)	508 (17.4%)	145 (17.5%)	1,105 (17.1%)	
III	138 (28.5%)	749 (33.9%)	918 (31.4%)	264 (31.9%)	2,069 (32.1%)	
IV	83 (17.1%)	340 (15.4%)	563 (19.3%)	147 (17.8%)	1,133 (17.6%)	
Unknown	117 (24.2%)	546 (24.7%)	759 (26.0%)	211 (25.5%)	1,633 (25.3%)	
Clinical T						
cTa	47 (10.7%)	262 (12.7%)	195 (7.1%)	85 (10.9%)	589 (9.1%)	<0.001
cTis	34 (7.7%)	166 (8.0%)	209 (7.6%)	66 (8.5%)	475 (7.4%)	
cT1	80 (18.1%)	408 (19.7%)	481 (17.6%)	141 (18.1%)	1,110 (17.2%)	
cT2	68 (15.4%)	300 (14.5%	342 (12.5%)	93 (11.9%)	803 (12.5%)	
cT3-4	62 (14.1%)	272 (13.1%)	610 (22.3%)	133 (17.1%)	1,077 (16.7%)	
cTx	150 (34.0%)	166 (31.9%)	901 (32.9%)	261 (33.5%)	1,972 (30.6%)	
Clinical N						
cN0	321 (66.3%)	1,466 (66.3%)	1,812 (62.0%)	525 (63.4%)	4,124 (64.0%)	0.005
cN1	17 (3.5%)	73 (3.3%)	134 (4.6%)	39 (4.7%)	263 (4.1%)	
cN2	22 (4.5%)	117 (5.3%)	222 (7.6%)	56 (6.8%)	417 (6.5%)	
cNx	114 (23.6%)	507 (22.9%)	667 (22.8%)	184 (22.2%)	1,472 (22.8%)	
Unknown	10 (2.1%)	47 (2.1%)	88 (3.0%)	24 (2.9%)	169 (2.6%)	
Clinical M						
cM0	432 (89.3%)	1,982 (89.7%)	2,586 (88.5%)	742 (89.6%)	5,742 (89.1%)	0.375
cM1	29 (6.0%)	141 (6.4%)	186 (6.4%)	56 (6.8%)	412 (6.4%)	
Unknown	23 (4.8%)	87 (3.9%)	151 (5.2%)	30 (3.6%)	291 (4.5%)	

CCCP = Comprehensive community cancer center; INCP = Integrated network cancer program; IQR = Interquartile range; SCC = squamous cell carcinoma.

