Outcomes of upper tract urothelial cancer managed non-surgically

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Introduction: *Approximately 7% of patients with localized upper tract urothelial cancer (UTUC) are treated without definitive therapy. Understanding outcomes and alternative therapy would aid in counseling older patients with comorbidities.*

Materials and methods: *We utilized the National Cancer Database to identify patients with localized UTUC managed non-surgically between 2004 and 2013. Patient demographics, comorbidity, tumor grade, and chemotherapy and radiation utilization were recorded. Survival analyses were performed with the Kaplan-Meier method and a cox proportional hazard regression model.*

Results: *We identified 3157 (10.9%) patients with localized UTUC who did not receive definitive surgery. Median age was 79 years, 55% were males, 79% had government health insurance, and 68% had a Charlson-Deyo Score (CDS) of 0. Tumor grade was low (grade 1 or 2) in 632 (36.4%) and high (grade 3 or 4) in 1104 (63.6%). Median overall survival (OS) for the cohort was 2.2 years, significantly shorter for patients with greater comorbidities. Chemotherapy or radiation was performed in 294 (9.3%) and 197 (6.3%) patients respectively. There were no OS differences for individuals receiving chemotherapy. Of patients who received radiation therapy, the median OS was 1.4 versus 2.0 years, ($p < 0.001$) favoring no radiation. Those with high grade tumors had worse survival (1.9 versus 3.8 years ($p < 0.001$). Significant predictors of shorter OS included older age, male gender, higher CDS, and government insurance.*

Conclusions: *In this population-based cohort, 10.9% of patients with localized UTUC were managed non-surgically. There was no OS advantage noted in cohorts receiving chemotherapy and radiation therapy. Median OS was significantly shorter for those with higher grade disease, increasing comorbidity profile, male gender, and those with government insurance status.*

Key Words: urothelial neoplasms, upper tract urothelial cancer, kidney, ureter, transitional cell carcinoma

Introduction

Upper tract urothelial cancer (UTUC) represents about 5%-10% of urothelial malignancies.[1] In the last few decades the incidence of UTUC has risen with an associated stage migration towards more localized tumors.[2] UTUC often effects the elderly with a median age of diagnosis of 75 years and associated risk factors include tobacco exposure and metabolic syndrome.[3] As such, it is not uncommon for patients with UTUC to have poor functional status or competing medical issues that may render surgical intervention high risk or even preclude surgical candidacy. The "gold-standard" form of therapy for localized UTUC is surgery and based on tumor characteristics, including radical nephroureterectomy, segmental ureterectomy, or endoscopic resection. These interventions can pose significant health risks with up to a 38% chance of perioperative complications for radical nephroureterectomy.[4,5] In addition, nephron loss from radical nephroureterectomy can lead to long term complications such as chronic kidney disease (CKD) which can limit treatment options upon recurrence.

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In various urologic malignancies, a "watchful waiting" or non-definitive approach has been developed to treat asymptomatic individuals conservatively with limited life expectancy due to significant competing risks of death. With various new systemic therapy approaches now approved for advanced urothelial carcinoma, initial non-definitive therapy with intervention upon disease progression may be a potential consideration for select patients who cannot undergo or are unwilling to pursue surgery. Non-surgical therapy in patients with UTUC has not been thoroughly explored, however, our recent work attempted to evaluate the outcomes with this approach.[6]

Using population data, it has been demonstrated that approximately 7% of patients with localized UTUC are treated with non-surgical therapy. The outcome of individuals with this approach is not uniformly poor as evidenced by a 3 year cumulative incidence of cancer-specific mortality of 26%. Mortality without surgical treatment of UTUC is also strongly influenced by tumor grade.[6] Due to database limitations and the small cohort of prior studies, there is still little known regarding additional treatment modalities such as radiation or systemic therapy in this patient population and whether such interventions alter the natural history of UTUC. Understanding the impact of comorbidities, chemotherapy, and radiation on survival for localized UTUC managed without surgery has not been previously assessed and could help in counseling and decision making for patients considering a non-definitive approach.

