Oncologic and surgical outcomes of endoscopic therapy compared to surgical treatment of upper tract urothelial carcinoma stratified by tumor grade: An analysis of the national cancer database

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KEY MESSAGES

- Increasing proportions of patients each year who are diagnosed with UTUC undergo endoscopic treatment.
- For patients with low-grade disease, endoscopic therapy may be associated with non-statistically significant difference in OS compared to radical nephroureterectomy/segmental ureterectomy.
- For patients with high-grade disease, endoscopic therapy may be associated with lower OS compared to radical nephroureterectomy/segmental ureterectomy.
- Patients undergoing endoscopic therapy are associated with better perioperative outcomes compared to those undergoing radical nephroureterectomy/segmental ureterectomy.

ABSTRACT

Introduction: Oncologic outcomes of endoscopic treatment (ET) vs. extirpative surgery (ES=radical nephroureterectomy/segmental ureterectomy [RNU, SU]) for upper tract urothelial carcinoma (UTUC) are not well-defined. We queried the National Cancer Database to compare the overall survival (OS) and surgical outcomes of ET to ES for localized UTUC stratified by grade.
Methods: We conducted a retrospective cohort study including patients 18–90 years old, diagnosed with localized UTUC from

2004−2021. The primary outcome was OS. Secondary outcomes included the surgical outcomes of postoperative mortality, length of hospital stay, and 30-day readmission rate. We conducted 1:1 propensity-score matching (PSM). Survival analysis by accelerated failure time model with Weibull distribution with clustering (reporting time ratio [TR] and 95% confidence interval [CI]) was conducted. Mann-Whitney test or Fisher's exact test were used to compare other outcomes.
Results: ET was used to treat 3.6% of UTUC cases in 2004 to 9.8% in 2020. After all inclusion and exclusion, there were 32 205 patients: 1747 (5.42%) in the ET arm and 30458 (94.58%) in the ES arm. After PSM, 1541 patients were included in each cohort. For high-grade UTUC, ET vs. ES was associated with reduced OS (TR: 0.51, 95% CI 0.39−0.65). For low-grade UTUC, ET vs. ES was not associated with diminished OS (TR 0.88, 95% CI 0.72−1.07).
Conclusions: In appropriately selected patients with low-grade UTUC, ET appears to confer comparable survival outcomes to extirpative approaches; however, in those with high-grade UTUC, we found lower OS among those managed with ET. This may be from poorer cancer control or may reflect residual confounding among those patients selected for ET (e.g., greater comorbidity or conditions precluding ES).

INTRODUCTION

Urothelial carcinoma of the ureter, renal pelvis, and intrarenal collecting system—collectively termed upper tract urothelial carcinoma (UTUC)—is a rare malignancy, accounting for less than 10% of all urothelial tumors.[1] The prognosis and treatment of localized UTUC depend on oncologic risk stratification based on tumor grade, size, multifocality, and other features. The American Urological Association (AUA) guidelines recommend radical nephroureterectomy with bladder cuff excision (RNU) as the standard of care, while kidney-sparing approaches such as segmental ureterectomy (SU) or endoscopic treatment (ET) may be considered in selected cases.[2] ET is typically indicated for low-risk, favorable disease or in patients with imperative indications such as solitary kidneys, bilateral tumors, or significant comorbidities precluding RNU.

Due in part to the rarity of UTUC, there are no randomized controlled trials assessing the oncological outcomes of ET to RNU. Prior evidence includes institutional retrospective studies. Some reported that ET and RNU were not associated with a significantly different overall survival (OS)[3–8] in LG disease while others reported worse OS associated with ET.[9] Prior population level evidence from National Cancer Database (NCDB) and Surveillance , Epidemiology and End Results (SEER) only included those with <cT2 and LG UTUC comparing patients who underwent ET to RNU. They reported that ET was associated with 43% (5-year OS from NCDB data) and 60% (8-year OS from SEER data) worse OS compared to RNU[10,11]. A recent meta-analysis including institutional and population level evidence concluded

no difference in OS associated with ET in LG-UTUC but worse 5-year OS in HG-UTUC associated with ET compared to RNU[12].

Despite improvements in endoscopic visualization and laser technology, concerns persist regarding incomplete tumor resection and early recurrence after ET.[13,14] Furthermore, existing population-level analyses exclude patients with SU, high-grade, or ≥T2 disease and only include cases treated up to 2012.[15] Contemporary evidence evaluating oncologic outcomes following ET compared to ES—particularly in the modern era of improved instrumentation and closer guideline-based surveillance post-ET, is lacking. To address this gap, we analyzed the National Cancer Database (NCDB) to compare survival outcomes between ET and ES (RNU + SU), stratified by tumor grade.

