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Trends in the utilization of imaging for upper tract urothelial carcinoma

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Abstract

Objectives—To evaluate the changes in use of the different imaging modalities for diagnosing upper tract urothelial carcinoma (UTUC) and assess how these changes have affected tumor stage at the time of surgery.

Materials and methods—We assessed the Surveillance, Epidemiology, and End Results (SEER) cancer registry and linked Medicare claims data (1992–2009) for 5377 patients who underwent surgery for UTUC. We utilized International Classification of Disease—Oncology 3 codes to identify UTUC. International Classification of Disease, ninth Revision, Clinical Modification and Current Procedure Terminology codes identified surgical treatment and imaging modalities. We assessed for use of intravenous pyelography, retrograde pyelography (RGP), computed tomography urography (CTU), magnetic resonance urography (MRU), and endoscopy. For each modality, patients were categorized as having received the modality at least once or not at all. Patient characteristics were compared using chi-squared tests. Usage of imaging modalities and tumor stage was trended using Cochran-Armitage tests. We stratified our data into 2 multivariate logistic regression models to determine the effect of imaging modalities on tumor stage: 1992 to 1999 with all modalities except MRU, and 2000 to 2009 with all modalities.

Results—Our patient population was predominantly White males of more than 70 years old. Intravenous pyelography and RGP declined in use (62% and 72% in 1992 vs. 6% and 58% in 2009, respectively) while computed tomography urography, MRU, and endoscopy increased in use (2%, 0%, and 37% in 1992 vs. 44%, 6%, and 66% in 2009, respectively). In both regression analyses, endoscopy was associated with lower-stage tumors. In the 2000 to 2009 model, RGP was associated with lower-stage tumors, and MRU was associated with higher-stage tumors. Finally, our data showed an increasing number of modalities utilized for each patient (1% receiving 4 modalities in 1992 vs. 20% in 2009).

Conclusions—We found trends toward the utilization of newer imaging modalities to diagnose UTUC and more modalities per patient. Endoscopy and RGP were associated with smaller tumors,

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whereas MRU was associated with larger tumors. Further studies are needed to evaluate the utility of the different modalities in diagnosing UTUC.

Keywords

Upper Tract Urothelial Cancer; Imaging; Diagnosis; Endoscopy; Surgery

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a devastating disease with late-stage presentation, high recurrence rate, and high cancer-specific mortality rates. At the time of diagnosis, 60% of UTUC is invasive, which is more than twice that of urothelial carcinoma found in the lower tract. Patients diagnosed with UTUC have an overall 5-year survival of only 57% [1–3]. The current gold standard for treatment of UTUC is surgical excision with lymph node dissection. However, even after surgery, up to 28% of patients recur within 1 year and nearly 60% of deaths are attributable to the disease [3]. The late presentation, high recurrence rate, and high mortality rates suggest a lack of screening and diagnostic modalities to identify and treat UTUC early in its disease course.

Diagnosis of UTUC generally involves a combination of cytology, imaging, and endoscopic biopsy. In the face of a negative cystoscopy, abnormal urine cytology can point to upper tract malignancy, but with limited positive predictive value, particularly in lower-stage disease [4]. As for imaging, UTUC has historically been detected using intravenous pyelography (IVP) and retrograde pyelography (RGP). Today, cross-sectional imaging modalities, such as magnetic resonance urography (MRU) and computerized tomographic urography (CTU), allow urologists to visualize the upper tract and potentially the invasiveness of a tumor into surrounding tissues. Furthermore, recent improvements to endoscopes make ureterorenoscopy an option to directly visualize and take biopsies of lesions in the upper tract.

In this study, we evaluated the changes in use of the different imaging modalities for diagnosing UTUC. Additionally, we assessed how these changes have affected the stage of patients who received definitive surgery. Although prior studies have shown that CTU, MRU, and endoscopy allow for better detection of UTUC compared with IVP and RGP, there are no data in the literature on whether these newer imaging modalities are actually associated with lower-stage tumors at the time of surgery.

2. Materials and methods

2.1. Identification of patient cohort

After receiving Institutional Review Board approval, we assessed the Surveillance, Epidemiology, and End Results (SEER) cancer registry and linked Medicare claims data (1992–2009) for patients who underwent surgical treatment for UTUC. Diagnosis of UTUC was defined as the intersection of the International Classification of Disease—Oncology 3 (ICD-O-3) histology codes for transitional cell carcinoma (8,010; 8,050; 8,120; and 8,130) and the ICD-O-3 diagnosis codes for ureteral and renal pelvis cancer (659 and 669). Surgical

treatment for UTUC included open and minimally invasive nephrectomy, ureterectomy, and distal ureterectomy and were identified using Current Procedure Terminology (CPT) codes (50,220; 50,225; 50,230; 50,234; 50,236; 50,240; 50,543; 50,545; 50,546; 50,548; 50,549; 50,650; 50,660; 50,947; 50,948; and 50,949).