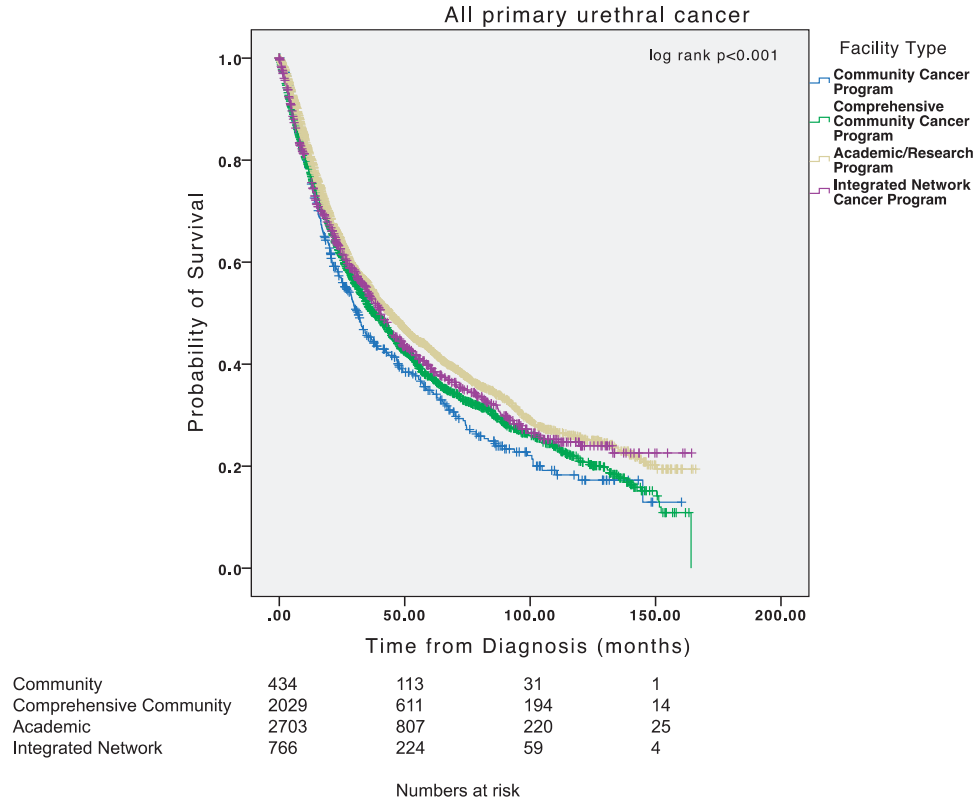

Fig. 1. Kaplan-Meier plot of overall survival, all patients with primary urethral cancer.

Fig. 1 (log rank $P < 0.001$). The 3-year overall survival estimates for community, comprehensive community, academic, and integrated network cancer programs were 45%, 51%, 55%, and 53%, respectively; 5-year overall survival estimates were 35%, 38%, 43%, and 40%, respectively. Using pairwise comparisons, academic centers had significantly greater overall survival compared to community cancer programs and comprehensive community cancer programs ($P < 0.001$). Integrated network cancer programs also had significantly greater overall survival compared to community cancer programs ($P = 0.040$).

For primary urethral SCC, median overall survival was 36.7 months (IQR 31.2−42.2 months). There was a significant difference in overall survival based upon type of treating facility, as shown in Fig. 2A (log rank $P = 0.001$). Using pairwise comparisons, academic centers had significantly greater overall survival compared to all other facility types ($P < 0.05$). For primary urethral urothelial carcinoma, median overall survival was 41.5 months (39.0−44.0 months). There was a significant difference in overall survival based upon type of treating facility, as shown in Fig. 2B (log rank $P = 0.007$). Using pairwise comparisons, academic centers had significantly greater overall survival compared to community cancer programs and comprehensive community cancer programs ($P < 0.05$). For primary urethral adenocarcinoma, median overall survival was 38.4 months (33.4−43.4 months). There was no statistically significant difference in overall survival based upon type of treating facility (log rank $P = 0.625$, Fig. 2C).

Multivariable Cox regression analysis was performed to determine independent predictors of overall survival. This analysis for the entire cohort is shown in Table 2. Variance inflation factors for covariates in the model ranged from 1.0 to 1.5, indicating absence of multicollinearity. Significant independent predictors of overall survival included younger age, non-black race, female gender, private or Medicare insurance status, higher educational attainment, lower Charlson/Deyo score, and greater distance to the hospital; cancer-specific predictors included grade and cTNM stage. Tumor histology was not a significant predictor of overall survival. Of note, treatment at an academic center was associated with a significant survival benefit, hazard ratio (HR) 0.858 (95% confidence interval [CI] 0.749−0.983).

Similar trends were seen in multivariable Cox regression analysis performed for primary urethral SCC and urothelial carcinoma (Table 3); this analysis is not included for adenocarcinoma, as this subgroup did not have a significant survival difference on Kaplan-Meier analysis. Facility type was not a significant independent predictor of overall survival in SCC. In urothelial carcinoma, facility type was again associated with a significant difference in overall survival, with treatment at academic centers (HR 0.805, 95% CI 0.681−0.952) and comprehensive community cancer centers (HR 0.833, 95% CI 0.707−0.981) both showing decreased hazard of death compared to treatment at a community center.

We performed a subgroup survival analysis of patients with invasive or clinically advanced disease (cT2-4, cN