METHODS

Data sources

NCDB captures data from more than 1500 hospitals across the US, from 2004 to 2022 with long term follow-up, capturing up to 70% of cancer incidence in the US. Moreover, it collects data that allows for comprehensive matching for facility-, patient- and disease-related characteristics for a more balanced comparison.[16] Since NCDB contains de-identified data, this study was exempt from institutional review board approval. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17]

Study population

Patients aged 18-90 years with UTUC were identified based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes – C65.x and C66.x with histology codes – 8120 and 8130. The study cohort included all patients from 2004 to 2021 with localized UTUC (N0 and M0) according to the American Joint Committee on Cancer staging system. We excluded patients with T0 stage, missing information, and nodal or distant metastases. We also excluded patient receiving neoadjuvant chemotherapy since it is only recommended to those undergoing ES.[2]

Exposures and covariates

The primary exposure was defined as endoscopic treatment (ET) vs extirpative surgery (ES: RNU, SU). The following covariates were included for propensity score matching (PSM): age at diagnosis, sex, race, Charleson-Deyo comorbidity index, facility type, distance to facility, insurance status, area of residence, income, education, primary site of the cancer (renal pelvis or ureter), AJCC clinical T stage ,grade of tumor and receipt of chemotherapy after the procedure.

Outcomes

The primary outcome was the overall survival (OS) of localized UTUC patients treated by ET vs ES, stratified by grade (high grade, HG or low grade, LG). OS was determined by the date of initial diagnosis to the date of death or censor at last follow-up.

The secondary outcomes included surgical outcomes – surgical inpatient length of stay, readmission within 30-days postoperatively, 30-day and 90-day mortality.

Subgroup analyses:

We conducted subgroup analysis stratified by grade for the primary outcome – overall survival – stratifying by age (<65 years, 65-80 years and >80 years), tumor size (<1.5cm and ≥1.5cm), location of tumor (renal or ureteral) and Charlson-Deyo score (CDS <2 and ≥2).

2.5 Statistical analyses

Continuous variables were reported as mean with standard deviation (SD) and number (percentage) for categorical variables. Following stratification by grade, propensity score matching (PSM) with 1:1 ratio between ET and ES was performed through a greedy algorithm based on a caliper of 0.004, which was equivalent to 0.08 standard deviation (SD) of the logit of the estimated propensity score.[18] A logistic regression model was fitted to the treatment as a binary dependent variable, while covariates included all variables in the table. Balance was assessed at absolute standardized mean difference (SMD)<0.1. Mann-Whitney test or Fisher's exact test with bootstrapping with 1000 repetitions to account for clustering by the PSM were used to compare the treatment groups.

All survival analyses were done post-PSM. Because proportional hazards assumptions were violated in both groups (p=0.010 in low grade and p=0.014 in high grade; with intersecting survival curves), an Accelerated Failure Time (AFT) Model with Weibull distribution was used to account for the clustering by the PSM. The AFT modeled the event time. Time ratios and 95% confidence interval (TR, 95%CI) were used to interpret the overall survival. Five-year and ten-year survival for each group with 95% CI were also reported. Statistical analyses were conducted using STATA version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). A two-tailed p-value threshold of 0.05 was considered statistically significant.

RESULTS

A total of 98,226 patients with UTUC were identified. After applying all inclusion and exclusion criteria, the final cohort consisted of 32,205 patients for analysis (Figure 1). Baseline characteristics of patients in the ET and ES arms are detailed in Table 1. All covariates were well balanced by PSM (SMD <0.1, Table 1). From 2004 to 2020, the usage of ET increased from 3.56% to 9.77% for all localized UTUC patient recorded annually. (Figure 2) Significant proportion of patients in either group after PSM had unknown histologic grade (45%). Only those with a reported were compared for all outcomes (HG disease: 396 ES v. 343 ET; LG disease: 450 ES v. 491 ET).

Primary outcome – overall survival

In patients with HG-UTUC, we found that receipt of ET as compared to ES was associated with an increased risk of all-cause mortality [TR 0.51 (95%CI: 0.39-0.65)] (Table-2, Figure-3). In patients with HG-UTUC, survival at five-years follow-up in the ET cohort was 34.51% (95% CI: 29.03-40.05) compared to 54.18% (95% CI: 48.33-59.65) in the ES cohort. In patients with HG-UTUC, survival at ten-years follow-up in the ET cohort was 18.79% (95% CI: 13.40-24.90) compared to 36.41% (95% CI: 29.45-43.40) in the ES cohort.