We included patients between 66 and 90 years of age who were eligible for Medicare by age only. Exclusion criteria included diagnosis of UTUC on death certificate or at autopsy, malignant histologic subtypes other than urothelial carcinoma, lack of coverage from Medicare A or B for 1 year before diagnosis, and enrollment in managed care for 1 year before diagnosis. Our final cohort included 5377 patients who received surgical treatment for UTUC.

2.2. Demographics and tumor characteristics

SEER data were used to identify patient demographics, including age, sex, and race. Also ascertained were the year of diagnosis, final tumor grade, and final tumor stage. Tumor grades provided by SEER followed a 4-grade system, ranging from well-differentiated (grade I) to undifferentiated or anaplastic (grade IV) [5]. The change in the World Health Organization tumor grade classification system in 2004 had no effect on our data. Patients were dichotomized based on disease stage at the time of surgical treatment: lower-stage disease was defined as Ta, carcinoma in situ, *T1*, or unknown stage; higher-stage disease was defined as *T2* or greater. We classified unknown-stage tumors as lower-stage disease because the tumors were likely too small to ascertain tumor stage.

2.3. Definitions of interventions

Using ICD, ninth Revision, Clinical Modification (ICD-9-CM) and CPT codes, we assessed the types of diagnostics used to evaluate for UTUC before the time of surgical treatment. Included diagnostic modalities were IVP (CPT 74,400; 74,410; and 74,415; and ICD-9 87.73), RGP (CPT 52,005; 74,420; and 74,425; and ICD-9 87.74), CTU (CPT 72,194 and 74,178), MRU (CPT 74,183 and 72,197), and endoscopy (CPT 50,551; 50,553; 50,555; 50,557; 50,559; 50,561; 50,562; 50,570; 50,572; 50,574; 50,575; 50,576; 50,578; 50,580; 50,951; 50,953; 50,955; 50,957; 50,959; 50,961; 50,970; 50,972; 50,974; 50,976; 50,978; 50,980; 52,335; 52,336; 52,337; 52,338; 52,339; 52,344; 52,345; 52,346; 52,351; 52,352; 52,353; 52,354; and 52,355). Endoscopy included all percutaneous and ureterorenoscopic assessment and management.

2.4. Statistical analysis

Chi-squared tests were used to compare demographics, final tumor grade, and final tumor stage. Usage of the different imaging modalities as well as tumor stage was trended over time using Cochran-Armitage tests of trend. Multivariable logistic regression models were fit to determine the effect of diagnostic modalities on tumor stage at surgery. Due to no use of MRU before 2000, we stratified our regression into 2 time-period regression models: (1) 1992 to 1999 with all modalities except MRU and (2) 2000 to 2009 with all modalities. In each regression model, age, sex, race, and year of diagnosis were included as possible confounders. We reported the adjusted odds ratio (OR) for each imaging modality where the reference was lack of that individual imaging modality. Finally, the number of different

imaging modalities used on each patient was organized as a histogram. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Trends in patient characteristics and tumor staging

Our patient population had more males than females. The vast majority of patients were Whites and more than 70 years of age. Age, race, tumor grade, and tumor stage varied significantly by year of diagnosis. In later years, we saw a greater proportion of patients more than 80 years old, more grade 4 tumors, and fewer grade 2 and grade 3 tumors (Table 1). Nearly all of our patients had urine cytology. Each year, 11% to 17% of tumors were of unknown stage. Lower-stage tumors comprised 50.4% of total tumors at the time of surgery in 1992, compared with 58.9% in 2009; this was not a statistically significant trend (Fig. 1; $P = 0.321$).