Herein, we utilized a large population based tumor registry to assess variations in overall survival (OS) for localized UTUC managed non-definitively with incorporation of co-morbidity and radiotherapy/chemotherapy data.

Materials and methods

Patient population

The National Cancer Data Base (NCDB), a shared project between the American College of Surgeons and American Cancer Society, was used to identify patients diagnosed with upper tract urothelial carcinoma (UTUC) from 2004 to 2013. The NCDB provides deidentified data from hospitals affiliated with the Commission on Cancer program and captures approximately 70% of new cancer diagnoses in the United States.[7] Demographic information is included such as treatment center (Academic, Community, Unknown), age of diagnosis, sex, race, primary insurance payer (Government, Private Insurance, Uninsured, Unknown Status), median income quartile of the county of residence, high school graduation of the county of residence, and distance traveled to treatment center. Detailed clinical information is also included such as Charlson-Deyo Comorbidity Score (0, 1, ≥ 2) (CDS), treatment modality (surgical management, non-operative management, chemotherapy, radiotherapy), histology, tumor size, primary disease site, and tumor grade. Medicare or Medicaid coverage were recoded as Government insurance. International Classification of Diseases for Oncology (ICD-O) site codes were used to identify patients with ureteral (C65.9) and kidney and renal pelvis (C66.9) cancers. We excluded patients based on the following criteria: unknown follow up, metastatic or locally advanced disease stage at presentation, Figure 1.

Statistical analysis

The Chi square test and student t-test were used to evaluate demographic characteristics by management strategy. Kaplan-Meier estimates were performed to assess for OS, while multivariate Cox proportional hazards models evaluated independent predictors of OS. The models were constructed in a forward-step fashion; univariate analysis was first conducted, and statistically significant predictors were pooled together for a multivariate analysis. Generalized linear regression analysis was used to assess trends over time. Statistical significance was considered if $p \leq 0.05$. Statistical analysis was performed using JMP 11.2.1 (SAS Institute Inc., Cary, NC, USA).

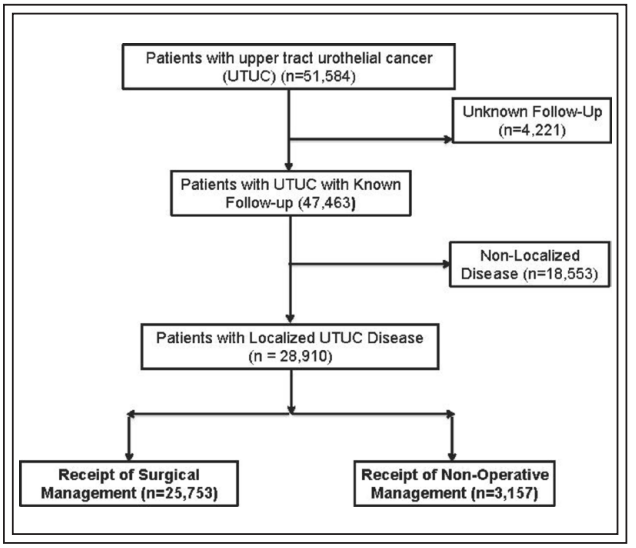

Figure 1. Flow diagram with inclusion and exclusion criteria.

TABLE 1. **Clinical characteristics of watchful waiting versus surgical management cohorts for patients with localized disease**