In patients with LG-UTUC, we found that receipt of ET as compared to ES was not associated with an increased risk of all-cause mortality [TR 0.88; 95%CI: (0.72-1.07)] (Table-2, Figure-3). In patients with LG-UTUC, survival at five-years follow-up in the ET cohort was 61.64%, (95% CI: 56.88-66.03) compared to 67.81%, (95%CI: 62.27-72.72) in the ES cohort. In patients with LG-UTUC, survival at ten-years follow-up in the ET cohort was 41.58% (95% CI: 35.95-47.11) compared to 41.55% (95% CI: 34.57-48.38) in the ES cohort.

Secondary outcomes

We examined post-operative outcomes of patients receiving ET or ES, stratified by UTUC grade. Among patients with HG-UTUC, ET was associated with shorter surgical inpatient stay (Median: 0 v/s 4 days, p<0.001) and a non-statistically different 30-day readmission rate, 30-day mortality, and 90-day postoperative mortality. (Table-3)

In patients with LG-UTUC, ET was associated with shorter surgical inpatient stay (Median: 0 v/s 3 days, p<0.001) compared to ES. There was a trend towards higher 30-day readmission rate associated with ES (p=0.053). There was no difference in 30-day mortality and 90-day mortality associated with ET compared to ES.(Table-3)

Subgroup analyses

We examined the heterogeneity of effect for the primary outcome among subgroups by age, tumor size, and tumor location. For HG-UTUC patients, the association between ET and lower OS was restricted to those aged ≥ 65years [TR for age<65: 0.35 (0.12-1.05)]. For HG-UTUC, irrespective of tumor location, ET was associated with worse all-cause mortality [p<0.001 in renal pelvis cancer, p= 0.002 in ureteral cancer]. For HG-UTUC, irrespective of tumor size, ET was associated with worse all-cause mortality [p=0.03 in <1.5cm tumors, p=0.001 in ≥1.5cm tumors]. For HG-UTUC, the association between ET and lower OS was restricted to those with CD score <2 [TR 0.45; 95% (0.34-0.60)].

For LG-UTUC patients, irrespective of age, there was no difference in all-cause mortality between ET and ES [p= 0.806 in <65 years; p=0.125 in 65-80 years; p=0.075 in >80 years]. For LG-UTUC, irrespective of tumor location, there was no difference in all-cause mortality between ET and ES [p=0.332 in renal pelvis cancer; p=0.139 in ureteral cancer]. For LG-UTUC, irrespective of tumor size, there was no difference in all-cause mortality between ET and ES [p=0.582 in <1.5cm tumors; p=563 in ≥1.5cm tumors]. For LG-UTUC, association of worse OS with ET was restricted to those with CDS ≥2 [TR 0.48; 95%CI (0.29-0.79)]. (Table-4)

DISCUSSION

In this multicenter retrospective cohort study, we examined outcomes of endoscopic therapy to extirpative surgery for UTUC stratified by grade. Among a highly selected cohort of patients who could be matched on observable characteristics, overall survival was comparable between ET and ES for low-grade disease, suggesting that endoscopic management may provide similar oncologic control in carefully selected patients. However, these findings should be interpreted in the context of substantial selection bias, as patients undergoing ES may represent a fitter and more operable subset of the broader UTUC population. In contrast, among patients with high-grade UTUC, where extirpative surgery remains the guideline-recommended approach, those treated with ET experienced nearly two-fold higher all-cause mortality. While this may reflect the selection of patients unfit for surgery, these findings underscore the need for improved treatment strategies in this high-risk population who are unable to undergo extirpative surgery.

For HG-UTUC, recent updates to guidelines recommend elective use of ET in selected cases of the favorable substrata of patients or for imperative indications mentioned previously.[2] We found a higher proportion of patients treated most years with ET compared to the previous, from 2004 to 2020 as reported previously.[10] While we found ET in HG-UTUC was associated with a two-fold worse OS in our study, there may be selection bias from the use of ET for imperative indications such as significant comorbidities which precludes undergoing RNU.

The absence of an observed difference in OS in LG-UTUC patients receiving ET or ES is consistent with prior meta-analyses of retrospective institutional and population-level studies.[12,19] As recommended by the AUA guideline[2], our study reinforces the notion that ET be offered for LR-UTUC for imperative as well as elective indications. However, it should be noted that a large portion of patients in the ES were excluded during 1:1 PSM, suggesting that the matched ES cohort may not be representative of the broader surgical population, and these findings should be interpreted with caution when applied to ES patients who may differ in baseline characteristics from the ET cohort. On subgroup analysis stratified by size of the lesion and age, we found that there was no difference associated with ET versus ES cohorts when stratified by <1.5cm and ≥1.5cm or by age <65, 65-79 and ≥80 years.