3.2. Imaging modalities

There have been significant changes in utilization of diagnostic and staging tests for UTUC over time (Fig. 2). The largest decline was seen in IVP, which decreased from being used in 62% of patients in 1992 to being used in 6% of patients in 2009 ($P < 0.001$). A much smaller decline was seen in RGP, which dropped from 72% usage in 1992 to 58% usage in 2009 ($P < 0.001$). Usage of CTU increased the most, going from 2% in 1992 to 44% in 2009 ($P < 0.001$). Less marked increases were seen in usage of MRU, which went from 0% to 6% ($P < 0.001$), and endoscopy, which went from 37% to 66% ($P < 0.001$). Our data also showed that nearly all instances of endoscopy involved ureterorenoscopy rather than percutaneous assessment. Of the patients who received endoscopy, 17.6% underwent at least 2 endoscopies, and 48.9% underwent at least one other imaging modality before endoscopy.

3.3. Predictors of lower-stage tumors

Multivariate logistic regression analysis for the 1992 to 1999 cohort ($N = 2208$), which excluded MRU as a variable, revealed endoscopy as a statistically significant predictor of tumor stage. Receiving at least 1 endoscopy was associated with lower-stage tumors (OR = 1.243, 95% CI: 1.038–1.488).

In the regression for the 2000 to 2009 cohort ($N = 3169$), race, MRU, and endoscopy were statistically significant variables. As in the other cohort, endoscopy was associated with lower-stage tumors (OR = 1.472, 95% CI: 1.266–1.712). RGP was also associated with lower-stage tumors (OR = 1.273, 95% CI: 1.091–1.484). MRU (OR = 0.617, 95% CI: 0.460–0.826) was associated with higher-stage tumors (Table 2).

3.4. Aggregate usage of imaging modalities

Over time, we saw an increase in the number of imaging modalities utilized for each patient (Fig. 3). In 1992, the percentages of patients receiving 2, 3, and 4 different modalities were 52, 24%, and 1%, respectively. In 2001, the group receiving 2 modalities had decreased to 32%, whereas the groups receiving 3 and 4 modalities had increased to 39% and 9%,

respectively. Continuing the trend, only 25% of patients receiving 2 modalities in 2009, compared with those 41% receiving 3 modalities and 20% receiving 4 modalities.

4. Discussion

Our study examined the trends in utilization of diagnostic modalities for UTUC and evaluated how these changes affected the stage of patients who received definitive surgery. From 1992 to 2009, utilization of the newer diagnostic modalities, CTU, MRU, and endoscopy, increased, whereas utilization of the older ones, RGP, and IVP, declined. Regression analyses showed that endoscopy was associated with lower-stage tumors throughout 1992 to 2009. From 2000 to 2009, RGP was associated with lower-stage tumors, and MRU was associated with higher-stage tumors. Our data also demonstrated that over the years of the study, patients received an increasing number of diagnostic modalities before definitive surgery.

Historically, diagnosis of UTUC utilized IVP and RGP. In the past 15 years, cross-sectional imaging and direct visualization of the upper tract using CTU, MRU, and endoscopy have become widely available. Reported sensitivities of IVP and RGP for detecting UTUC are 37.5% to 85% [6–8] and 25% to 100% [6,7,9,10], respectively. In comparison, MRU, CTU, and endoscopy boast sensitivities of 75% to 87.5% [8,11], 67% to 100% [12–19], and 89% to 95% [20,21], respectively. The superior ability of these newer diagnostic modalities in detecting UTUC suggests the trend for increasing use of newer diagnostic modalities that is both appropriate and beneficial to patients.

With improvements in diagnostic modalities for UTUC, we would expect to detect and treat UTUC earlier in the disease course. Furthermore, 2 large studies using the SEER database have documented an impressive degree of stage migration in UTUC in the past 30 years. Munoz and Ellison found that rates of in situ tumors increased from 7.2% in 1973 to 23.1% in 1996, whereas rates of higher-stage local tumors decreased from 50.4% to 31.8%. Similarly, between 1973 and 2005, Raman et al. saw rates of in situ tumors increase from 7.2% to 31%, balanced by a decrease in higher-stage local tumors from 50.4% to 23.6%. Both series found statistically longer survival with lower-stage tumors [9,22]. The percentage of lower-stage tumors in our patient sample decreased from 1992 to 2009; however, the trend was not statistically significant. This may be because we used a more contemporary cohort of patients, and the trend toward lower-stage tumors had plateaued. Regarding the stage migration in prior studies, our regression analyses suggest that the use of endoscopy, in particular, may have played a role, as it was associated with lower-stage tumors throughout the years of our study; however, this finding may be confounded by physician bias, as physicians may have forgone endoscopy when imaging showed a larger tumor. Finally, our data also showed increasing tumor grade over time. We suspect that modern imaging modalities allow for the detection of high-grade lesions at an earlier, less-invasive stage while older imaging modalities only detected these lesions at a later stage.