Variable		Non-surgical cohort	Surgical cohort
Number of patients		3157	25753
Facility type, %	Academic	40.4	47.8
	Community	59.1	51.7
	Unknown	0.5	0.5
Age at diagnosis, yrs	Mean (SD)	76.7 (11.0)	71.8 (10.7)
	Median	79.0	73.0
Size of tumor, cm	Mean (SD)	3.8 (6.84)	3.7 (3.74)
	Median	3.0	3.1
Sex, %	Female	44.9	39.2
	Male	55.1	60.8
Race, %	African American	4.9	4.0
	Asian	2.5	2.3
	Caucasian	91.3	92.2
	Other/unknown	1.3	1.5
Primary payor, %	Government	78.6	70.6
	Private insurance	17.7	25.9
	Uninsured	1.1	1.4
	Unknown status	2.6	2.1
Median income quartiles 2008-2012, %	1	15.0	14.9
	2	22.9	24.0
	3	25.9	28.0
	4	36.2	33.1
Percent number high school degree, 2008-2012, %	1	14.9	13.7
	2	24.6	25.1
	3	33.6	35.2
	4	26.9	26.0
Charlson-Deyo score, %	0	68.5	67.4
	1	22.3	24.0
	2	9.2	8.6
Primary site, %	Renal pelvis	54.5	57.0
	Ureter	45.5	43.0
Histology classificant, n	Classic	3153	25385
	Variant	4	368
Grade, %	Cell type not determined	45.0	13.5
	Grade I: well differentiated	10.3	11.4
	Grade II: moderately differentiated	9.7	17.6
	Grade III: poorly differentiated	19.3	35.1
	Grade IV: undifferentiated	15.7	22.4
Chemotherapy, %	No	90.7	87.1
	Yes	9.3	12.9
Radiation treatment, %	No	93.7	65.4
	Yes	6.3	4.6

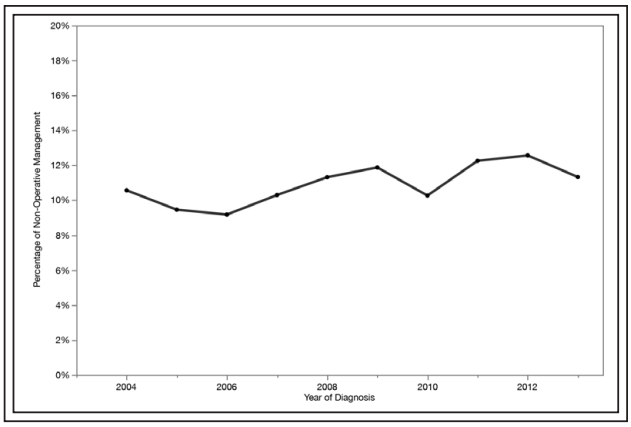

Figure 2. Non-operative management trends over time.

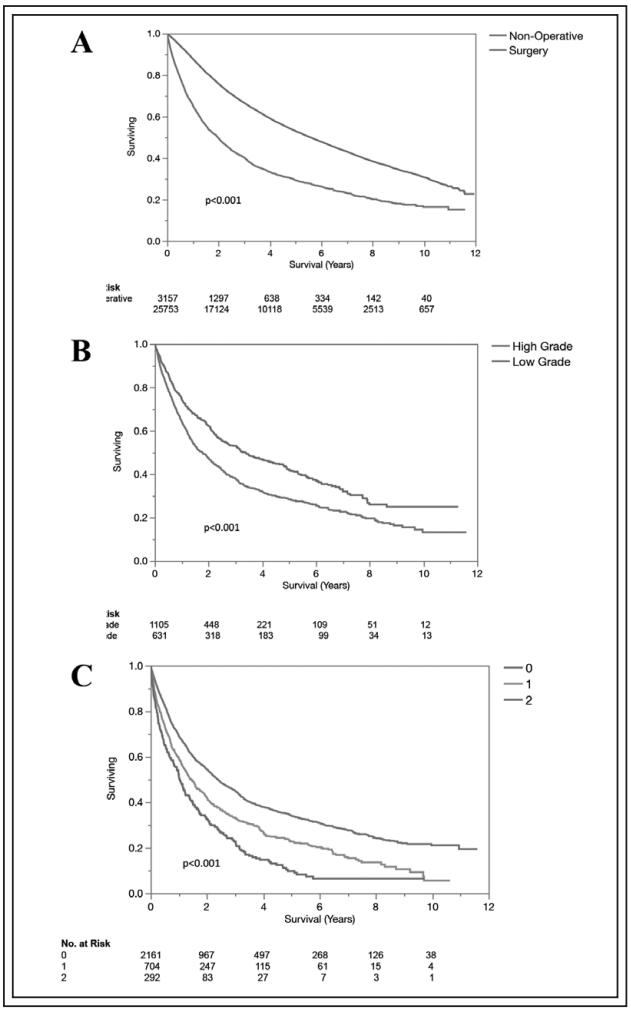

Figure 3a. Comparison of OS of watchful waiting versus surgical management. **3b.** Comparison of OS of non-operative candidates with high versus low grade. **3c.** Comparison of OS of non-operative candidates by Charlson-Deyo score.