ES is associated with higher perioperative morbidity such as higher unplanned 30-day readmission rates (trending to statistical significance with $p = 0.053$), as demonstrated in our study. In the absence of level 1 evidence from randomized controlled trials (which is unlikely to be feasible in this setting) comparing ES to ET indicating better overall survival for LG-UTUC and continued widespread use of ES, our findings from a large contemporary real world NCDB cohort align with the current guidelines[2] and prior meta-analyses[12], collectively supporting that when feasible, ET may provide a safer option with similar oncological outcome for appropriately selected patients. Despite the consistency of the findings from different sources, the slow uptake of ET despite the addition of elective indications for use in recent guidelines. This may be on account of emerging and existing approaches for topical chemotherapy (e.g. UGN-101[20]), which were not captured in this present study. Conversely among patients with HG-UTUC on subgroup analysis, the association between ET and worse OS was restricted to patients with lower comorbidity burden (CDS <2), indicating that the observed effect was not driven by treatment selection in medically frail individuals. Collectively, these results highlight that while ET remains a reasonable option for low-grade UTUC, caution is warranted when considering ET for high-grade disease, particularly in healthier patients in whom oncologic risk may outweigh the benefits of renal preservation.

The current study has limitations consistent with retrospective design. Firstly, the retrospective nature study has inherent residual confounding despite PSM such as unreliable accuracy of clinical staging in these tumors. Other pertinent factors such as tumor focality and renal function were not available for matching as they are not recorded in the NCDB. Furthermore, the exclusion of large proportion of patients from the ES cohort during PSM, limits the generalizability of these finds to ES patients whose baseline characteristics differ from the post-matching cohort. Secondly, the NCDB does not report data regarding cancer-specific mortality. This prohibits interpretation of whether ET is oncologically equivalent since patients undergoing ET for HG-UTUC may have worse comorbidities and cannot undergo surgical resection, as indicated by higher 90-day postoperative mortality associated with ET. Due to the multicenter nature of this study, surveillance regimen for patients undergoing ET may not be uniform across different hospitals.

CONCLUSIONS

There may be no difference in all-cause mortality associated with endoscopic therapy versus extirpative surgery for low-grade upper tract urothelial carcinoma, but it may be associated with safer 30-day postoperative mortality. Among patients with high grade disease, endoscopic therapy may be associated with increased risk of all-cause mortality and should be used with caution. These data are limited by potential residual confounding related to the selection of endoscopic therapy in patients with greater comorbidities, especially among patients with high grade disease.

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FIGURES AND TABLES

Figure 1. Flowchart for patient inclusion and exclusion using NCDB 2004−2021. ET: endoscopic therapy; ES: extirpative surgery – radical nephroureterectomy and segmental ureterectomy; PSM: propensity score matching.