Another interesting finding in our study was that newer imaging modalities did not necessarily supplant older ones: the number of different imaging modalities used on each patient increased over time. In 1992, about 1 in 4 patients received 3 diagnostic modalities

and 1 in 50 received 4 modalities. In 2009, these had jumped to nearly 1 in 2 receiving 3 modalities and 1 in 5 receiving 4 modalities. With IVP and MRU minimally utilized, this means that most of the patients with UTUC are undergoing CTU, RGP, and endoscopy. More than 70% of patients with UTUC present with hematuria, initiating a full hematuria work-up [23]. The hematuria work-up includes CTU to assess for UTUC, a practice that maintains a strong recommendation (grade A) from the European Association of Urology (EAU). In contrast, it is unclear if all patients need endoscopy, especially given the risk of adverse events, such as ureteral perforation [21,24]. The EAU gives endoscopy a weak recommendation (grade C), given the lack of evidence supporting its diagnostic utility [21]. Likewise, Campbell et al. believe that endoscopy is only necessary if the diagnosis remains in question after other diagnostic studies, or if endoscopy may adjust the treatment plan, for instance, toward endoscopic management [25]. It is unlikely that two-thirds of patients fell into one of those categories. Thus, further studies are needed to weigh the diagnostic utility of endoscopy against the high cost and risk of adverse events.

There are a few important limitations to our study. First of all, use of Medicare data restricted our patient sample to only those greater than 66 years of age. However, it is unlikely that this significantly biased our results as patients with UTUC tend to be more than 70 years of age. Another limitation of our study was the use of SEER staging data. SEER records the highest pathologic stage over time, or in the absence of pathologic staging, the highest imaging stage. Although this probably led to over-staging of tumors, this bias was consistent throughout our data set. Finally, relying on billing and diagnosis codes to ascertain imaging modalities may have introduced coding errors to our data set. For example, some instances of CTU and MRU may have been coded as nonurographic studies and consequently excluded from our data. Reliance on codes also limited our interpretation of endoscopy, as we were not able to differentiate between diagnostic endoscopy and endoscopic treatment of UTUC. The usage of endoscopy to treat, rather than diagnose, UTUC could explain both the increase in usage as well as the association with smaller tumors. However, patients who undergo endoscopic treatment generally receive another imaging modality beforehand, and the majority of our patients did not.

5. Conclusion

We found significant trends over time toward the utilization of newer imaging modalities to diagnose UTUC, lower-stage tumors, and usage of more imaging modalities. Endoscopy was associated with smaller tumors while CTU and MRU were associated with larger tumors. Given the findings of this and previous works on UTUC, more detailed studies are needed to evaluate the utility of the different imaging modalities in diagnosing UTUC, and in particular, which patients benefit from diagnostic endoscopy.

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Fig. 1.

Rates of lower-stage tumors by year of diagnosis with trend line and P value for Cochran-Armitage test of trend are shown. The rates of lower-stage tumors did not significantly increase from 1992 to 2009 ($P = 0.321$). In 1992, 50.4% of tumors were lower-stage, and by 2009, 58.9% were lower-stage.

Fig. 2.

Utilization rates of diagnostic modalities. Utilization rates of each diagnostic modality by year of diagnosis are shown. Usage of intravenous pyelography (IVP) and retrograde pyelography (RGP) decreased over time. In contrast, usage of computerized tomographic urography (CTU), magnetic resonance urography (MRU), and endoscopy increased over time. Results of Cochran-Armitage tests of trend: $P < 0.001$ for IVP, $P < 0.001$ for RGP, $P < 0.001$ for CTU, $P = 0.006$ for MRU, and $P < 0.001$ for endoscopy.

Fig. 3. Number of imaging modalities utilized. The number of imaging modalities used for each patient increased over time. In 1992, about 1 in 4 patients underwent 3 diagnostic modalities and 1 in 50 underwent 4 modalities. By 2009, nearly 1 in 2 patients underwent 3 modalities and 1 in 5 underwent 4 modalities.

Table 1

Patient demographics and tumor characteristics as percentages and P values for chi-squared tests.