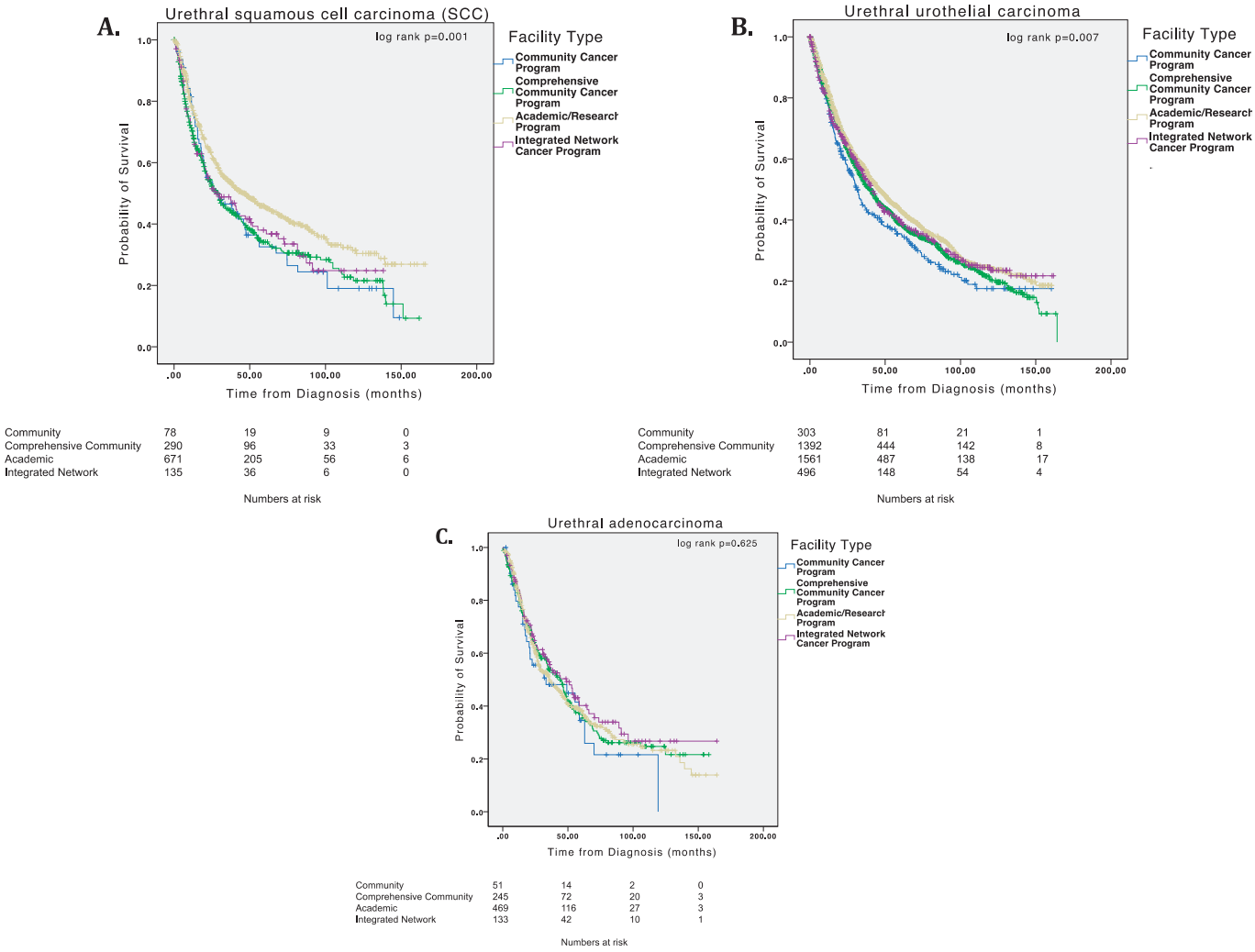

Fig. 2. Kaplan-Meier plot of overall survival in primary urethral SCC (A), urothelial carcinoma (B) and adenocarcinoma (C).

+, cM+) who would be expected to gain the greatest benefit from centralization of care ($n = 2{,}179$). Median overall survival was 22.2 months (IQR 20.3–24.1 months). There was a significant difference in overall survival based upon type of treating facility, as shown in Fig. 3 (log rank $P < 0.001$). Academic centers (median survival 25.9 months, IQR 22.8–29.0) had significantly greater survival on pairwise comparisons versus the 3 other facility types ($P < 0.001$). None of the other facility types showed significant pairwise differences in survival. Multivariable Cox regression analysis in this cohort again revealed a statistically significant survival advantage associated with academic centers (HR 0.799, 95% CI 0.640–0.996).