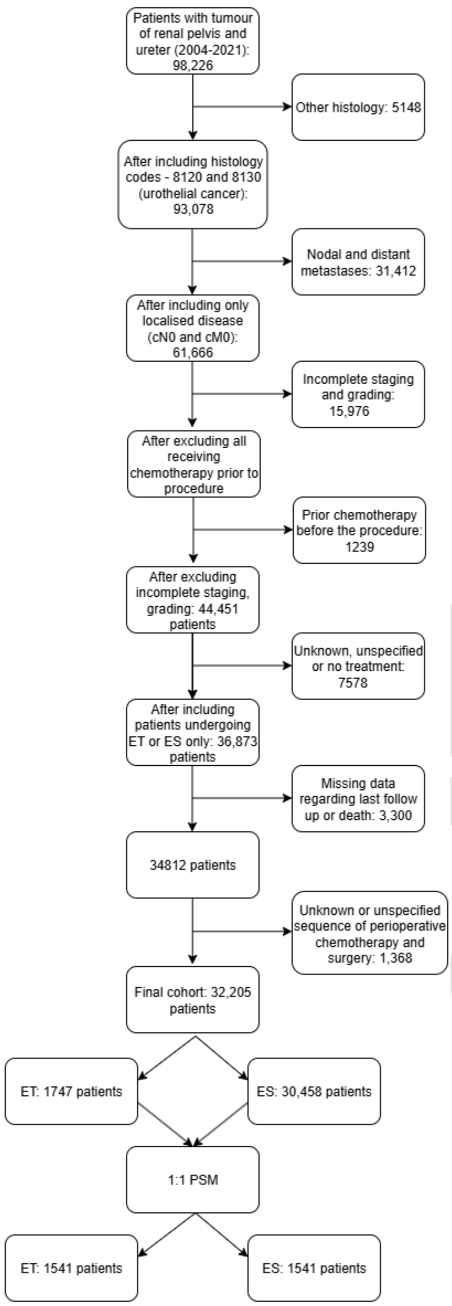

Figure 2. Uptake of endoscopic therapy (proportion of total upper tract urothelial carcinoma cases treated). X-axis: time (year); Y-axis: proportion (percentage) of cases.

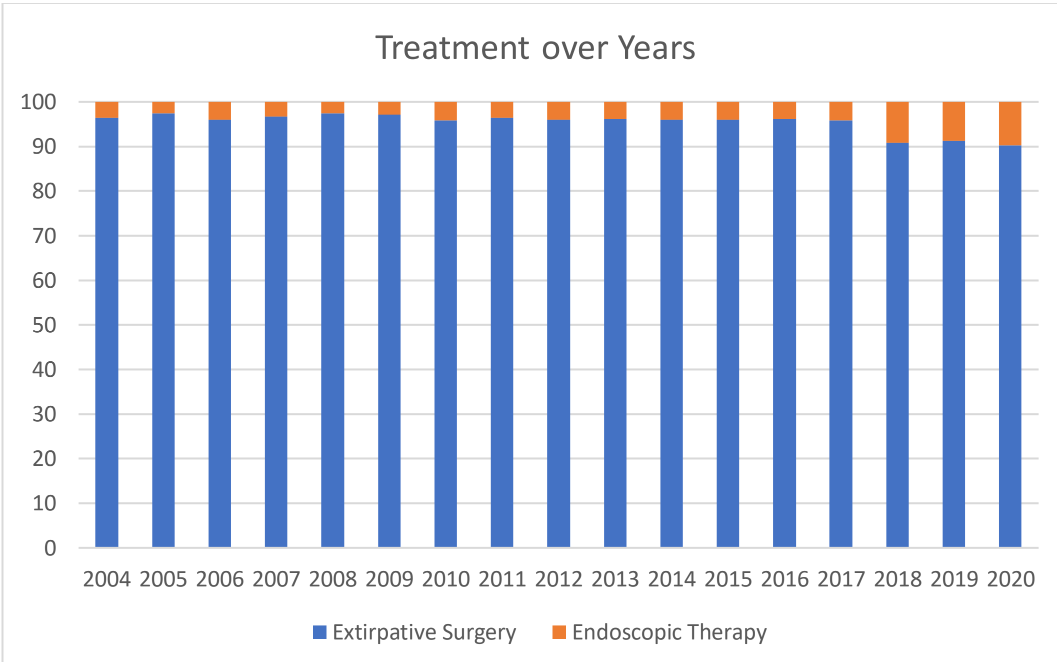

Figure 3. Weibull accelerated failure time survival plot of treatments in patients with upper tract urothelial carcinoma. ES: extirpative surgery (radical nephroureterectomy and segmental ureterectomy); ET: endoscopic therapy.