Patients	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total
	288	258	280	273	276	285	278	270	260	269	294	342	334	319	342	327	346	336	5377
<i>Age</i>	<i>Column percentages by year</i>																		
65–69	18.4	19.0	18.2	16.9	13.4	12.6	14.8	11.1	12.3	12.6	11.2	12.0	15.9	15.4	13.5	11.9	11.3	12.5	<0.001
70–74	27.4	22.5	27.9	28.6	28.6	26.0	21.6	28.9	24.6	26.0	21.1	19.9	22.5	13.8	19.3	19.0	15.9	17.3	
75–79	23.6	29.1	28.2	25.3	20.7	30.9	25.2	29.3	23.5	27.5	32.7	25.7	25.2	31.4	26.3	24.8	22.5	27.1	
80+	30.6	29.5	25.7	29.3	37.3	30.5	38.5	30.7	39.6	33.8	35.0	42.4	36.5	39.5	40.9	44.3	50.3	43.2	
<i>Sex</i>																			
Male	57.3	49.6	56.1	53.9	54.0	55.1	57.2	59.3	56.2	54.7	61.9	57.9	59.6	57.7	52.3	59.0	54.9	56.0	0.463
Female	42.7	50.4	43.9	46.2	46.0	44.9	42.8	40.7	43.9	45.4	38.1	42.1	40.4	42.3	47.7	41.0	45.1	44.1	
<i>Race</i>																			
White	93.1	91.1	92.9	92.7	91.7	88.8	89.9	91.1	91.2	90.3	88.8	89.2	88.9	91.5	90.1	90.8	87.0	91.4	0.027
Black	2.1	3.5	3.6	2.9	3.3	3.9	2.5	5.2	3.5	4.8	4.1	2.3	3.6	1.3	3.8	0.6	3.5	1.2	
Other	4.9	5.4	3.6	4.4	5.1	7.4	7.6	3.7	5.4	4.8	7.1	8.5	7.5	7.2	6.1	8.6	9.5	7.4	
<i>Grade</i>																			
1	8.3	5.8	5.7	5.5	6.5	8.4	5.0	5.2	4.6	8.9	6.5	4.4	6.6	9.1	5.3	9.2	9.0	5.7	<0.001
2	34.0	33.3	36.4	34.4	35.1	29.1	30.2	31.5	31.2	30.1	31.3	24.3	22.2	23.8	22.8	20.8	16.5	21.1	
3	36.1	36.8	33.2	35.9	34.1	38.3	39.6	27.8	30.0	27.5	28.9	29.2	32.6	27.3	26.6	25.1	21.4	19.1	
4	5.6	8.9	9.6	10.6	9.1	11.9	11.2	19.3	17.7	19.3	20.4	30.1	23.7	26.0	30.7	31.2	39.3	40.8	
Unknown	16.0	15.1	15.0	13.6	15.2	12.3	14.0	16.3	16.5	14.1	12.9	12.0	15.0	13.8	14.6	13.8	13.9	13.4	
<i>Final stage</i>																			
Ta, CIS, and Unknown	26.0	29.8	30.0	26.4	30.8	30.5	28.1	33.7	31.5	36.1	32.3	30.1	32.0	36.2	30.4	32.8	29.8	39.6	0.043
T1	24.3	25.2	28.6	27.8	26.5	24.6	28.4	23.3	28.9	21.9	21.8	25.4	23.7	25.8	22.8	23.9	24.9	19.8	
T2	13.5	11.6	9.6	10.3	9.4	8.4	9.0	7.4	6.9	11.2	9.5	8.8	9.6	11.6	16.1	11.4	11.6	12.6	
T3 and T4	36.1	33.3	31.8	35.5	33.3	36.5	34.5	35.6	32.7	30.9	36.4	35.7	34.7	26.4	30.7	31.9	33.8	27.9	

Table 2

Multivariable logistic regression model evaluating imaging modalities as predictors of low-stage tumor separated by year of diagnosis. Reference for the odds ratio (OR) for each imaging modality was not using that individual modality

Imaging modality	Adjusted OR	95% CI	P value
<i>1992–1999</i>			
Year of diagnosis	1.025	0.988 1.064	0.188
Endoscopy	1.243	1.038 1.488	0.0181
Computerized tomographic urography	0.849	0.55 1.31	0.4589
Intravenous pyelography	1.131	0.952 1.345	0.1614
Retrograde pyelography	1.037	0.857 1.256	0.7062
<i>2000–2009</i>			
Year of diagnosis	1.005	0.977 1.034	0.7216
Endoscopy	1.472	1.266 1.712	<0.0001
Computerized tomographic urography	0.976	0.826 1.154	0.7791
Magnetic resonance urography	0.617	0.46 0.826	0.0012
Intravenous pyelography	1.144	0.953 1.372	0.1483
Retrograde pyelography	1.273	1.091 1.484	0.0021