We then evaluated trends in practice patterns across facility types that may, in part, explain the differences in overall survival (Table 4). Academic centers were associated with a significantly greater frequency of treatment with neoadjuvant and adjuvant chemotherapy and radiation ($P < 0.001$). Of note, only 3.8% of patients in this cohort were reported to have not received chemotherapy due to patient risk factors or contraindications. There was also a significant difference in surgical treatment among facility types. Academic centers performed radical surgery in 34.1% of patients compared to just 14.5% in community programs and 15.7% in comprehensive community cancer programs ($P < 0.001$). Further, academic centers performed nearly 3 times more regional lymph node dissections than community programs and comprehensive community cancer programs (31.6%, 13.2%, 11.9% respectively, $P < 0.001$).

Due to specific guidelines for multimodal therapy for patients with clinically advanced disease, we performed a subgroup analysis of patients with cT3-4 or node-positive, M0 disease; there were again significant differences in practice patterns with academic centers having greater frequency of neoadjuvant chemotherapy, radical surgery, and regional lymph node dissections ($P < 0.05$) (Table 5). At academic centers neoadjuvant chemotherapy was given in only 11.6% of clinically advanced patients and regional lymph node dissection was performed in 43.3%, though these were substantially greater than the rates of 4.1% and

Table 2
Cox regression analysis, all primary urethral cancer

Variable	HR	*P* value
Age	1.036 (1.032−1.040)	<0.001
Race		
White	Ref	
Black	1.114 (1.002−1.240)	0.047
Asian/Pacific Islander	0.719 (0.522−0.991)	0.044
Hispanic ethnicity	0.944 (0.771−1.154)	0.572
Gender		
Male	Ref	
Female	0.904 (0.829−0.985)	0.021
Insurance status		
Uninsured	Ref	
Private insurance	0.658 (0.511−0.846)	0.001
Medicaid	1.182 (0.882−1.586)	0.263
Medicare	0.675 (0.525−0.868)	0.002
Other government	0.716 (0.470−1.091)	0.120
% without HS degree		
≥21%	Ref	
13.0−20.9%	1.054 (0.946−1.175)	0.342
7.0−12.9%	0.976 (0.878−1.087)	0.663
<7.0%	0.885 (0.786−0.997)	0.045
Urban/Rural residence		
Rural	Ref	
Metropolitan	0.886 (0.760−01.032)	0.119
Facility type		
Community	Ref	
Comprehensive Community	0.885 (0.773−1.013)	0.077
Academic	0.858 (0.749−0.983)	0.027
Integrated Network	0.897 (0.768−1.049)	0.174
Charlson/Deyo Score		
0	Ref	
1	1.137 (1.043−1.239)	0.004
2	1.609 (1.396−1.855)	<0.001
≥3	1.579 (1.255−1.987)	<0.001
Distance to hospital	0.999 (0.999−1.000)	<0.001
Histology		
SCC	Ref	
Urothelial	0.963 (0.874−1.062)	0.451
Adenocarcinoma	0.951 (0.844−1.071)	0.406
Grade		
1	Ref	
2	1.248 (1.066−1.461)	0.006
3	1.296 (1.121−1.498)	<0.001
4	1.235 (1.053−1.448)	0.010
Clinical T		
cT1	Ref	
cTx	1.279 (1.126−1.452)	<0.001
cTa	0.758 (0.642−0.894)	0.001
cTis	0.779 (0.660−0.918)	0.003
cT2	1.270 (1.118−1.443)	<0.001
cT3	1.767 (1.539−2.029)	<0.001
cT4	2.178 (1.870−2.536)	<0.001

24.4%, respectively, at community centers. There was a significant difference in administration of radiation for clinically advanced disease, utilized more in nonacademic centers ($P = 0.007$). A subgroup analysis of patients with metastatic disease showed no significant differences in practice patterns across facility types (Supplementary Table 1).

Pathologic staging after radical surgery across facility types is shown in Table 6. Of note, there was no difference in pathologic T or M stage, though were differences in the proportions of patients with node-positive disease across facility types. Among patients with adverse pathologic features (pT3-4 or N1-2) there was no difference between facility types in administration of adjuvant chemotherapy, but there were significant differences in adjuvant radiotherapy, utilized least frequently at academic centers (16.6%) and most frequently at comprehensive community cancer centers (30.5%).