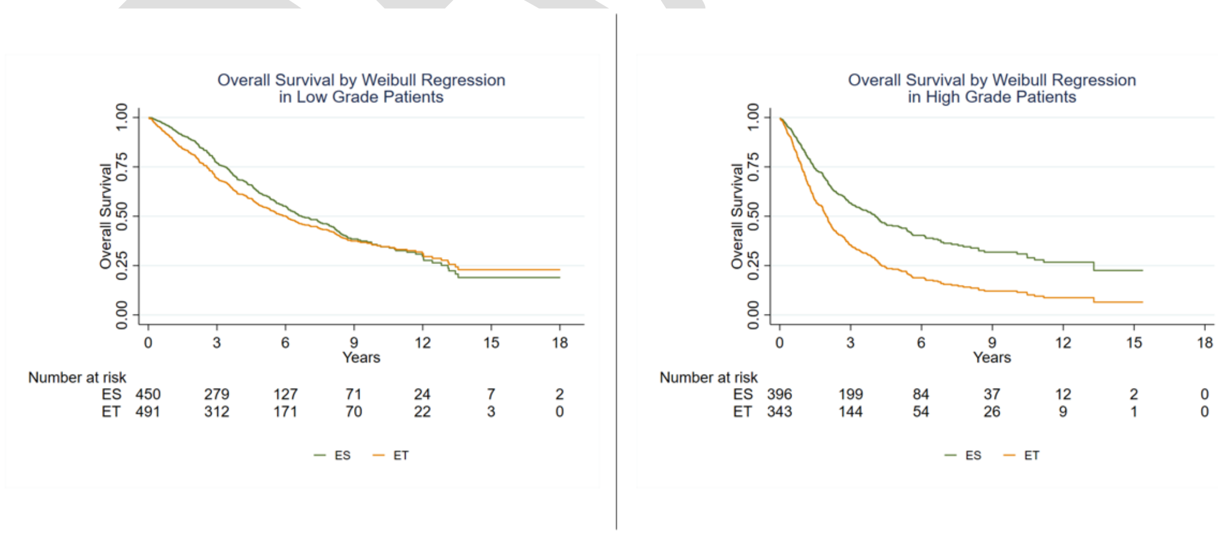

Table 1. Socio-economic, demographic, and clinical characteristics of patients with localized UTUC undergoing ES or ET before propensity score matching

Covariate	**Total**	**ES (before PSM)**	**ET (before PSM)**	**SMD**	**ES (after PSM)**	**ET (after PSM)**	**SMD**
	N=32 205	**n=30 458**	**n=1747**		**n=1541**	**n=1541**	
Age	72.31±10.27	72.13±10.25	75.40±10.20	0.320	74.55±9.67	74.56±10.34	0.001
Gender				0.019			0.008
Male	19 681 (61.11)	18 598 (61.06)	1083 (61.99)		946 (61.39)	952 (61.78)	
Female	12 524 (38.89)	11 860 (38.94)	664 (38.01)		595 (38.61)	589 (38.22)	
Race				0.056			0.044
White	29 482 (91.54)	27 866 (91.49)	1616 (92.50)		1432 (92.93)	1426 (92.54)	
Black	1357 (4.21)	1284 (4.22)	73 (4.18)		64 (4.15)	60 (3.89)	
Other	1098 (3.41)	1054 (3.46)	44 (2.52)		32 (2.08)	42 (2.73)	
Unknown	268 (0.83)	254 (0.83)	14 (0.80)		13 (0.84)	13 (0.84)	
Charlson-Deyo score				0.106			0.041
0	20 416 (63.39)	19 346 (63.52)	1070 (61.25)		979 (63.53)	956 (62.04)	
1	7037 (21.85)	6675 (21.92)	362 (20.72)		319 (20.70)	322 (20.90)	
2	2798 (8.69)	2630 (8.63)	168 (9.62)		127 (8.24)	143 (9.28)	
3	1954 (6.07)	1807 (5.93)	147 (8.41)		116 (7.53)	120 (7.79)	
Facility type*				0.107			0.063
1	1873 (5.82)	1760 (5.78)	113 (6.47)		102 (6.62)	98 (6.36)	

2	11 994 (37.24)	11 411 (37.46)	583 (33.37)		503 (32.64)	525 (34.07)	
3	11 801 (36.64)	11 088 (36.40)	713 (40.81)		656 (42.57)	621 (40.30)	
4	6430 (19.97)	6096 (20.01)	334 (19.12)		273 (17.72)	293 (19.01)	
Unknown	107 (0.33)	103 (0.34)	4 (0.23)		7 (0.45)	4 (0.26)	
Distance to facility (miles)				0.075			0.042
<5	7143 (22.18)	6772 (22.23)	371 (21.24)		349 (22.65)	330 (21.41)	
5−9	5880 (18.26)	5569 (18.28)	311 (17.80)		298 (19.34)	283 (18.36)	
10−19	5790 (17.98)	5483 (18.00)	307 (17.57)		240 (15.57)	267 (17.33)	
≥20	9322 (28.95)	8827 (28.98)	495 (28.33)		440 (28.55)	440 (28.55)	
Unknown	4070 (12.64)	3807 (12.50)	263 (15.05)		214 (13.89)	221 (14.34)	
Insurance				0.166			0.019
Private	7279 (22.60)	6981 (22.92)	298 (17.06)		286 (18.56)	279 (18.11)	
Uninsured/Medicaid	1591 (4.94)	1525 (5.01)	66 (3.78)		59 (3.83)	64 (4.15)	
Medicare/ other government	23 335 (72.46)	21 952 (72.07)	1383 (79.16)		1196 (77.61)	1198 (77.74)	
Urban/Rural				0.068			0.069
Metro	25 959 (80.61)	24 569 (80.67)	1390 (79.56)		1208 (78.39)	1227 (79.62)	
Urban	4455 (13.83)	4189 (13.75)	266 (15.23)		222 (14.41)	229 (14.86)	
Rural	583 (1.81)	562 (1.85)	21 (1.20)		26 (1.69)	20 (1.30)	

