



Original Article

Primary urethral cancer: treatment patterns and associated outcomes

Roy Mano^{1,2} , Emily A. Vertosick³, Joseph Sarcona^{1,4}, Daniel D. Sjoberg³, Nicole E. Benfante¹, Timothy F. Donahue¹, Harry W. Herr¹, S. Machele Donat¹, Bernard H. Bochner¹, Guido Dalbagni¹ and Alvin C. Goh¹ 

¹Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Centre, New York, NY, USA, ²Department of Urology, Tel-Aviv Sourasky Medical Centre, Sackler School of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel,

³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Centre, New York, NY, USA, and

⁴Department of Urology, Lenox Hill Hospital, New York, NY, USA

Objectives

To evaluate treatment patterns and associated outcomes of patients with urethral cancer.

Patients and Methods

After obtaining institutional review board approval we identified 165 patients treated for primary urethral cancer between 1956 and 2017. Treatment included monotherapy (surgery or radiation), dual therapy (surgery+radiation, surgery+chemotherapy, or chemotherapy+radiation) or triple therapy (surgery+radiation+chemotherapy). Rates of different treatments were described by treatment year. The association between treatment type and outcomes was evaluated with multivariable Cox regression models, adjusting for disease characteristics.

Results

The study cohort included 74 men and 91 women, with a median age of 61 years. Common histologies were squamous cell (36%), urothelial (27%) and adenocarcinoma (25%). At presentation, 72% of patients had invasive disease, 24% had nodal involvement, and 5% had metastases. Treatment included monotherapy (57%), dual therapy (21%), and triple therapy (10%). The use of monotherapy decreased over time, while rates of dual therapy remained consistent, and rates of triple therapy increased. The median follow-up was 4.7 years. Estimated 5-year local recurrence-free, disease-specific and overall survival were 51%, 48% and 41%, respectively. Monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex and year of treatment ($P = 0.017$). There was no evidence that treatment type was associated with distant recurrence, cancer-specific or overall survival.

Conclusions

We found preliminary evidence that multimodal therapy, more commonly used in recent years, was of benefit in patients with primary urethral cancer. This finding should be confirmed in further studies involving multiple centres because of the low incidence of the disease.

Keywords

multimodal treatment, outcome, radiation, surgery, urethral tumour

Introduction

Primary urethral carcinomas are rare, accounting for <1% of all genitourinary malignancies [1]. Common histologies include squamous cell carcinoma (SCC; 30–40%), urothelial carcinoma (UC; 22–47%) and adenocarcinoma (11–26%) [2–5]. Most patients are diagnosed with advanced disease [2–6]. These tumours have an aggressive natural history, with reported 5-year overall survival rates of 32–54% [2–3,7,8].

Patient and tumour characteristics associated with oncological outcome include sex, age, tumour location, stage and nodal status [2–3,5,9,10].

Treatment of primary urethral carcinoma in early series consisted mostly of monotherapy with either surgery or radiation [2,3]. Subsequent series suggested there may be an advantage in combining multiple treatment methods; however, small cohort size and lack of a consistent treatment

protocol limited the reproducibility of the reported findings [4,11–14]. Few reports have shown an outcome benefit associated with the use of multimodal therapy [15–17]. A large international multicentre cohort showed increased recurrence-free and overall survival rates in patients with locally advanced disease treated with neoadjuvant chemotherapy [15]. Additionally, in a series from the National Cancer Database (NCDB), an improved overall survival was reported for patients with locally advanced urethral tumours of urothelial origin treated with definitive multimodal therapy [16,17]. However, the quality and extent of local excisional therapies were not standardized, and cancer-specific survival was not reported. Because of the limited number of studies evaluating the association between treatment of primary urethral carcinoma and oncological outcome, and the lack of prospective data, optimal management and the role of multimodal therapy are still under investigation.

In the present study we describe a large, single-centre cohort of patients with primary urethral cancer and evaluate changing treatment patterns over time and the associated oncological outcomes.

Patients and Methods

After institutional review board approval, we identified a cohort of 176 consecutive patients diagnosed with primary urethral carcinoma at Memorial Sloan Kettering Cancer Centre between 1956 and 2017. Patients with primary urethral melanomas ($n = 11$) were excluded.