5. Discussion

Primary UC is a rare but aggressive malignancy with a critical dearth of evidence regarding prognostic factors and optimal clinical management. In this study we reveal important differences in facility-level practice patterns and clinical outcomes in 6,445 patients with primary UC. This study shows a significant overall survival benefit associated with treatment at academic centers; this survival benefit was significant among all patients and on subgroup analysis of the 2 most common histologic subtypes, SCC and urothelial carcinoma. On multivariable analysis, academic centers were associated with improved survival compared to treatment at community cancer centers for all UC and in patients with primary urethral urothelial carcinoma (HR 0.852 and 0.796, respectively). Evaluation of practice patterns revealed that, in concordance with published guidelines, academic centers performed significantly higher rates of radical surgery with regional lymphadenectomy, and were more likely to administer neoadjuvant or adjuvant chemotherapy and radiation; these differences were significant in all patients and, more importantly, for those with advanced disease (≥cT3, node-positive) at initial diagnosis.

The importance of centralization of care to high-volume, academic centers has become increasingly well studied in urologic oncology. Treatment at larger-volume centers has been shown in retrospective studies to provide improved survival and improved clinical outcomes for bladder, prostate, penile, testicular, and renal cancer [1,5]. Treatment at an academic center and private or Medicare insurance status have been shown to be associated with guideline-based care in non-muscle invasive bladder cancer [6]. However, due to the comparatively low incidence of primary UC, there remains inadequate evidence regarding optimal clinical management. Authors from the largest international collaborative group on primary UC have identified the existing literature gap as an urgent clinical need [3].

In 2013 the European Association of Urology published guidelines for primary urethral carcinoma, which recommend consideration of regional lymphadenectomy for clinically node-positive patients or those with invasive tumors. The guidelines further advocate for aggressive surgical management, as ablative techniques such as transurethral resection or laser ablation have high failure rates. Importantly, for locally advanced UC the guidelines recommend

Table 3
Cox regression analysis, urethral SCC, and urothelial carcinoma

	SCC		Urothelial	
Variable	HR	*P* value	HR	*P* value
Age	1.033 (1.025−1.042)	<0.001	1.042 (1.037−1.048)	<0.001
Race				
White	Ref		Ref	
Black	1.084 (0.877−1.340)	0.455	1.105 (0.941−1.299)	0.223
Asian/Pacific Islander	0.769 (0.388−1.525)	0.452	0.621 (0.387−0.998)	0.049
Hispanic ethnicity	1.081 (0.752−1.555)	0.674	0.945 (0.715−1.249)	0.691
Gender				
Male	Ref		Ref	
Female	0.739 (0.625−0.872)	<0.001	0.910 (0.803−1.032)	0.140
Insurance status				
Uninsured	Ref		Ref	
Private insurance	0.609 (0.370−1.001)	0.050	0.688 (0.485−0.976)	0.036
Medicaid	1.078 (0.616−1.887)	0.792	1.389 (0.895−2.157)	0.143
Medicare	0.712 (0.429−1.183)	0.190	0.666 (0.472−0.939)	0.020
Other government	0.819 (0.349−1.924)	0.647	0.688 (0.391−1.211)	0.195
% without HS degree				
≥21%	Ref		Ref	
13.0-20.9%	1.002 (0.790−1.272)	0.985	1.136 (0.983−1.312)	0.085
7.0-12.9%	1.120 (0.882−1.422)	0.353	1.001 (0.869−1.152)	0.992
<7.0%	0.997 (0.767−1.295)	0.981	0.868 (0.744−1.013)	0.072
Urban/Rural residence				
Rural	Ref		Ref	
Metropolitan	1.078 (0.753−1.542)	0.682	0.836 (0.697−1.002	0.053
Facility type				
Community	Ref		Ref	
Comprehensive Community	1.002 (0.731−1.374)	0.991	0.833 (0.707−0.981)	0.029
Academic	0.838 (0.613−1.147)	0.269	0.805 (0.681−0.952)	0.011
Integrated Network	1.078 (0.745−1.561)	0.690	0.866 (0.715−1.049)	0.142
Charlson/Deyo Score				
0	Ref		Ref	
1	1.081 (0.891−1.311)	0.428	1.131 (1.015−1.261)	0.026
2	1.088 (0.762−1.554)	0.644	1.677 (1.408−1.997)	<0.001
≥3	1.270 (0.787−2.050)	0.328	1.659 (1.246−2.210)	0.001
Distance to hospital	0.999 (0.998−1.000)	0.017	0.999 (0.999−1.000)	0.030
Grade				
1	Ref		Ref	
2	0.938 (0.702−1.253)	0.667	1.142 (0.915−1.425)	0.240
3	0.722 (0.539−0.967)	0.029	1.585 (1.317−1.908)	<0.001
4	0.686 (0.501−0.940)	0.019	1.449 (1.195−1.758)	<0.001
Clinical T				
cT1	Ref		Ref	
cTx	1.208 (0.916−1.593)	0.180	1.297 (1.106−1.521)	0.001
cTa	0.773 (0.242−2.467)	0.663	0.769 (0.644−0.918)	0.004
cTis	0.628 (0.402−0.981)	0.041	0.765 (0.634−0.922)	0.005
cT2	1.189 (0.888−1.593)	0.245	1.212 (1.037−1.417)	0.016
cT3	1.769 (1.339−2.336)	<0.001	1.853 (1.515−2.265)	<0.001
cT4	3.489 (2.558−4.758)	<0.001	1.915 (1.562−2.349)	<0.001
Clinical N				
cN0	Ref		Ref	
cN1	0.837 (0.632−1.110)	0.218	0.978 (0.754−1.268)	0.864
cN2	1.490 (1.161−1.913)	0.002	1.285 (1.035−1.595)	0.023
cNx	1.328 (1.048−1.682)	0.019	0.864 (0.750−0.995)	0.043
Clinical M				
cM0	Ref		Ref	
cM1	2.867 (2.192−3.749)	<0.001	3.599 (3.006−4.309)	<0.001

