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Original article

Contemporary practice patterns and survival outcomes for locally advanced urethral malignancies: A National Cancer Database Analysis

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Abstract

Purpose: Primary urethral carcinoma (PUC) has an aggressive natural history; however, controversy exists regarding the role of multimodal therapy for its treatment. Our objective was to examine practice patterns and survival outcomes for locally advanced urethral cancers.

Methods: The National Cancer Database was queried for patients with T2–4 or N1–2M0 PUC with urothelial, squamous, or adenocarcinoma histology from 2004 to 2013. Temporal trends for receipt of local or definitive surgery, radiotherapy (XRT), and systemic therapy were assessed. Adjusting for clinicopathologic characteristics, we evaluated the effect of tumor stage and histology on receipt of definitive multimodal therapy (cystectomy + chemotherapy ± XRT) and effects of treatment on overall survival.

Results: A total of 1,749 patients met inclusion criteria (22.2% adenocarcinoma, 29.3% squamous, and 48.5% urothelial). Only 29.6% underwent cystectomy ± XRT, and 15.6% underwent definitive multimodal therapy. Following adjustment, older patients (age 50–75: odds ratio [OR] = 0.42 [95% CI: 0.28–0.63]; age 75+: OR = 0.06 [95% CI: 0.03–0.13]) and those with squamous histology (OR = 0.46 [95% CI: 0.3–0.7]) were less likely to receive definitive multimodal therapy. More advanced stage (T3: OR = 1.66 [95% CI: 1.15–2.41]; T4: OR = 3.57 [95% CI: 2.47–5.16]); and N2 status (OR = 1.88 [95% CI: 1.27–2.78]) were more likely to receive definitive multimodal therapy. On adjusted analysis, an overall survival benefit was only observed with definitive multimodal therapy for PUC of urothelial origin (hazard ratio = 0.61 [95% CI: 0.45–0.83]).

Conclusions: Despite a survival benefit, most patients with locally advanced PUC do not undergo definitive multimodal therapy. We advocate for a multidisciplinary-based treatment approach for these patients. Future prospective trials of multimodal therapy are crucial.

Keywords: Urethral carcinoma; Locally advanced; Temporal trends; Multimodal therapy; Survival outcomes; NCDB

1. Introduction

Primary urethral carcinoma (PUC) is a rare clinical entity representing <1% of all malignancies [1,2]. PUC has an aggressive natural history with reported 5-year overall (OS) and disease-specific survival of 40% to 60% [1–5]. Worse prognoses have been associated with a more proximal tumor location (which are thought to present later and are more challenging to manage) and stage [3–5]. However, there are conflicting data associating histology and survival outcomes, as previously published National Cancer Database (NCDB) and Surveillance, Epidemiology, and End

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Results Program analyses have not coincided [3,4]. Multiple studies have demonstrated that urothelial histology is the most common subtype, ranging from 55% to 64%, followed by squamous cell, and finally, adenocarcinoma [1–3].

Owing to its rarity, PUC lacks robust trials to support broad evidence-based treatment algorithms; thus, controversy exists regarding optimal management strategies [5]. Definitive multimodal therapy (i.e., the combination of definitive surgery, radiation, and systemic therapies) is accepted in other advanced solid tumors [6–8]. The National Comprehensive Cancer Network (NCCN) guidelines support neoadjuvant chemotherapy (NAC) or chemoradiotherapy as a category 2B recommendation for clinical stage 3 to 4 urethral malignancies [7]. Despite these recommendations, the role of definitive multimodal therapy in locally advanced (and thus potentially curable) urethral cancers remains poorly understood. Our objective was to examine contemporary practice patterns and survival outcomes for locally advanced urethral cancers using a large national tumor registry to highlight potential opportunities for improvement in care.

2. Methods

2.1. Data source

Established in 1989, the NCDB, a program of the American College of Surgeons Commission on Cancer and the American Cancer Society, is a national cancer registry that serves as a comprehensive clinical surveillance resource for cancer care in the United States [9,10]. Capturing greater than 70% of all newly diagnosed cancer cases, the NCDB compiles data from more than 1,500 commission-accredited cancer programs in the United States and Puerto Rico [9,10]. Variables include patient demographics, facility information and treatment modalities, and OS outcomes [9,10].