Patient characteristics including sex, age, race and presenting symptoms were collected. Tumour location, histology and TNM stage were obtained from pathology reports. Treatment of loco-regional disease included surgery and/or radiation with/without peri-operative chemotherapy. Regional lymph node dissection was performed at the discretion of the treating surgeon. The dissection template was based on the location of the primary tumour; patients with a proximal tumour underwent pelvic lymph node dissection and those with a distal tumour underwent inguinal lymph node dissection with or without pelvic lymph node dissection. Postoperative follow-up consisted of a physical examination, cystoscopy for patients undergoing limited excision, laboratory examinations, cytology and axial imaging performed every 3 to 4 months for the first year and at longer intervals thereafter. Patient status at follow-up was determined based on documented office visits. Disease recurrence was defined based on findings described in imaging study reports, with subsequent pathological confirmation when available. Recurrence was categorized as local when involving the pelvic viscera, soft tissue or lymph nodes and distant when located outside the pelvis.

We calculated descriptive statistics for clinicopathological characteristics, treatment patterns and recurrence sites, and compared them by sex. We also estimated the association between patient and disease characteristics (pathological T, N and M stages, histology and sex) and recurrence-free, cancer-specific and overall survival using univariate Cox proportional hazards models.

To assess changes in treatment patterns over time, we graphically depicted the rate of different treatments by year of treatment using locally weighted scatterplot smoothing. Treatment was categorized as monotherapy (surgery only or radiation only), dual therapy (surgery and radiation, surgery and chemotherapy, or chemotherapy and radiation) or triple therapy (surgery, radiation and chemotherapy), accounting for primary, neoadjuvant and adjuvant treatments but excluding any salvage treatments given after disease recurrence or progression.

Oncological outcomes were assessed based on the type of treatment received. Outcomes studied were local recurrence, distant recurrence, urethral cancer death and death from any cause. Since we hypothesized that treatment patterns changed significantly over time, we aimed to investigate whether there was an association between treatment and oncological outcome after adjusting for disease characteristics and year of treatment.

Because of the small cohort size and limited number of events, we were unable to include all desired covariates in our multivariable model; therefore, a multivariable Cox proportional hazards model was created for the outcome of cancer-specific death adjusted for pathological T stage (non-invasive $\leq T1$ vs invasive $\geq T2$), pathological N stage (node-negative vs node-positive), pathological M stage (M0 vs M1), histology (UC vs all other types), sex and year of treatment. A linear predictor from this model was then calculated.

Multivariable Cox regression models were created that included treatment type (monotherapy vs dual therapy vs triple therapy) and this linear predictor. Treatment decisions were highly dependent on the time that patients were treated. While treatment year does not fully explain changes in management, we attempted to control for these secular changes over time by including treatment year in the multivariable analyses. All analyses were conducted using STATA 15 (StataCorp, College Station, TX, USA).

Results

The study cohort consisted of 165 patients (45% men) diagnosed with primary urethral carcinoma. Patient and disease characteristics by type of therapy are presented in Table 1. Commonly reported presenting symptoms were obstructive symptoms (40%), irritative symptoms (33%) and haematuria (31%). Common tumour histologies included SCC

Table 1 Patient and disease characteristics, by type of treatment.

	Monotherapy (N = 94)	Dual therapy (N = 34)	Triple therapy (N = 17)	No definitive primary treatment (N = 20)	P
Men, n (%)	44 (47)	17 (50)	5 (29)	8 (40)	0.5
Age at diagnosis, years	63 (52, 70)	61 (54, 69)	57 (42, 63)	60 (51, 64)	0.2
Race (N = 146), n (%)					
White	67 (81)	21 (70)	11 (79)	13 (68)	0.4
Black	11 (13)	8 (27)	3 (21)	6 (32)	
Hispanic	5 (6.0)	1 (3.3)	0 (0)	0 (0)	
Site of primary urethral tumour, n (%)					
Distal	45 (48)	13 (38)	2 (12)	6 (30)	0.069
Proximal	30 (32)	11 (32)	6 (35)	10 (50)	
Whole urethra	17 (18)	9 (26)	7 (41)	4 (20)	
Diverticulum	2 (2.1)	1 (2.9)	2 (12)	0 (0)	
Histology, n (%)					
SCC	31 (33)	13 (38)	7 (41)	8 (40)	0.7
Urothelial carcinoma	29 (31)	9 (26)	3 (18)	3 (15)	
Adenocarcinoma	20 (21)	9 (26)	7 (41)	6 (30)	
Epidermoid	10 (11)	2 (5.9)	0 (0)	3 (15)	
Anaplastic	3 (3.2)	0 (0)	0 (0)	0 (0)	
Small-cell	0 (0)	1 (2.9)	0 (0)	0 (0)	
Lymphoma	1 (1.1)	0 (0)	0 (0)	0 (0)	
Pathological T stage, n (%)					
≤T1	23 (24)	6 (18)	2 (12)	1 (5.0)	0.001
T2	21 (22)	8 (24)	2 (12)	1 (5.0)	
T3	31 (33)	12 (35)	7 (41)	5 (25)	
T4	9 (10)	6 (18)	5 (29)	11 (55)	
Unknown	10 (11)	2 (5.9)	1 (5.9)	2 (10)	
Pathological N stage, n (%)					
N0	19 (20)	14 (41)	8 (47)	6 (30)	0.005
N1–N3	18 (19)	9 (26)	4 (24)	8 (40)	
Nx	53 (56)	9 (26)	4 (24)	5 (25)	
Unknown	4 (4.3)	2 (5.9)	1 (5.9)	1 (5.0)	
Pathological M stage, n (%)					
M0	91 (97)	33 (97)	17 (100)	16 (80)	0.009
M1	3 (3.2)	1 (2.9)	0 (0)	4 (20)	
Presenting symptoms (N = 164), n (%)					
Obstructive symptoms	30 (32)	13 (38)	11 (65)	11 (55)	0.035
Irritative symptoms	27 (29)	15 (44)	6 (35)	6 (30)	0.4
Haematuria	25 (27)	13 (38)	6 (35)	7 (35)	0.6
Mass	21 (23)	11 (32)	12 (71)	5 (25)	0.001
Spotting	23 (25)	10 (29)	5 (29)	3 (15)	0.7
Discomfort	10 (11)	6 (18)	5 (29)	2 (10)	0.2
Discharge	7 (7.5)	4 (12)	0 (0)	1 (5.0)	0.5
Abscess	4 (4.3)	2 (5.9)	1 (5.9)	3 (15)	0.3
Incidental finding	5 (5.4)	0 (0)	0 (0)	0 (0)	0.3