platinum-based neoadjuvant chemotherapy, with neoadjuvant chemoradiation for those with SCC [2]. Other more recent retrospective studies have also shown a survival benefit associated with neoadjuvant chemotherapy, including in patients with advanced disease (≥cT3 or clinically node-positive) [3,4,7].

Table 4
Variations in practice patterns across facility types

Facility type	Community	CCCP	Academic	INCP	Total	*P* value
Any chemotherapy	18.0%	17.9%	30.2%	22.0%	24.0%	<0.001
Neoadjuvant	1.0%	1.2%	5.3%	1.3%	2.6%	<0.001
Adjuvant	10.6%	12.0%	16.3%	14.6%	12.1%	
Any radiation	16.1%	16.6%	18.8%	17.9%	17.7%	0.171
Neoadjuvant	0.2%	0.1%	1.0%	1.1%	0.7%	<0.001
Adjuvant	8.3%	9.8%	9.7%	9.3%	9.6%	
Surgery						
Ablative	1.2%	1.9%	1.4%	1.4%	1.6%	<0.001
Local excision	50.6%	48.1%	29.0%	45.2%	39.1%	
Simple excision	8.3%	8.6%	12.3%	8.6%	10.3%	
Radical surgery	14.5%	15.7%	34.1%	20.5%	24.6%	
Lymph node dissection	13.2%	11.9%	31.6%	17.0%	21.6%	<0.001

CCCP = Comprehensive community cancer center; INCP = Integrated network cancer program.

Our study reveals that adherence to guidelines and expert opinion appears to be low, with a minority of patients with clinically advanced disease receiving neoadjuvant chemotherapy, chemoradiation, or radical surgery with regional lymph node dissection. However, these treatments occurred at significantly higher rates at academic centers, and this may in part explain the survival benefit associated with treatment at these sites. Interestingly, for primary urethral SCC there was a survival benefit associated with treatment at academic centers on Kaplan Meier analysis, but facility type was not an independent predictor of survival on multivariable Cox regression analysis. This may in part be explained by the high proportion of patients with advanced disease treated with radiation at non-academic centers, as radiation has been reported to be successful in case reports and small series of urethral SCC[2].

/As has previously been shown in other studies, we show that age, Charlson/Deyo score, grade and clinical stage are significant predictors of overall survival [2,8]. Tumor histology was not a significant independent predictor of overall survival. It is interesting to note that greater distance traveled to the hospital was associated with decreased hazard of death, which may indicate greater distance traveled to