2.2. Cohort definition

We identified all patients in the NCDB with PUC diagnosed from 2004 through 2013 using International Classification of Diseases for Oncology, 3rd edition site codes C680. Inclusion criteria included patients ≥18 years with locally advanced urethral cancers with urothelial, squamous, or adenocarcinoma histology. Locally advanced urethral carcinoma was defined as T2–4 or N1–2 and M0. Patients with metastatic disease at diagnosis or missing survival data were excluded from analysis, as shown in Fig. 1.

Patients were stratified into 1 of 3 cohorts based upon treatment: (1) definitive multimodal therapy (definitive surgery [cystectomy] + systemic therapy ± radiotherapy [XRT]), (2) definitive surgery (cystectomy ± XRT), and (3) local excision or chemotherapy or XRT alone.

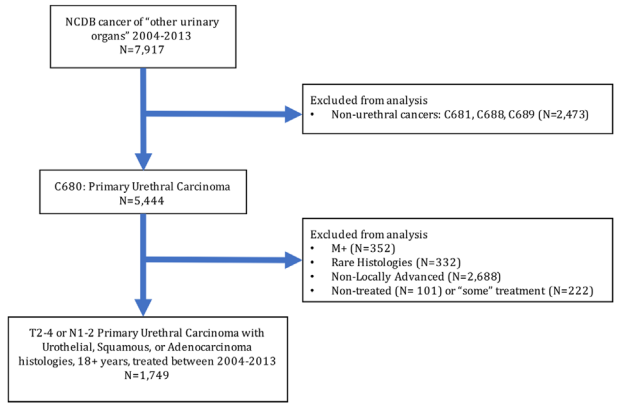

Fig. 1. Consort flow diagram demonstrating inclusion and exclusion of subjects in this NCDB primary urethral carcinoma analysis.

2.3. Covariates

Patient socioeconomic characteristics were obtained from the United States Census tract data. Demographic covariates included sex, age, race (White, African American, or other), ethnicity (Hispanic, non-Hispanic, or other/unknown), insurance status, Charlson-Deyo score, high school degree, and income quartile. Additionally, based on case volume and access to cancer-related services and specialists, the NCDB classifies hospitals as community (100–500 new cancer cases/year), comprehensive community (>500 cases/year), and teaching/research (academic), as defined by the National Cancer Institute designation or a medical school affiliation. Tumor is stratified by histology, grade, and tumor, node, and metastatic stage. The NCDB uses analytic staging, where the variable preferentially assigns pathologic stage, unless not reported, when clinical stage is used.

2.4. Outcomes and survival analysis

Adjusting for clinicopathologic characteristics, generalized estimating equations were used to evaluate the effect of tumor stage and histology on receipt of definitive multimodal therapy (defined as definitive surgery [± XRT] and systemic therapy) [11]. Systemic therapy was defined as chemotherapy as first course of treatment. Kaplan-Meier curves and Cox regression analyses were used to assess the effect of multimodal therapy on OS, our primary outcome of interest. To determine the effect of multimodal therapy by histologic subtype, we included an interaction between histology and treatment in the regression model. Temporal trends for receipt of local (excisional) and definitive (cystectomy) surgery, XRT, and systemic therapy were assessed using Cochran Armitage tests, our secondary outcome measure. Statistical analysis was done with SAS,

Table 1
Demographic, clinical, and pathologic characteristics of patients with advanced urethral carcinoma in the NCDB, stratified by treatment type

