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Survival Comparison Between Endoscopic and Surgical Management for Patients With Upper Tract Urothelial Cancer: A Matched Propensity Score Analysis Using Surveillance, Epidemiology and End Results-Medicare Data

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Abstract

OBJECTIVE—To determine survival differences among patients receiving endoscopic vs surgical management for upper tract urothelial carcinoma (UTUC).

MATERIALS AND METHODS—Using Surveillance, Epidemiology and End Results-Medicare data, patients diagnosed with nonmuscle-invasive, low-grade UTUC as their first cancer diagnosis between 2004 and 2009 were identified. Receipts of endoscopic and surgical interventions were assessed, and patients were separated into surgical or endoscopic management cohorts. Two-to-one propensity score analysis was performed to control for baseline characteristics between groups.

RESULTS—The endoscopic management ($n = 151$) and matched surgical management ($n = 302$) groups demonstrated no significant differences in age, gender, race, marital status, Charlson comorbidity index, or year of diagnosis. Endoscopic management was an independent and significant predictor of all-cause and cancer-specific mortality (hazard ratio 1.6 for overall survival [OS], hazard ratio 2.1 for cancer-specific survival [CSS]). Kaplan-Meier estimated survival was significantly lower for endoscopic management, with both OS and CSS curves diverging at approximately 24–36 months. A subset of patients initially receiving endoscopic management went on to receive surgical intervention ($80/151 = 53\%$) at a median of 8.8 months from diagnosis. For these patients, Kaplan-Meier-estimated CSS was not significantly different from those who continued with only endoscopic management, and remained significantly lower than patients who received upfront surgery.

CONCLUSION—Although initial survival outcomes (first 24 months) are similar for endoscopic and surgical management of nonmuscle-invasive, low-grade UTUC, both CSS and OS are significantly inferior for the endoscopic management group in the longer term. Furthermore, transition from initial endoscopic management to surgical intervention appears to have limited impact on survival.

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Upper tract urothelial carcinoma (UTUC) is a disease of low incidence accounting for about 5% of all urothelial cancers.¹ Nephroureterectomy with excision of a cuff of the bladder is the gold standard for the management of UTUC.² However, removal of the renal unit is not optimal in some patients, such as those with renal insufficiency, an absent contralateral kidney, or severe medical comorbidities. For these patients, endoscopic management of UTUC became an alternative management strategy to nephroureterectomy, allowing for resection and ablation of UTUC with preservation of renal function.^{3–5} Similar to the evolution of partial nephrectomy, endoscopic management of nonmuscle-invasive, low-grade UTUC has moved beyond its initial restricted niche to acceptance as an alternative management strategy for all patients.^{6,7}

Despite the clinical utilization of endoscopic management for UTUC, few studies directly compare endoscopic resection to definitive surgery.^{4,5,8,9} Although these studies demonstrate oncologic efficacy for endoscopic management of lower grade and superficial tumors, the ability to accurately grade and stage UTUC remains limited,¹⁰ which creates uncertainty when attempting to safely select patients for endoscopic management. Furthermore, comparative effectiveness studies of definitive surgical management vs endoscopic management are lacking.

Due to the rarity of UTUC, the differences in cancer-specific survival (CSS) and overall survival (OS) between endoscopic and definitive surgery remain unclear. To better understand differences in survival for patients with nonmuscle-invasive, low-grade UTUC managed by surgical vs endoscopic management, we examined a contemporary cohort of patients with UTUC through combined Surveillance, Epidemiology and End Results (SEER)-Medicare data.

MATERIALS AND METHODS

Identification of Overall Cohort

We assessed SEER-Medicare data for patients diagnosed with nonmuscle-invasive (American Joint Committee on Cancer stage Ta, Tis, T1),¹¹ low-grade UTUC based on diagnosis codes between years 2004 and 2009 with follow-up data available through 2011. We excluded patients with nodal or metastatic disease based on the SEER historical staging system variable. Information on recurrence is not available in the SEER data. Per the SEER grading guidelines,¹² transitional cell carcinoma is classified by a 4-grade system; we included all patients with SEER grade 1 or 2 UTUC. SEER instructions to registrars from 2004 to 2009 echo the 2004 WHO grading system,¹³ with patients with low-grade disease considered a “2” in the SEER grading system and those with high-grade disease considered a “4.” If the registrar received a report using the older 3-grade system (1973 WHO grading system), low grade was called a “2,” intermediate grade a “3,” and high grade a “4.” We excluded patients younger than 65 or older than 90 years of age, those who were enrolled in Medicare for reasons other than age eligibility, and any diagnoses from autopsy or death certificates. All included patients had continuous Medicare parts A and B coverage with no health maintenance organization enrollment for 1 year prior to diagnosis of UTUC. To reduce treatment bias and minimize the impact on survival of other cancer diagnoses,

patients with other cancer diagnoses prior to diagnosis of UTUC were excluded (n = 290). Our final cohort included 803 patients with UTUC.