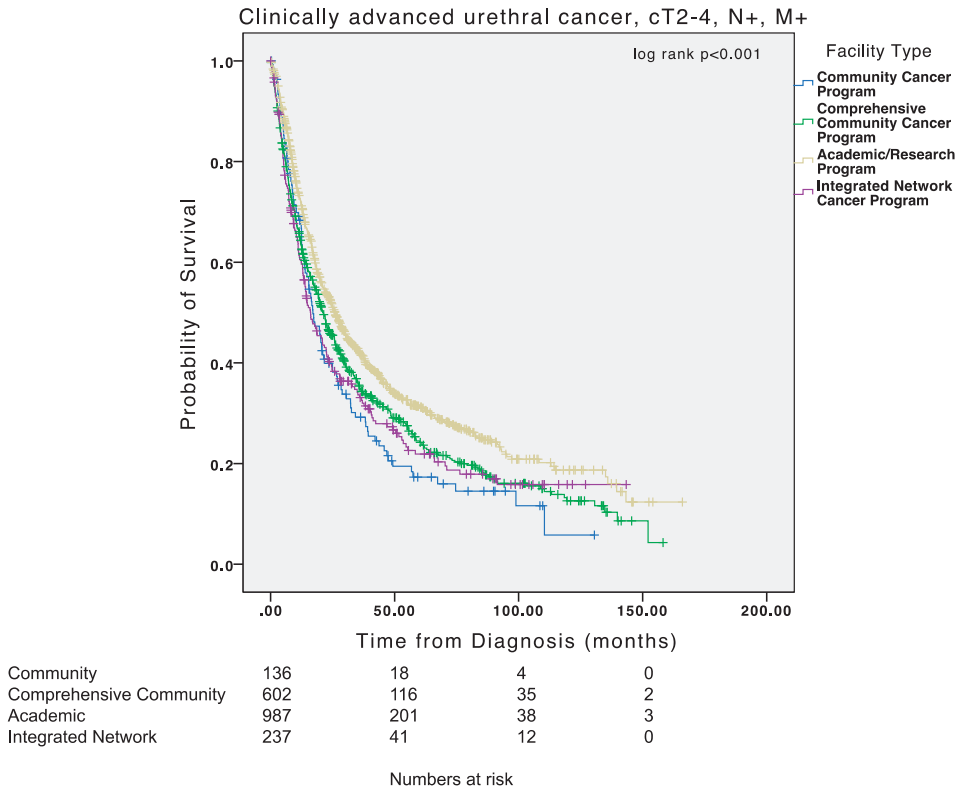

Fig. 3. Kaplan-Meier plot of overall survival, patients with cT2-4, N+, M+ disease.

Table 5
Variations in practice patterns across facility types, patients with ≥cT3 or cN+, M0 disease

Facility type	Community	CCCP	Academic	INCP	*P* value
Any chemotherapy	51.2%	50.6%	59.4%	50.9%	0.022
Neoadjuvant	4.1%	3.4%	11.6%	2.7%	0.002
Adjuvant	16.4%	22.6%	21.4%	24.5%	
Any radiation	39.0%	46.7%	36.8%	46.6%	0.007
Neoadjuvant	1.2%	0.6%	3.1%	3.1%	0.018
Adjuvant	12.2%	22.8%	14.0%	22.7%	
Surgery	54%	51.8%	60.6%	59.5%	
Ablative	0.0%	0.6%	0.6%	0.0%	
Local excision	25.6%	25.7%	15.4%	27.0%	<0.001
Simple excision	8.5%	7.2%	6.7%	5.5%	
Radical surgery	19.5%	18.3%	38.0%	27.0%	
Lymph node dissection	24.4%	22.8%	43.3%	31.3%	<0.001

CCCP = Comprehensive community cancer center; INCP = Integrated network cancer program.

major academic centers. Private and Medicare insurance status were associated with improved overall survival as was higher educational attainment; these findings, along with the improved survival seen at academic centers, indicate an important effect of access to high quality care and underscore the critical need for ameliorating disparities in access in order to improve outcomes for this rare malignancy. We further found that male gender and black race were associated with decreased overall survival. While race and gender have been demonstrated to be associated with disparities in care and survival in other urologic malignancies including bladder cancer [9−11, previous studies have not shown similar differences in primary UC. Analysis of the cohort of 154 patients (109 men, 45 women) from the international collaboration on primary UC found no gender-based differences in overall survival, and did not report data according to race [3]. A previous analysis of data from the NCDB found inferior survival for black patients, but no survival differences based upon gender [3,8]. This study is the first administrative data analysis to our knowledge that has shown disparities in outcomes based on both gender and race in primary UC, and these results warrant further investigation in future studies.