SCC, squamous cell carcinoma. Data are presented as median (quartiles) unless otherwise indicated.

(36%), UC (27%) and adenocarcinoma (25%). Over half the patients had locally advanced, stage T3–T4, disease. Nodal involvement was apparent in approximately 25% of patients and 5% were metastatic at presentation. Women had a higher rate of tumours involving the whole urethra, a higher rate of adenocarcinoma and a higher rate of locally advanced disease (Table S1). A similar number of patients were treated in each decade of the study (Table S2).

Among the 165 patients, 10 patients received no definitive treatment, and an additional 10 patients were reported as receiving salvage surgery with no information on primary treatment. Among the remaining 145 patients, 94 received monotherapy, 34 received dual therapy and 17 received triple

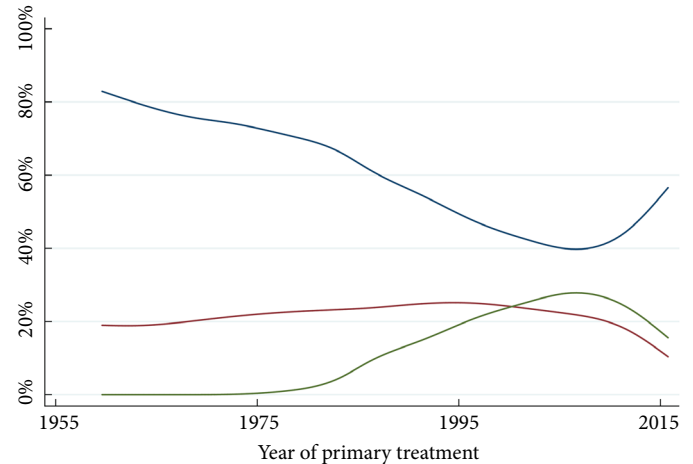
therapy. Patients receiving triple therapy presented more frequently with obstructive symptoms and a urethral mass and had a higher rate of locally advanced disease. These patients were also more likely to undergo lymph node dissection and have pathological stage N0 disease (Table 1). Most patients in both the monotherapy and dual therapy groups received surgery. Treatment patterns were different among men and women, with a higher rate of women receiving radiotherapy as part of their primary treatment (51/79, 65%) when compared to men (12/66, 18%; Table 2). The use of monotherapy decreased over time, while rates of dual therapy remained relatively consistent, and rates of triple therapy increased (Fig. 1).

Table 2 Treatment category and types of treatment received by sex ($P < 0.001$), $N = 145$.