Results

A total of 28,910 patients with localized UTUC were identified, Table 1. Of the cohort, 25,753 (89.1%) individuals received surgery, while 3,157 (10.9%) patients received non-operative management. During the study period, trends in non-operative management for patients with localized UTUC did not greatly change ($r^2 = 0.506$, $p = 0.0211$), Figure 2. Patients receiving non-surgical management were more commonly older (mean age at diagnosis: 76.7 versus 71.8, $p < 0.0001$), female (44.9% versus 39.2%, $p < 0.0001$), had government subsidized health insurance (78.6% versus 70.5%, $p < 0.0001$), and had lower grade tumors (55.3% versus 24.7% $p < 0.0001$) compared to patients who received surgery. No statistically significant differences were observed in mean tumor size ($p = 0.625$), co-morbidity status ($p = 0.0655$), or race ($p = 0.1047$) between surgical and non-surgical cohorts. Patients treated non-definitively were less likely to receive chemotherapy (9.3% versus 12.9%, $p < 0.0001$), but more likely to receive radiation therapy (6.3% versus 4.6%, $p < 0.0001$).

Patients treated without surgery demonstrated worse survival outcomes compared to those who

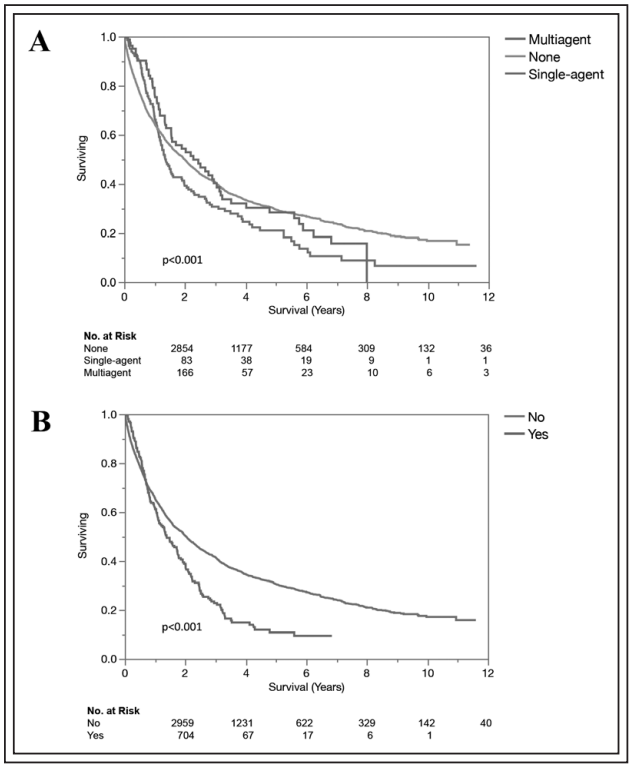

Figure 4a. Comparison of OS of non-operative patients by receipt of chemotherapy. **4b.** Receipt of radiotherapy in non-operative patients.