Unknown	1208 (3.75)	1138 (3.74)	70 (4.01)		85 (5.52)	65 (4.22)	
Income (quartiles)				0.087			0.060
1	3877 (12.04)	3689 (12.11)	188 (10.76)		176 (11.42)	173 (11.23)	
2	6200 (19.25)	5861 (19.24)	339 (19.40)		298 (19.34)	288 (18.69)	
3	7162 (22.24)	6796 (22.31)	366 (20.95)		298 (19.34)	333 (21.61)	
4	10 673 (33.14)	10 097 (33.15)	576 (32.97)		540 (35.04)	515 (33.42)	
Unknown	4293 (13.33)	4015 (13.18)	278 (15.91)		229 (14.86)	232 (15.06)	
Education^				0.087			0.042
1	4189 (13.01)	3988 (13.09)	201 (11.51)		166 (10.77)	179 (11.62)	
2	7173 (22.27)	6773 (22.24)	400 (22.90)		356 (23.10)	353 (22.91)	
3	8873 (27.55)	7325 (24.05)	401 (22.95)		411 (26.67)	418 (27.13)	
4	7726 (23.99)	7616 (24.04)	406 (22.98)		384 (24.92)	361 (23.43)	
Unknown	4244 (13.18)	3971 (13.04)	273 (15.63)		224 (14.54)	230 (14.93)	
Primary site				0.183			0.038
C65.9	19 172 (59.53)	18 282 (60.02)	890 (50.94)		788 (51.14)	817 (53.02)	
C66.9	13 033 (40.47)	12 176 (39.98)	857 (49.06)		753 (48.86)	724 (46.98)	
T stage				0.889			0.094
T1	7782 (24.16)	7237 (23.76)	545 (31.20)		529 (34.33)	540 (35.04)	
T2	2499 (7.76)	2452 (8.05)	47 (2.69)		51 (3.31)	47 (3.05)	

T3	3701 (11.49)	3677 (12.07)	24 (1.37)		41 (2.66)	24 (1.56)	
T4	448 (1.39)	436 (1.43)	12 (0.69)		9 (0.58)	12 (0.78)	
Ta	3610 (11.21)	2975 (9.77)	635 (36.35)		459 (29.79)	436 (28.29)	
Tis	331 (1.03)	294 (0.97)	37 (2.12)		34 (2.21)	35 (2.27)	
Unknown	13 834 (42.96)	13 387 (43.95)	447 (25.59)		418 (27.13)	447 (29.01)	
Perioperative chemotherapy				0.182			0.004
No chemotherapy	27 767 (83.03)	26 232 (82.81)	1535 (86.87)		1355 (87.93)	1357 (88.06)	
Chemotherapy post-procedure	4438 (13.78)	4226 (13.34)	212 (12.00)		186 (12.07)	184 (11.94)	
Histological Grade				1.213			0.086
Low	6737 (20.92)	6246 (20.51)	491 (28.11)		450 (29.20)	491 (31.86)	
High	21 035 (65.32)	20 692 (67.94)	343 (19.63)		396 (25.70)	343 (22.26)	
Unknown	4433 (13.76)	3520 (11.56)	913 (52.26)		695 (45.10)	707 (45.88)	

Data were presented as mean ± standard deviation for continuous variables, and n (%) for categorical variables. *Facility type: 1) community cancer program; 2) comprehensive community cancer program; 3) academic/research program (includes NCI-designated comprehensive cancer centers); 4) integrated network cancer program. ^Education: Percent without high school degree as per NCDB data dictionary. ES: extirpative surgery (radical nephroureterectomy and segmental ureterectomy); ET: endoscopic therapy; SMD: standardized mean difference; UTUC: upper tract urothelial carcinoma.