Treatment category	Treatment	Women (N = 79), n (%)	Men (N = 66), n (%)
Monotherapy	Radiotherapy	25 (32)	1 (1.5)
	Surgery	25 (32)	43 (65)
	Chemotherapy	0 (0)	0 (0)
Dual therapy	Radiotherapy and chemotherapy	3 (3.8)	1 (1.5)
	Surgery and chemotherapy	3 (3.8)	11 (17)
	Surgery and radiotherapy	11 (14)	5 (7.6)
Triple therapy	Surgery, radiotherapy and chemotherapy	12 (15)	5 (7.6)

The primary treatment given to the 145 treated patients is shown in Table 3. Surgery and concomitant intra-operative radiation therapy were used to treat 13 patients, all of whom received either neoadjuvant or adjuvant chemotherapy, comprising most of the triple therapy group (13/17, 76%). In this cohort, 63/145 patients (43%) underwent lymph node dissection. Forty-four patients received radiation therapy as part of their primary treatment. Over the years of the study there was a decrease in the use of brachytherapy and an increase in the use of intra-operative radiation therapy (Fig. 2). Forty-three patients received neoadjuvant treatment (27 chemotherapy, 15 radiotherapy, one chemoradiation), all but two of whom underwent planned definitive treatment. Five chemotherapy patients (19%) and three radiotherapy patients (20%) had $\leq T1$ stage disease at definitive surgery, including two patients treated with radiotherapy who had T0 disease. Among patients who did not receive neoadjuvant treatment, three received adjuvant chemotherapy and four adjuvant chemoradiation. Six patients received adjuvant treatment after neoadjuvant chemotherapy. In the whole cohort, the rate of patients receiving neoadjuvant or adjuvant chemotherapy was similar among the three major histological groups: UC (23%), adenocarcinoma (26%) and SCC (24%). Data regarding chemotherapy regimens were available for 23/35 patients who underwent primary treatment and received chemotherapy. Cisplatin-based regimens were commonly used for all histologies (Fig. S1). Furthermore, 16/27 patients who received neoadjuvant chemotherapy had data regarding chemotherapy type, 14 of whom (88%) received cisplatin-based regimens.

The median (interquartile range) follow-up for survivors was 4.7 years (1.2, 9.7); 67 patients had a local recurrence, 61 patients had a distant recurrence, and 105 patients died (77 from urethral carcinoma). The most common sites of distant recurrence were lung (48%) and lymph nodes outside the pelvis (36%; Table S3). Nineteen patients had distant recurrences at multiple sites (31%). Estimated 5-year local recurrence-free, distant recurrence-free, disease-specific and overall survival were 51% (95% CI 41, 60), 53% (95% CI 43,

Fig. 1 Rates of monotherapy (blue line), dual therapy (red line) and triple therapy (green line), by year of treatment.

61), 48% (95% CI 40, 57) and 41% (95% CI 32, 49), respectively. Pathological T stage and M stage were associated with an increased risk of recurrence and/or death. Urothelial histology was associated with improved overall survival and cancer-specific survival. Pathological N stage was significantly associated with worsening overall survival but not with distant recurrence-free and cancer-specific survival, despite similar effect sizes (Table S4).

For the analysis of oncological outcomes after treatment, patients were excluded if they received no definitive treatment ($n = 10$) or salvage surgery with no information on primary treatment ($n = 10$). Patients were also excluded if they had no information on pathological T stage ($n = 13$), leaving 132 patients included in the survival analysis cohort. Among these 132 patients, there were 50 local and 48 distant recurrences, 54 deaths from urethral cancer and 25 deaths from other causes. Treatment type was significantly associated with time to local recurrence after adjusting for pathological stage, histology, sex and year of treatment, with patients receiving monotherapy having lower recurrence-free survival than patients receiving dual or triple therapy ($P = 0.017$; Fig. 3A, Table 4). Adjusted distant recurrence-free survival was non-significantly lower in patients receiving triple therapy ($P = 0.8$; Fig. 3B, Table 4). Patients receiving dual or triple therapy appeared to have higher rates of urethral cancer death but lower rates of all-cause mortality, although neither of these associations was statistically significant ($P > 0.9$ and $P = 0.7$; Fig. 3C,D, respectively [Table 4]). A subgroup analysis of patients treated since 1991, after which there was a rise in the use of multimodal therapy, showed similar outcomes (Fig. S2).

Discussion

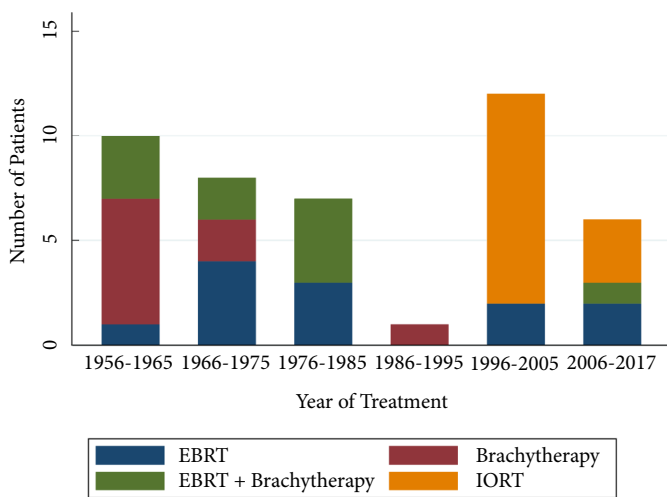
In the present study, we evaluated clinical characteristics and treatment outcomes of primary urethral tumours in a large

Table 3 Specific types of primary treatment received for locoregional disease, N = 145.