TABLE 2. **Non-operative candidates and receipt of chemotherapy and radiation**

Variable	Chemotherapy			Radiation		
	None	Yes	p value	No	Yes	p value
Number of patients	2863	294		2959	198	
Facility type, %			< 0.01			< 0.01
Academic	39.0	54.1		41.1	30.3	
Community	60.5	45.9		58.4	69.7	
Unknown	0.5	0.0		0.5	0.0	
Age at diagnosis, yrs			< 0.01			< 0.01
Mean (SD)	77.1 (11.0)	73.0 (10.1)		76.3 (11.1)	82.2 (7.8)	
Median	79.0	74.0		79.0	85.0	
Size of tumor, cm			0.98			0.10
Mean (SD)	38.8 (71.8)	38.7 (20.5)		39.5 (71.1)	30.7 (16.6)	
Median	30.0	36.0		30.0	29.5	
Sex, %			0.45			0.23
Female	45.1	42.9		44.6	49.0	
Male	54.9	57.1		55.4	51.0	
Race, %			0.76			0.13
African American	4.7	6.1		5.0	2.5	
Asian	2.5	2.7		2.6	1.5	
Caucasian	91.4	89.8		91.0	95.5	
Other/unknown	1.3	1.4		1.4	0.5	
Primary payor, %			< 0.01			0.03
Government	79.4	71.1		78.1	86.4	
Private insurance	17.7	17.7		18.2	10.6	
Uninsured	1.1	1.4		1.1	1.0	
Unknown status	1.8	9.9		2.6	2.0	
Median income quartiles, 2008-2012, %			0.56			0.24
1	14.9	16.4		14.8	19.5	
2	23.1	20.6		22.8	23.6	
3	25.6	28.3		26.2	21.5	
4	36.4	34.6		36.3	35.4	
Percent number high school degree, 2008-2012, %			0.70			0.96
1	15.0	14.7		15.0	14.4	
2	24.5	25.5		24.6	24.1	
3	33.9	30.8		33.5	35.4	
4	26.7	29.0		26.9	26.2	
Charlson-Deyo score, %			0.13			0.12
0	68.0	73.1		68.8	62.6	
1	22.5	20.1		21.9	28.3	
2	9.5	6.8		9.3	9.1	
Primary site, %			0.16			< 0.01
Renal pelvis	54.9	50.7		55.4	41.9	
Ureter	45.1	49.3		44.6	58.1	
Histology classificant, n			0.37			0.47
Classic	2859	294		2955	198	
Variant	4	0		4	0	

TABLE 2 (Cont'd). **Non-operative candidates and receipt of chemotherapy and radiation**

Variable	Chemotherapy			Radiation		
	None	Yes	p value	No	Yes	p value
Grade, %			< 0.01			0.60
Cell type not determined	46.0	35.4		44.9	46.5	
Grade I: well differentiated	10.7	6.5		10.3	10.6	
Grade II: moderately differentiated	9.9	7.5		9.9	6.6	
Grade III: poorly differentiated	18.4	27.9		19.3	19.2	
Grade IV: undifferentiated	15.0	22.8		15.6	17.2	
Radiation treatment, %						
No	94.8	83.0		100.0	0.0	
Yes	5.2	17.0		0.0	100.0	
Type of chemotherapy, %			< 0.01			< 0.01
Multiagent	0.0	56.5		5.0	9.6	
None	99.7	0.0		91.5	74.2	
Single-agent	0.0	28.2		2.0	11.6	
Unknown	0.3	0.0		0.3	0.5	
Unknown type received	0.0	15.3		1.3	4.0	

received surgery (median survival: 2.0 versus 5.6 years, $p < 0.0001$), Figure 3a. At 3 years following diagnosis, survival rate was 40.2% amongst those treated non-surgically compared to 66.6% in those who received surgery. For patients treated without surgery, those with high grade tumors demonstrated worse survival than those with low grade tumors (median survival: 1.8 years versus 3.4 years, $p < 0.0001$) with 3 year survival rates of 38.1% and 53.0%, respectively, Figure 3b. Patients with higher co-morbidity scores had worse median survival, (2.4, 1.5, and 1.0 year for scores of 0, 1, and ≥ 2, respectively, $p < 0.0001$, log-rank test), Figure 3c. The 3 year survival rate was 45.1%, 33.2%, and 22.7% for patients with scores of 0, 1, and ≥ 2, respectively.

For patients managed non-operatively, 294 (9.3%) received chemotherapy, Table 2, while 198 (6.2%) received radiation therapy. Those receiving chemotherapy were younger compared to those who did not (73.0 versus 77.1 years, $p < 0.0001$). Receipt of chemotherapy was associated with care at academic centers (54.1% versus 39.0% in those receiving care at community centers, $p < 0.0001$) and having a high tumor grade ($p < 0.0001$). Patients who received radiation therapy were older (82.2 versus 76.3 years, $p < 0.0001$). Those who received radiation were more likely to be seen in a community center (69.7% versus 58.4%, $p < 0.0001$), have a smaller mean tumor size (3.1 cm versus 3.9 cm, $p < 0.0001$), and have government insurance (86.4% versus 78.1%, $p < 0.0001$).