Descriptive groups		Definitive surgery + CT ± XRT	Definitive surgery ± XRT	Local excision or CT or XRT	*P* value
N	1,749	15.6	29.6	54.8	
Histology (%)					<0.0001
	Adenocarcinoma	21.4	38.1	41.5	
	Squamous cell	12.5	25.7	61.8	
	Urothelial	14.7	28.1	57.2	
Sex (%)					<0.0001
	Male	13.2	28.1	58.7	
	Female	19.5	32.3	48.2	
Age (%)					<0.0001
	<50	31.9	23.8	44.4	
	50–75	20	33.5	46.5	
	76+	2.8	24.3	72.9	
Race (%)					0.2006
	White	15	29.4	55.6	
	African American	18.3	13.7	50	
	Other/unknown	12.7	23.8	63.5	
Ethnicity (%)					0.0368
	NonHispanic	15.7	30.1	54.3	
	Hispanic	11.3	14.5	74.2	
	Unknown	15.8	31.6	52.6	
Insurance payer status (%)					<0.0001
	Uninsured	12.7	25.5	61.8	
	Private insurance/managed care	23.7	28.2	48.1	
	Medicaid	23.33	24.4	52.2	
	Medicare	10.2	30.1	58.9	
	Other government	11.1	44.4	44.4	
	Unknown	19.2	28.9	51.9	
Income quartile (%)					0.0155
	First: <$30,000	19.8	26.3	53.9	
	Second: $30,000-$34,999	15.4	35.3	49.3	
	Third: $35,000-$45,999	14.1	29.1	56.8	
	Fourth: >$46,000	72	27.8	58	
Treatment location (%)					0.0311
	Large metro	16.4	27.5	56.1	
	Small metro	14.7	28.3	57	
	Suburban	11.9	40.7	47.5	
	Rural	19.7	31.2	49.2	
	Unknown	12.7	36.4	50.9	
Charlston-Deyo score (%)					0.217
	0	15.9	28.7	55.4	
	1	16.1	31.3	52.6	
	2	8.8	36.3	54.9	
Histologic grade (%)					0.002
	I/II	14.9	32.4	52.7	
	III/IV	16.6	30.4	53	
	Unknown	11.9	21.4	66.7	
Tumor stage (%)					<0.0001
	T2	9.2	29.4	61.4	
	T3	16.2	34.5	49.3	
	T4	30.1	27.4	41.6	
	Other	6.9	4.1	89	
Nodal stage (%)					<0.0001
	N0	12.7	33.9	53.4	
	N1	22.5	12.2	58.2	
	N2	24	16.9	59.1	
Facility type (%)					<0.0001
	Community cancer	8.1	18.8	73.2	
	Comprehensive community	10.7	25.1	64.3	
	Academic/research	19.9	35.5	44.6	
	Integrated network cancer	10.8	22.5	66.7	

Univariate analysis is of statistical significance when $P < 0.05$.

version 9.3, and Stata, version 12.1, where $P < 0.05$ is considered statistically significant.

3. Results

3.1. Demographics and temporal trends

A total of 1,749 patients were identified in the NCDB with the diagnosis of PUC and met inclusion criteria (Fig. 1). Histologically, 22.2% were adenocarcinomas ($n = 388$), 29.3% squamous cell ($n = 513$), and 48.5% urothelial ($n = 848$). Additionally, 54.8% ($n = 959$) of the cohort was treated with local excision or chemotherapy or radiation alone, 29.6% ($n = 518$) underwent cystectomy ± XRT, and only 15.6% ($n = 272$) underwent definitive multimodal therapy (21.4% adenocarcinoma, 12.5% squamous, and 14.7% urothelial), as demonstrated in Table 1. Table 2 stratifies the cohort histology by sex.

Univariate analysis, stratified by treatment type (cohorts 1–3), of demographic, clinical, and pathologic characteristics is demonstrated in Table 1. In summary, patients receiving local excision tended to be males, increased age, Hispanic, and had a higher tumor grade or stage (all $P < 0.04$). Fig. 2 demonstrates temporal trends stratified by treatment cohort, where there were no observed differences in the use of any treatment cohort by year (all $P > 0.5$).

3.2. Factors associated with receipt of definitive multimodal therapy

Following adjustment, patients with higher-stage tumors (T3: odds ratio [OR] = 1.66 [95% CI: 1.15–2.41]); (T4: OR = 3.57 [95% CI: 2.47–5.16]); and N2 status (OR = 1.88 [95% CI: 1.27–2.78]) were more likely to receive definitive multimodal therapy (all $P < 0.01$). Patients of older age (age 50–75: OR = 0.42 [95% CI: 0.28–0.63]; age 75+: OR = 0.06 [95% CI: 0.03–0.13]), Medicare insurance (OR = 0.63 [95% CI: 0.45–0.90]), and squamous histologies (OR = 0.46 [95% CI: 0.3–0.7]) were less likely to receive definitive multimodal therapy (all $P < 0.02$). Year of diagnosis, sex, Hispanic ethnicity, high school diploma quartile, hospital location, Charlston-Deyo score, facility type, race, income quartile, and facility location had no effect on receipt of definitive multimodal therapy (all $P > 0.05$).