Treatment	N (%)
Surgery only	
Local excision/transurethral resection	19 (13)
Urethrectomy/penectomy (partial or total)	43 (30)
Anterior pelvic exenteration/cystectomy with urethrectomy/penectomy	39 (27)
Radiation only	
EBRT	12 (8.3)
Brachytherapy	8 (5.5)
EBRT and brachytherapy	10 (6.9)
Combined modalities	
Anterior exenteration/radical cystectomy with urethrectomy/penectomy and IORT	11 (7.6)
Partial urethrectomy + IORT	2 (1.4)
Cystectomy + radioactive seed implant	1 (0.7)

EBRT, external beam radiation therapy; IORT, intra-operative radiation therapy.

Fig. 2 Types of radiation received for primary treatment categorized by year of treatment (n = 44); EBRT, external beam radiation therapy; IORT, intra-operative radiation therapy.



single-centre cohort. Patient characteristics were consistent with previous reports; common histologies were SCC, UC and adenocarcinoma, and over half the patients presented with advanced disease. In addition, our findings confirm the poor prognosis, with an estimated 5-year overall survival of 41%, and support pathological T stage, M stage and histology as predictors of outcome. We found evidence that multimodal therapy has a benefit over monotherapy for local recurrence, but not for distant recurrence, cancer-specific death or overall survival.

The treatment of urethral carcinoma in early series included mostly surgery or radiation as monotherapies and only 14% of patients who underwent surgery received planned peri-operative radiation. Outcomes in these series were poor, with an estimated 5-year overall survival of 32–42% [2,3]. These

results led to the use of multimodal therapy for the treatment of primary urethral cancer [4,11–14]. Reported treatment combinations for women included surgery with either high-dose intra-operative radiation therapy using ¹⁹²iridium or external peri-operative radiotherapy with or without peri-operative platinum-based chemotherapy [4,11]. In men with invasive urethral SCC, a combination of chemotherapy (5-fluorouracil and mitomycin-C) and external radiation was offered as a potential organ-preserving treatment, with a complete response apparent in 79–83% of patients and 5-year overall survival rates of 52–60% [12,13]. A similar response rate to chemotherapy of 72% was observed in a cohort of 44 patients (64% women), most of whom had locally advanced or lymph-node-positive primary urethral carcinoma. Moreover, in a subgroup of nine patients with lymph-node metastatic disease treated with a combination of platinum-based chemotherapy followed by salvage surgery, 44% experienced disease-free survival of >3 years [14].

Despite these encouraging results, the rate of multimodal therapy remained low in large published series [5,6]. In a single-centre study from the MD Anderson Cancer Centre including 106 patients treated between 1984 and 2014, all patients were surgically treated and 27% received additional therapy including chemoradiation (14%), chemotherapy (9.4%) and radiation therapy (3.8%) [6]. A multi-institutional collaborative effort from 10 international tertiary academic centres, reported on 154 consecutive patients treated for primary urethral carcinoma between the years 1993 and 2012. Most patients (83%) underwent surgery as their primary treatment. Peri-operative treatment included neoadjuvant chemotherapy (10%), neoadjuvant chemoradiotherapy (6%) and adjuvant chemotherapy (15%) [5]. Practice patterns and survival outcomes for locally advanced primary urethral cancers (T2–4/N1–2, M0) were recently evaluated in a group of 1749 patients from the NCDB, treated between the years 2004 and 2013. In all, 54.8% of patients underwent either local excision, chemotherapy or radiation alone, 29.6% underwent cystectomy with or without radiation therapy, and 15.6% underwent definitive multimodal therapy. Patients with higher-stage tumours and N2 status were more likely to receive multimodal therapy. No differences were observed in the use of any treatment method by the study year [16]. In the present series, surgery remained a backbone of definitive treatment, with 79% of patients (115/145) undergoing resection with or without additional therapy. While the overall rate of different treatment methods was similar to previous reports, with 57% receiving monotherapy, the rate of monotherapy decreased over time and that of triple therapy increased, consistent with the decision to increase the use of multimodal treatment in appropriate candidates within our institute. This trend was consistent throughout the study period, aside from an increase in the use of monotherapy since the year 2015. The small number of patients treated

during these years, most of whom (4/6) were not appropriate candidates for multimodal therapy, is the likely cause of the observed increase in the use of monotherapy. Most patients in our cohort received neoadjuvant rather than adjuvant

treatment. Only 2/43 patients (5%) had a complete response at definitive surgery after receiving neoadjuvant treatment.