On multivariate Cox proportional hazards analysis of patients managed non-definitively, older age (HR: 1.05, 95% CI: 1.04-1.06, $p < 0.0001$), larger tumor size (HR: 1.001, 95% CI: 1.001-1.0022, $p = 0.0013$), higher co-morbiditiy score (≥ 2 versus 0, HR: 1.65, 95% CI:1.30-2.11, $p < 0.0001$), and male sex (HR: 1.18, 95% CI: 1.01-1.38, $p = 0.0381$) were independent predictors of worse OS, Table 3. Patients who had private insurance relative to government insurance (HR: 0.74, 95% CI: 0.579-0.48, $p = 0.0172$) and of the highest income quartile relative to the lowest quartile (HR: 0.701, 95% CI: 0.511-0.962, $p = 0.0281$) demonstrated more favorable outcomes. Patients receiving chemotherapy did not demonstrate improvement in overall survival outcomes when stratified by single-agent or multi-agent treatments ($p = 0.1254$, log-rank test), Figure 4a. The receipt of radiation treatment was associated with worse survival outcomes ($p < 0.0001$, log-rank test), Figure 4b.

Discussion

Upper urinary tract neoplasms account for 5% of urothelial tumors and have an estimated incidence of ~2/100,000 individuals in western countries.[1] With a peak incidence between 70-90 years many patients with UTUC are routinely found with significant co-morbidities including smoking-related pulmonary disease, CKD, hypertension, and diabetes. As

TABLE 3. **Cox proportional hazards model assessing overall survival**

Variable	Sub-distribution HR (95% CI)	p value
Facility type		0.8031
Community	1.000 (Ref)	
Academic	1.055 (0.899-1.236)	
Age at diagnosis	1.050 (1.041-1.061)	< 0.0001*
Sex		0.0381*
Female	1.000 (Ref)	
Male	1.181 (1.009-1.381)	
Race		0.1981
Caucasian	1.000 (Ref)	
Asian	0.834 (0.5111-1.361)	
African American	1.162 (0.806-1.676)	
Other/unknown	0.394 (0.147-1.057)	
Primary payor		0.1167
Private	1.000 (Ref)	
Government	1.349 (1.055-1.727)	
Uninsured	1.299 (0.522-3.233)	
Unknown	1.096 (0.561-2.140)	
Median income quartiles		0.1024
1	1.000 (Ref)	
2	0.892 (0.667-1.191)	
3	0.768 (0.573-1.030)	
4	0.701 (0.511-0.962)	
% Number high school degree		0.1261
1	1.000 (Ref)	
2	1.322 (1.002-1.743)	
3	1.359 (1.026-1.800)	
4	1.214 (0.884-1.665)	
Great circle distance	1.000 (0.999-1.000)	0.0986
Charlson-Deyo score		< 0.0001*
0	1.000 (Ref)	
1	1.369 (1.141-1.643)	
2	1.655 (1.299-2.108)	
Size of tumor	1.001 (1.001-1.002)	0.0013*
Grade		0.0071*
Low	1.000 (Ref)	
High	1.225 (0.973-1.542)	
Radiation		0.5274
Yes	1.000 (Ref)	
No	1.090 (0.835-1.423)	

such, consideration of treatment options and risks of complications are of particular importance when determing the optimal treatment strategy.

About 40% of UTUCs are non-invasive at time of diagnosis.[8] Similar to bladder cancer where low grade neoplasms have been safely observed with a conservative approach,[9] for patients with localized UTUC and complex medical co-morbidities limiting treatment options, a trial of active surveillance may not be unreasonable. However, there is a paucity of data regarding conservative management and resultant survival outcomes. We have previously shown, using

data from the Survival, Epidemiology, and End Results (SEER) program, that this approach is currently being utilized in 7% of individuals.[6] With a larger cohort of patients included in the NCDB, we show similarly, a small but non-negligible proportion of individuals (10.9%) with histologically proven UTUC were managed with non-surgical therapy. This estimate has remained consistent over time without any major deviations. Compared to those receiving surgical treatment, individuals that were managed non-surgically were more likely to be older, female, or have lower grade tumors. Surprisingly, there were no differences in the distribution of comorbidity scores between those who received surgery and those who didn't.