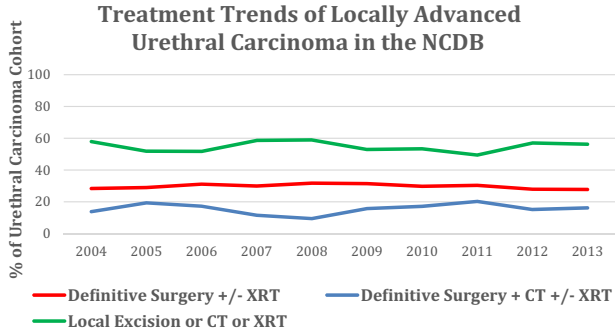

Fig. 2. Temporal trends of 3 cohort treatment modalities of PUC in the NCDB.

3.3. OS analysis based on treatment received

For patients treated with definitive multimodal therapy, median OS was 33.4 months (95% CI: 27.1–46.6). In patients treated with definitive surgery ± XRT, median OS was 42.6 months (95% CI: 35.4–48.6). Lastly, patients treated by local excision or chemotherapy or radiotherapy alone had a median OS of 30.1 months (95% CI: 26.1–35.3). Overall, no differences in survival were present on multivariate adjusted analysis ($P = 0.185$).

3.4. OS based on primary histology

When stratified by histologic subtype, patients treated with definitive multimodal therapy had a median OS of 52.6 months (95% CI: 30.9–79.2), 27.6 months (95% CI: 20.2–NA [undefined]), and 27.1 months (95% CI: 21.8–39.3) for urothelial, squamous, and adenocarcinoma histologies, respectively (Table 3 and Figs. 3–5). After adjustment for clinicopathologic characteristics, an OS benefit was observed with definitive multimodal therapy for urethral cancers of urothelial origin (Hazard ratio, HR = 0.61 [95% CI: 0.45–0.83], $P = 0.0016$), but not for urethral cancers of squamous (HR = 1.22 [95% CI: 0.80–1.85]) or adenocarcinoma (HR = 1.11 [95% CI: 0.79–1.57]) histologies. No statistically significant survival differences were observed between the various histologic subtypes in patients treated with definitive surgery ± XRT (all $P > 0.05$). The number of deaths in the overall cohort, stratified by histologic subtype, is displayed in Table 4.

Table 2
Patient sex stratified by cohort histology

Histology	Male	Female	Total
Adenocarcinoma	76	312	388
Squamous	339	174	513
Urothelial	689	159	848
Total	1,104	645	1,749

Table 3
Summary of treatment effects and overall survival outcomes, as compared to local excision or Chemo or XRT, stratified by histology using multivariate analysis, where $P < 0.05$ is considered statistically significant

Histology	Treatment group	HR	95% CI	P value	Median OS (months)	95% CI
Urothelial	Definitive surgery + CT ± XRT	0.61	0.45–0.83	0.0016	52.6	30.9–79.2
	Definitive surgery ± XRT	0.84	0.67–1.06	0.1375	36.1	27.4–43.7
	Local excision or CT or XRT	–	–	–	23.9	19.8–29.5
Squamous	Definitive surgery + CT ± XRT	1.22	0.80–1.85	0.3582	27.6	20.2—Undefined
	Definitive surgery ± XRT	0.96	0.70–1.32	0.8012	47.8	29.3–75.8
	Local excision or CT or XRT	–	–	–	40.5	30.4–53.1
Adenocarcinoma	Definitive surgery + CT ± XRT	1.11	0.79–1.57	0.535	27.1	21.8–39.3
	Definitive surgery ± XRT	0.83	0.60–1.16	0.2845	47.6	35.3–73.7
	Local excision or CT or XRT	–	–	–	30.7	23.7–47.5

4. Discussion

Using the NCDB database, we conducted a retrospective analysis of treatment patterns and outcomes in PUC. Fewer than 16% of patients with locally advanced urethral carcinoma received definitive multimodal therapy. Given the rarity of this malignancy, we believe that these findings are representative of the national population and may suggest gross undertreatment of this aggressive disease.