Few comparative studies have shown a benefit associated with the use of multimodal therapy. In early series, the use of

Fig. 3 Adjusted survival estimates of (A) local recurrence-free survival, (B) distant recurrence-free survival, (C) cancer-specific survival and (D) overall survival for patients receiving monotherapy (blue line), dual therapy (red line) and triple therapy (green line).

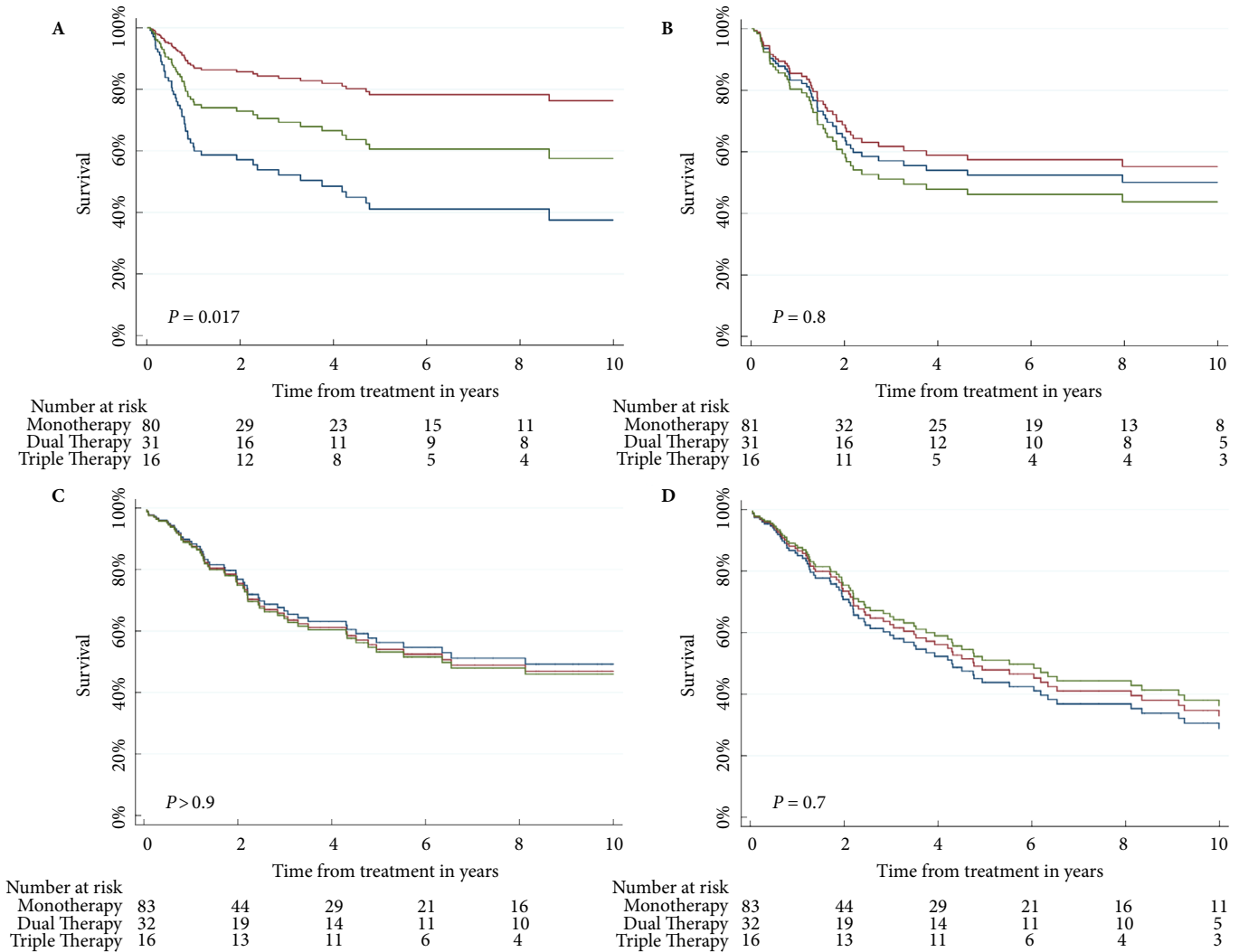


Table 4 Multivariable Cox regression models for the outcomes of local recurrence, distant recurrence, death from urethral carcinoma, and death from any cause.