The overall median survival for those treated with non-surgical therapy was 1.8 years, which is similar to the prior SEER study (1.9 years). A major limitation of the SEER series was that there were no data regarding patient comorbidity. In this analysis, patients with higher comorbidities were found to have worse survival outcomes. When stratified by comorbidity score, scores of 0, 1, and ≥ 2 had median survivals of 2.4, 1.4, and 1 year, respectively ($p < 0.001$). While we have no information about cancer-specific death, grade significantly influences prognosis and it has been previously shown that for those with low grade disease, 3 year disease specific survival was 83%.[6] In this analysis, the overall 3 year survival was 53% for those with low grade disease and managed without surgery.

A second limitation of our prior SEER analysis was that treatment regarding the receipt of chemo/radiotherapy was unknown. We now demonstrate that 9.3% of patients managed with non-surgical therapy received some form of chemotherapy. While neoadjuvant chemotherapy has been associated with pathologic complete responses and a possible improvement in outcome in advanced high grade UTUC,[10] systemic chemotherapy is not believed to be effective in those with non-invasive disease. Localized chemotherapeutic agents and immunomodulators (bacillus Calmette-Guerin, (BCG)) have also been used for the treatment for non-invasive UTUC in patients who are not eligible for radical surgery, however, their use is still regarded as investigational and are not currently approved for use in the upper urinary tract by the Food and Drug Administration. In the NCDB, chemotherapy is coded as either multi-agent or single agent chemotherapy without further qualifiers. As the majority of urothelial chemotherapy regimens use platinum-based agents (cisplatin or carboplatin) in combination with gemcitabine (GC) or methotrexate, vinblastine, and doxorubin (MVAC) multi-agent therapy, it is reasonable to assume that multi-agent therapy denotes the use of systemic chemotherapy. Single agent chemotherapy in NCDB includes immunotherapy (until 2014) and may denote local treatment within the urinary tract. Both single and multi-agent chemotherapy use did not improve overall survival when compared to those that didn't receive chemotherapy (median survival: 1.4 years, 2.3 years, 2 years, respectively). While worse disease characteristics may influence use of chemotherapy, when controlling for other factors in our multivariate model, receiving chemotherapy also did not improve outcome. Our data contribute to evidence that chemotherapy does not improve survival for localized UTUC managed without surgery.

Radiotherapy is not part of the standard treatnent guidelines for UTUC and it is not surprising that utilization was low (6.2%). Although we did not have detailed information regarding the types of radiotherapy and location of treatment, in the absence of metastatic disease, radiation may have been focused on the primary tumor. Stereotactic body radiotherapy has been shown, at least in one small case review to offer local control with minimal acute adverse events for UTUC alone.[11] We demonstrate that overall survival was not improved with radiation and patients actually had worse survival outcomes when treated in this fashion.

Although we review the largest cohort of individuals with localized UTUC managed non-operatively, we recognize several limitations of our study. As with any study using a large population database, our analysis was limited by data availability. We did not have access to information regarding disease-specific survival, chemotherapy/radiotherapy indications, reasons for not pursuing surgery, and detailed staging methodology. We were limited to only patients with pathologic diagnoses, and tumor histology was not assessed under central pathology review. In addition, the specific chemotherapy regimens used were not known. Despite our limitations, the large sample size and detailed clinical followup has allowed us to describe relevant survival outcomes and may be useful for counseling patients who are not surgical candidates.

Conclusions

Using the NCDB it is demonstrated that 10.9% of individuals with upper tract urothelial cancer do not receive any form of surgery and are managed conservatively. Older age, male gender, larger tumor size, higher grade, and greater comorbidities were all significant predictors of worse overall survival. Reciept of chemotherapy or radiotherapy were not shown to provide a survival benefit. □

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