Current NCCN recommendations place NAC or chemoradiotherapy before definitive surgery as a category 2B recommendation [7]. A retrospective evaluation of 44 patients with PUC treated at MD Anderson Cancer Center over a 5-year period demonstrated a 72% response rate with the use of cisplatin-based chemotherapy [12]. No statistically significant differences were demonstrated in survival based on squamous vs. nonsquamous histology [12]. Regimens used were cisplatin, gemcitabine, and ifosfamide; gemcitabine, 5-fluorouracil, leukovorin, and cisplatin; and methotrexate, vinblastine, doxorubicin, and cisplatin [12]. Median OS for patients who underwent surgery and NAC compared to NAC alone was 46.9 and 21.7 months, respectively [12]. Additionally, a 2015 multiinstitutional study of 124 patients demonstrated a significant overall and relapse-free statistically significant survival advantage in patients with advanced disease (>cT3 or cN+) treated with NAC ($n = 5$) or chemoradiotherapy ($n = 3$), compared to surgery alone ($n = 10$) (3-yr OS: 100% vs. 50%) [13]. Our NCDB analysis should be used to compliment these retrospective studies by examining multimodal therapy in a much larger sample size across multiple treatment centers, albeit with less granularity.

In support of definitive multimodal therapy, we found that this treatment conferred an OS benefit relative to local excision or chemotherapy or radiation and cystectomy ± XRT in patients with urothelial histology only. The benefit of multimodal therapy parallels previous work in advanced solid-organ malignancies including bladder, breast, and colorectal cancers. In urothelial carcinoma of the bladder, NAC has demonstrated an OS benefit and is a category 1 recommendation before definitive surgery [7]. Similarly, breast cancers have level 1 evidence to support multimodal therapy in advanced malignancies [6]. Additionally, adjuvant chemotherapy in resectable node positive or T3–4

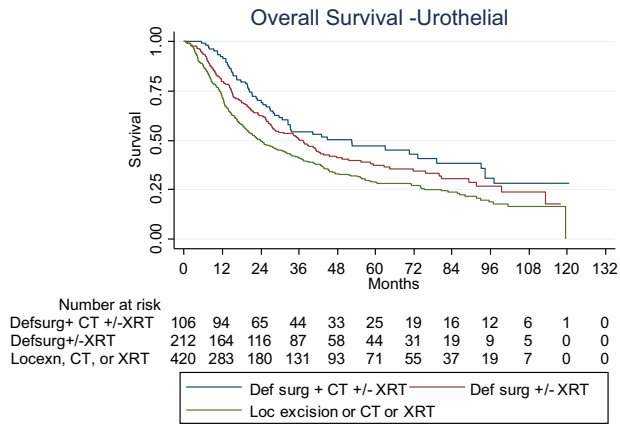

Fig. 3. Kaplan-Meyer curves demonstrating overall survival by treatment group for urothelial urethral carcinoma in the NCDB, where a statistically significant survival advantage is demonstrated for definitive surgery + CT ± XRT ($P = 0.0016$), but not for definitive surgery ± XRT ($P = 0.1375$), compared to local excision or CT or XRT alone.

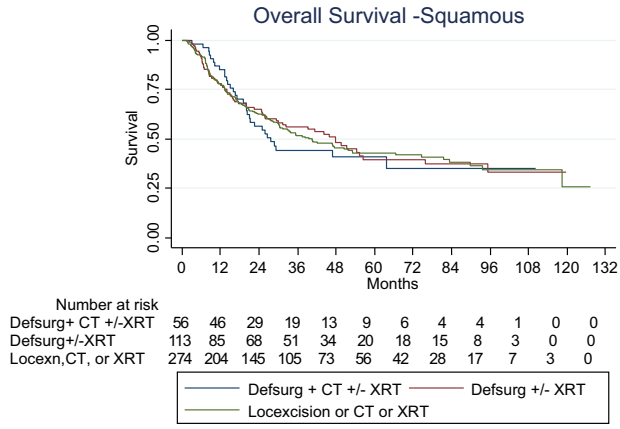

Fig. 4. Kaplan-Meyer curves demonstrating overall survival by treatment group for squamous cell urethral carcinoma in the NCDB, where no survival differences are noted between treatment groups (definitive surgery + CT ± XRT [$P = 0.3582$]; definitive surgery ± XRT [$P = 0.8012$]), compared to local excision or CT or XRT alone.