	Local recurrence (N = 127)			Distant recurrence (N = 128)			Death from urethral carcinoma (N = 131)			Death from any cause (N = 131)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Treatment type												
Monotherapy	Reference	–	0.017	Reference	–	0.8	Reference	–	>0.9	Reference	–	0.7
Dual therapy	0.28	0.11, 0.70		0.86	0.42, 1.74		1.04	0.55, 1.96		0.88	0.52, 1.50	
Triple therapy	0.56	0.24, 1.34		1.20	0.56, 2.55		1.05	0.50, 2.21		0.78	0.39, 1.56	

HR, hazard ratio. Each model was adjusted for pathological T stage, pathological N stage, pathological M stage, histology, sex and year of treatment.

neoadjuvant radiation had no impact on overall survival; however, local recurrence-free survival was significantly improved when radiotherapy was given preoperatively in women [2,3]. In the multicentre study by Gakis et al. [15], in a subgroup of 124 patients who underwent primary surgical treatment, no association was found between recurrence-free/overall survival and the type or number of peri-operative chemotherapy cycles. However, among 26 patients with stage cT3 and/ or cN+ disease, 62% of whom received peri-operative chemotherapy, treatment with neoadjuvant chemotherapy was significantly associated with improved recurrence-free (relative risk 0.14, 95% CI 0.01–0.78, $P = 0.022$) and overall survival (relative risk 0.1, 95% CI 0.01–0.71, $P = 0.02$) when compared to patients who had upfront surgery with or without adjuvant chemotherapy [15]. In a cohort of 2614 patients with non-metastatic primary urethral carcinoma from the NCDB, a combination of surgery and radiation was associated with better overall survival compared to surgery alone (hazard ratio 0.77, 95% CI 0.64–0.93; $P < 0.01$). When analysed separately based on disease stage, a benefit was reported in a subgroup of 501 patients treated for locally advanced, T3+ or N+ disease (hazard ratio 0.58, 95% CI 0.42–0.8; $P < 0.01$); however, no significant outcome difference was seen in cohorts with earlier-stage disease [16,17]. Furthermore, the outcome benefit of combining surgery and radiation in locally advanced disease was apparent in patients with UC and adenocarcinoma, but not in patients with SCC [16,17]. This finding is consistent with the improved outcome we observed in our cohort for patients with UC.

Our findings support the current recommendations of the European Association of Urology and National Comprehensive Cancer Network, which advocate the use of a multimodal treatment approach for patients with advanced primary urethral carcinoma combining surgery and/or radiation with systemic therapy [18,19]. The present study demonstrated an association between multimodal treatment and increased local recurrence-free survival, despite treating patients with advanced disease. Given the symptomatic nature of local recurrence, combining multiple treatment methods may have a substantial effect on the patient's quality of life; therefore, for patients with invasive urethral tumours, it is our current practice to use triple multimodal therapy combining surgery, radiation (preferably in the intra-operative setting, enabling the delivery of localized high doses of radiation) and chemotherapy.

The limitations of the present study include referral bias, as evident by the high rate of advanced disease in our cohort, restricting our findings to this group of patients. Because of the retrospective nature of our study, several patients were excluded from the analyses due to missing data, nor did we have data regarding the patient's functional status or comorbidities which may have altered treatment decision. Furthermore, our study cohort, which spans more than six

decades because of the rarity of the disease, is heterogenous as a result of different treatment patterns based on sex and study year, and the advances made in axial imaging, surgical interventions/techniques and tumour staging systems over this time. While the year of treatment and disease characteristics were accounted for in our analysis, the rise in the use of multimodal treatments over time also corresponds to staging changes and improvement in treatments that cannot be fully controlled for by modelling and may contribute to the improvement in local recurrence-free survival seen among multimodal-treated patients, who were treated the most recently. Moreover, we were unable to evaluate the role of lymph-node dissection, more commonly performed in patients receiving multimodal therapy, in decreasing local recurrence. However, the relatively high number of inguinal lymph node recurrences suggest further studies should focus on the role of inguinal lymph node dissection in patients with urethral cancer. Given the rarity of primary urethral carcinoma and the lack of level I evidence, prospective multi-institutional studies are required to identify the optimal treatment for this disease [20].

In conclusion, our findings support the aggressive nature and poor outcome associated with primary urethral cancer. We observed an increase in the utilization of multimodal therapy at our institution in recent years, consistent with guideline recommendations. We found preliminary evidence that the use of multimodal therapy in our cohort was associated with improved local recurrence-free survival, but did not lead to a significant difference in cancer-specific survival or overall survival. Further studies are needed to confirm the effect of this treatment approach. Because of the low incidence of primary urethral cancer, future observational and experimental studies need to involve multiple centres.

Acknowledgements

This work was funded by the Sidney Kimmel Centre for Prostate and Urologic Cancers. This work was funded in part through the National Institutes of Health/National Cancer Institute Cancer Centre Support Grant P30 CA008748.

Conflict of Interest

None declared.