No previous study has evaluated type of treating facility as a prognostic factor on overall survival in primary UC, and our results serve to reinforce suggestions in the literature that treatment be performed at academic centers capable of carrying out complex multidisciplinary treatment. Importantly, though the effects did not reach statistical significance, both comprehensive community care programs and integrated network care programs have similar hazard ratios as academic centers; further studies with larger

Table 6
Pathologic staging after radical surgery and adjuvant treatment for adverse pathologic features across facility types

	Community	CCCP	Academic	INCP	Total	*P* value
Pathologic T						
pTa	4 (5.7%)	14 (4.0%)	22 (2.2%)	4 (2.4%)	44 (2.8%)	0.153
pTis	3 (4.3%)	16 (4.6%)	52 (5.2%)	7 (4.1%)	78 (4.9%)	
pT1	5 (7.1%)	27 (7.8%)	75 (7.5%)	14 (8.2%)	121 (7.6%)	
pT2	14 (20.0%)	85 (24.5%)	204 (20.5%)	36 (21.2%)	339 (21.4%)	
pT3-4	28 (40.0%)	102 (29.4%)	398 (40.0%)	60 (35.3%)	588 (37.2%)	
pTx/unknown	16 (22.9%)	103 (29.7%)	246 (24.7%)	49 (28.8%)	414 (26.1%)	
Pathologic N						
pN0	40 (57.1%)	157 (45.2%)	556 (55.8%)	76 (44.7%)	829 (52.3%)	<0.001
pN1	2 (2.9%)	15 (4.3%)	55 (5.5%)	12 (7.1%)	84 (5.3%)	
pN2	7 (10.0%)	19 (5.5%)	95 (9.5%)	8 (4.7%)	129 (8.1%)	
pNx	19 (27.1%)	132 (38.0%)	251 (25.2%)	68 (40.0%)	470 (29.7%)	
Unknown	2 (2.9%)	24 (6.9%)	40 (4.0%)	6 (3.5%)	72 (4.5%)	
Pathologic M						
pM1	2 (2.9%)	7 (2.0%)	13 (1.3%)	1 (0.6%)	23 (1.5%)	0.111
Adjuvant chemotherapy for adverse features ($n = 614$)	23.1%	25.7%	24.6%	27.9%	25.1%	0.946
Adjuvant radiotherapy for adverse features ($n = 614$)	23.1%	30.5%	16.6%	24.6%	20.0%	0.011

CCCP = Comprehensive community cancer center; INCP = Integrated network cancer program.
Adverse features = pT3-4 or N1-2.

sample sizes thus may additionally show a survival benefit associated with centralization to non-academic centers.

This study has several important limitations. The NCDB does not include granular details on case complexity; in general, more complex cases tend to be referred to high-volume academic centers, so the actual survival benefit associated with centralization of care is likely more pronounced than shown in this study. Though reports to the NCDB include all cumulative treatment at multiple facilities, there may be some cases in which further treatment was received at a non-CoC facility, and treatment not reported to the NCDB would thus not be captured in this dataset. The NCDB also does not report on tumor location, which is an important prognostic factor in UC. Additionally, though we report which patients received systemic chemotherapy, data is not available regarding the type of chemotherapy or number of cycles received. We are unable to report on disease-specific survival, only overall survival though we are able to control for Charlson/Deyo score to account for the effect of comorbid conditions. Finally, we cannot differentiate prostatic urethral urothelial carcinoma from other urethral urothelial carcinoma in this dataset, though its treatment algorithm is different and may include TUR and BCG or radical cystoprostatectomy for extensive prostatic ductal involvement; similarly, radical surgery may refer to urethrectomy or radical cystectomy with urethrectomy depending on clinical factors, and this difference is not clearly coded in the NCDB, nor is the extent of regional lymphadenectomy (e.g., inguinal versus pelvis versus both). It is unknown how many patients in this study had undergone prior cystectomy, though the dataset is importantly limited to those with primary urethral malignancy and not primary bladder cancer. In spite of these limitations, this study represents an important contribution to the literature revealing a significant survival benefit and increased guideline-based care for patients with UC treated at academic centers.

6. Conclusion

There exist significant differences in overall survival for patients with primary UC based upon the type of facility at which they receive their care. Variations in practice patterns, including multimodality treatment, extent of radical surgery, and performance of regional lymphadenectomy may contribute to the observed differences in clinical outcomes.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.09.020.

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