Table 2. Association of treatment (ES or ET) with overall survival after PSM				
	5-year overall survival, % survival (95% CI)	**10-year overall survival, % survival, (95%CI)**	**Time ratio, (95% CI)***	**p**
Low grade				
ES (n=450)	67.81% (62.27−72.72)	41.55% (34.57−48.38)	Reference	
ET (n=491)	61.64% (56.88−66.03)	41.58% (35.95−47.11)	0.88 (0.72−1.07)	0.202
High grade				
ES (n=396)	54.18% (48.33−59.65)	36.41% (29.45−43.40)	Reference	
ET (n=343)	34.51% (29.03−40.05)	18.79% (13.40−24.90)	0.51 (0.39-0.65)	<0.001

*Since proportional hazards assumptions were violated in both groups (intersecting survival curves), the Accelerated Failure Time (AFT) Model with Weibull distribution was used with clustering to account for the clustering by the PSM. The Weibull distribution model had the lowest AIC and BIC. The AFT modeled the event time. Interpretation: Patients with ET reduced the median survival time by 49% (=1−0.51) in the high grade compared with those with ES (p<0.001). ES: extirpative surgery (radical nephroureterectomy and segmental ureterectomy); ET: endoscopic therapy.

Table 3. Association of treatment (ES or ET) with secondary outcomes								
Outcome	**Low grade**				**High grade**			
	Total	**Extirpative surgery**	**Endoscopic**	**p**	**Total**	**Extirpative surgery**	**Endoscopic**	**p**
	N=941	**n=450**	**n=491**		**N=739**	**n=396**	**n=343**	
Surgical inpatient stay (days)	1 (0−4)	3 (2−5)	0 (0−0)	**<0.001**	2 (0−4)	4 (2−6)	0 (0−1)	**<0.001**
Readmission within 30 days				**0.053**				0.96
0	891 (96)	425 (95)	466 (96)		698 (95)	376 (95)	322 (96)	
1	17 (2)	13 (3)	4 (1)		23 (3)	13 (3)	10 (3)	
2	20 (2)	8 (2)	12 (2)		10 (1)	5 (1)	5 (1)	

3	1 (0)	0 (0)	1 (0)					
30-day mortality				0.11				0.35
0	929 (99.36)	439 (98.87)	490 (99.80)		724 (98.64)	386 (98.22)	338 (99.12)	
1	6 (0.64)	5 (1.13)	1 (0.20)		10 (1.36)	7 (1.78)	3 (0.88)	
90-day mortality				0.65				0.42
0	912 (97.85)	434 (98.19)	478 (97.55)		708 (96.59)	382 (97.20)	326 (95.88)	
1	20 (2.15)	8 (1.81)	12 (2.45)		25 (3.41)	11 (2.80)	14 (4.12)	

*Key for readmission – 0: Patient was not readmitted within 30 days of discharged postoperatively; 1: Unplanned readmission within 30 days of being discharged postoperatively; 2: Planned readmission of the patient within 30 days of being discharged postoperatively; 3: Patient had both a planned and an unplanned readmission after being discharged postoperatively. **Key for mortality – 0: Patient alive or died >30 (or 90 for 90-day mortality) days after surgery; 1: Patient died ≤30 (or 90 for 90-day mortality) days after surgery. ES: extirpative surgery (radical nephroureterectomy and segmental ureterectomy); ET: endoscopic therapy; IQR: interquartile range.

Table 4. Association of ET vs. ES with overall survival by subgroups after propensity score matching for age, tumor size, tumor location, and perioperative chemotherapy receipt

	Low-grade UTUC		**High-grade UTUC**	
	Time ratio (95% CI)	**p**	**Time ratio (95% CI)**	**p**
Age (years)				
<65	1.06 (0.67−1.69)	0.806	**0.35 (0.12−1.05)**	0.061
65−80	0.82 (0.64−1.06)	0.125	**0.62 (0.44−0.86)**	0.004
>80	0.77 (0.58−1.03)	0.075	**0.64 (0.48−0.87)**	0.004
Tumor size (cm)				
<1.5	1.11 (0.76−1.63)	0.582	**0.46 (0.23−0.93)**	0.030
≥1.5	0.92 (0.70−1.21)	0.563	**0.56 (0.40−0.79)**	0.001
Location				
Renal	0.88 (0.68−1.14)	0.332	**0.54 (0.40−0.73)**	<0.001
Ureteral	0.77 (0.70−1.21)	0.563	**0.64 (0.48−0.79)**	0.002
Charlson-Deyo Score				
<2	0.94 (0.76−1.16)	0.564	**0.45 (0.34−0.60)**	<0.001
≥2	0.48 (0.29−0.79)	0.004	0.78 (0.51−1.19)	0.254

*Not evaluable due to the small number of events. Example for interpretation of time ratio: Patients with ET reduced the median survival time by 49% (=1-0.51) in the high-grade disease not receiving perioperative chemotherapy compared with those with ES (p<0.001). CI: confidence interval; ET: endoscopic therapy; ES: extirpative surgery; UTUC: upper tract urothelial carcinoma.