References

- 1 Gatta G, van der Zwan JM, Casali PG et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011; 47: 2493
- 2 Dalbagni G, Zhang ZF, Lacombe L et al. Female urethral carcinoma: an analysis of treatment outcome and a plea for a standardized management strategy. *Br J Urol* 1998; 82: 835
- 3 Dalbagni G, Zhang ZF, Lacombe L et al. Male urethral carcinoma: analysis of treatment outcome. *Urology* 1999; 53: 1126
- 4 Dimarco DS, Dimarco CS, Zincke H et al. Surgical treatment for local control of female urethral carcinoma. *Urol Oncol* 2004; 22: 404

- 5 Gakis G, Morgan TM, Efstathiou JA et al. Prognostic factors and outcomes in primary urethral cancer: results from the international collaboration on primary urethral carcinoma. *World J Urol* 2016; 34: 97
- 6 Zhang M, Adeniran AJ, Vikram R et al. Carcinoma of the urethra. *Hum Pathol* 2018; 72: 35
- 7 Sui W, RoyChoudhury A, Wenske S et al. Outcomes and prognostic factors of primary urethral cancer. *Urology* 2017; 100: 180
- 8 Visser O, Adolfsson J, Rossi S et al. Incidence and survival of rare urogenital cancers in Europe. *Eur J Cancer* 2012; 48: 456
- 9 Aleksic I, Rais-Bahrami S, Daugherty M et al. Primary urethral carcinoma: a surveillance, epidemiology, and end results data analysis identifying predictors of cancer-specific survival. *Urol Ann* 2018; 10: 170
- 10 Wei Y, Wu YP, Xu N et al. Sex-related differences in clinicopathological features and survival of patients with primary urethral carcinoma: a population-based study. *Oncotargets Ther* 2017; 10: 3381
- 11 Dalbagni G, Donat SM, Eschwege P et al. Results of high dose rate brachytherapy, anterior pelvic exenteration and external beam radiotherapy for carcinoma of the female urethra. *J Urol* 2001; 166: 1759
- 12 Cohen MS, Triaca V, Billmeyer B et al. Coordinated chemoradiation therapy with genital preservation for the treatment of primary invasive carcinoma of the male urethra. *J Urol* 2008; 179: 536
- 13 Kent M, Zinman L, Girshovich L et al. Combined chemoradiation as primary treatment for invasive male urethral cancer. *J Urol* 2015; 193: 532
- 14 Dayyani F, Pettaway CA, Kamat AM et al. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. *Urol Oncol* 2013; 31: 1171
- 15 Gakis G, Morgan TM, Daneshmand S et al. Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: results of the international collaboration on primary urethral carcinoma. *Ann Oncol* 2015; 26: 1754
- 16 Cahn DB, Handorf E, Ristau BT et al. Contemporary practice patterns and survival outcomes for locally advanced urethral malignancies: a National Cancer Database Analysis. *Urol Oncol* 2017; 35: 670.e15.
- 17 Son CH, Liauw SL, Hasan Y et al. Optimizing the role of surgery and radiation therapy in urethral cancer based on histology and disease extent. *Int J Radiat Oncol Biol Phys* 2018; 102: 304
- 18 Network National Comprehensive Cancer. Bladder Cancer (Version 1.2019). vol. 2019
- 19 Gakis G, Witjes JA, Bruins M et al. EAU guidelines on primary urethral carcinoma 2018. In *European Association of Urology Guidelines*, 2018 edn. Arnhem, The Netherlands: European Association of Urology Guidelines Office, vol. presented at the EAU Annual Congress Copenhagen 2018, 2018
- 20 Dayyani F, Hoffman K, Eifel P et al. Management of advanced primary urethral carcinomas. *BJU Int* 2014; 114: 25

Correspondence: Alvin C. Goh, Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Centre, 1275 York Ave., New York, NY 10065, USA.

e-mail: goha@mskcc.org

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Chemotherapy regimens received by patients undergoing primary treatment categorized by tumour histology ($n = 35$).

Fig. S2. Adjusted survival estimates of (A) local recurrence-free survival, (B) distant recurrence-free survival, (C) cancer-specific survival and (D) overall survival for the subgroup of patients treated since 1991 receiving monotherapy (blue line), dual therapy (red line) and triple therapy (green line).

Table S1. Patient and disease characteristics, by sex. Data are presented as median (quartiles) or frequency (%).

Table S2. Number of patients treated during each decade of the study ($n = 165$).

Table S3. Site of distant recurrence, $N = 61$. Patients may have had distant recurrences at multiple sites.

Table S4. Univariate Cox proportional hazard models for the association between disease characteristics and local and distant recurrence free survival, cancer-specific survival and overall survival.