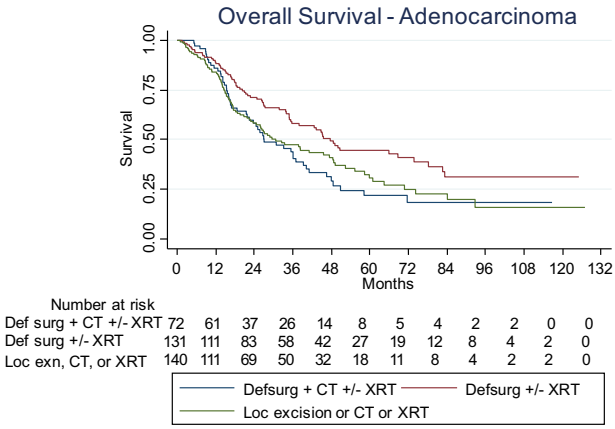

Fig. 5. Kaplan-Meyer curves demonstrating overall survival by treatment group for adenocarcinoma of the urethra in the NCDB, where no survival differences are noted between treatment groups (definitive surgery + CT ± XRT [$P = 0.535$]; definitive surgery ± XRT [$P = 0.2845$]), compared to local excision or CT or XRT alone.

colon cancers or NAC for unresectable lesions is an NCCN category 2A recommendation [8].

However, this survival benefit was not demonstrated with squamous or adenocarcinoma histologies. Although the etiology of these patterns in urethral carcinoma remains unclear, this is consistent with the treatment of bladder cancer, where the data to support perioperative chemotherapy for nonurothelial subtypes are limited [7]. Extrapolating from bladder cancers, variant histologies increase the likelihood of locally advanced disease and clinical understaging with less chemosensitivity [14].

The lack of use of multimodal therapy for treatment of malignancies in the NCDB is not restricted to urethral carcinomas. Previous studies have demonstrated that only 40% of patients treated in the NCDB for muscle-invasive bladder cancer received NAC or adjuvant chemotherapy [15], despite level 1 evidence [7]. A separate analysis determined that only half of patients with stage II to IV bladder cancer receive treatment with curative intent (radical or partial cystectomy, or definitive chemoradiotherapy) [16].

Limitations of this study include its retrospective nature and lack of evaluation of tumor location in the NCDB, as proximal tumors typically have a worse prognosis and are less amenable to local excision compared to their distal counterparts [3–5]. Additionally, reconstructive considerations are likely to have strong influences in treatment choice as smaller distal tumors in men might be more amenable to local excision given urethral length. Conversely, proximal lesions and tumors in females are closer in distance to the rhabdosphincter and may cause concern regarding continence preservation.

Additional limitations include the lack of disease-specific outcomes that were studied, and only OS can be evaluated using the NCDB. Also, our study is limited to centers reporting to the NCDB. Essential physiologic data are not captured, and any additional therapy/treatments at nonNCDB centers are unavailable for analysis. Also, we did not evaluate patients treated with immunotherapy. Using the NCDB, we are unable to assess type of chemotherapeutic regimen or number of cycles administered. Lastly, we are unable to evaluate the quality or extent of local excisional therapy that the patient has received. However, the large sample size in a very rare malignancy is the fundamental strength of this analysis.

Overall, a lack of prospective multicentered clinical trial evidence exists in this space given the rarity of disease, and future large trials are unlikely. A recent publication also examined survival outcomes in patients with urethral carcinoma using the NCDB [4]. However, our study provides the added benefit of stratifying the survival outcomes by histology and treatment group. Our data may be used along with previously published reports to help refine these treatment algorithms, in order to more clearly direct urologists and medical and radiation oncologists to the optimal care of urethral carcinomas, stressing in particular the consideration for multimodal therapy in locally advanced urothelial urethral carcinoma.

5. Conclusion

In patients captured by the NCDB, fewer than 50% of patients with locally advanced urethral cancer undergo definitive surgery. Despite a significant survival benefit, most patients with urothelial carcinoma of the urethra do not undergo aggressive multimodal therapy. We advocate for a multimodal-based treatment approach with medical and radiation oncology consultations before extirpative surgery for patients with locally advanced primary urothelial urethral carcinomas. Locally advanced squamous and adenocarcinomas of the urethra do not benefit from multimodal treatment. As prognosis is poor for locally advanced urethral malignancies and most data are generated from

Table 4
Number of any-cause deaths, stratified by histologic subtype

Histology	Deceased	Living	Missing	Total
Adenocarcinoma	204	140	44	388
Squamous	234	212	67	513
Urothelial	468	274	106	848
Total	906	626	217	1,749

small single-center trials or administrative retrospective cohort studies, prospective clinical trials of multimodal therapy are necessary.

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