Receipt of Surgical Intervention

Definitive surgical management included open and minimally invasive extirpative interventions defined by Current Procedural Terminology (Appendix S1). To ensure correct assignment of surgical intervention, we also examined the data for evidence of anesthesia codes, pathology codes, and inpatient hospitalization temporally related to the time of the surgical procedure from physician billing data (7 days before to 7 days after). We also examined SEER data for ascertainment of surgery. Patients with no evidence of surgery by any of these criteria were considered to have not had surgery. The date of surgery was defined from the physician billing files, with the exception of cases where there was evidence of surgery from the SEER data without corresponding surgical billing. In these cases, the date of surgery was based on the inpatient hospitalization dates. If there was only evidence of surgery from the SEER data with no supporting billing data from hospitalizations or physician billing, the patients were considered to have not had surgical intervention.

Receipt of Endoscopic Intervention

Patient records were assessed for evidence of endoscopic management, either retrograde or antegrade, to evaluate or treat UTUC as defined by Current Procedural Terminology codes (Appendix S2). The dates of endoscopic management from the physician billing files were obtained and compared to the dates of surgery.

Final Assignments of Patients to Surgical and Endoscopic Management Groups

Patients who did not receive surgical or endoscopic interventions were excluded from analysis (n = 91). The surgical management cohort included patients who (1) received surgical intervention with no evidence of endoscopic intervention prior to surgery, and (2) received surgical intervention within 90 days of an endoscopic procedure, as they were considered to have received diagnostic endoscopy prior to surgery (n = 561). The endoscopic management cohort included patients who (1) received endoscopic intervention with no evidence of surgical intervention (n = 71), or (2) received surgical intervention more than 90 days after the initial endoscopic intervention (n = 80).

Statistical Analysis

Our primary analysis examined overall survival (OS) and cancer-specific survival (CSS) comparing endoscopic management and surgical management with matched propensity score analysis. Matching on patient age, cancer grade, marital status, race, gender, year of diagnosis, and Charlson comorbidity index,¹⁴ we used nearest neighbor (2:1) propensity score matching to match a subset of surgical management patients (n = 302) to patients treated with endoscopic management (n = 151). We performed Kaplan-Meier estimated survival analysis for CSS and OS comparing endoscopic to surgical management within the matched cohort. We then performed Cox proportional hazards regression to control for potential confounding variables.

As a hypothesis-generating secondary analysis, we compared Kaplan-Meier estimated survival for the propensity score matched cohort of patients who received surgical management ($n = 302$) to those who received initial endoscopic management followed by eventual surgical management ($n = 80$). We also examined for differences in survival for patients who had only endoscopic management ($n = 71$) vs patients who had initial endoscopic management followed by surgery ($n = 80$).

All analysis was performed with SAS version 9.3 and R version 2.15.1. P values of $<.05$ were considered statistically significant.

RESULTS

Table 1 summarizes the baseline clinical information for the patients who received endoscopic management and the matched cohort of patients who received surgical management. As expected, based on the matching algorithm, there were no significant differences in age, gender, race, marital status, Charlson comorbidity index, or year of diagnosis between the 2 groups. In the cohort, 83% of all patients who had definitive surgery had final pathologic stage of T1 or less. Among patients with definitive surgery after initial endoscopic management, 87.5% had a final stage of T1 or less.

Comparison of Kaplan-Meier estimated survival between patients receiving endoscopic management and upfront surgical management is provided in Figure 1. For both OS (Fig. 1A) and CSS (Fig. 1B), there is significantly lower survival rates for those receiving endoscopic management. During the first 24 months following diagnosis, OS and CSS remain similar between the endoscopic and surgical management groups. Between 24 and 36 months from diagnosis, both survival curves noticeably diverge and are significantly different by the end of the study period ($P < .01$ for OS and $P = .02$ for CSS). After controlling for potential confounding variables in the matched propensity score analysis, receipt of endoscopic management rather than upfront surgical management was a significant and independent predictor of death from any cause and death from UTUC (hazard ratio 1.6, 95% confidence interval 1.3 to 2.2 for OS; hazard ratio 2.1, 95% confidence interval 1.0 to 4.1 for CSS).

For patients who initially received endoscopic management and went on to receive surgical management, surgical intervention was performed at median 269 days (8.8 months) from diagnosis. Comparison of Kaplan-Meier estimated survival between this group and the matched subset of patients receiving upfront surgical management is provided in Figure 2. Although OS (Fig. 2A) is not significantly lower for patients who converted from endoscopic to surgical management, CSS (Fig. 2B) is significantly lower for these patients ($P = .02$).

Comparison of Kaplan-Meier estimated survival between patients who received only endoscopic management as well as those that went on to receive eventual surgical management is provided in Figure 3. Although OS (Fig. 3A) is significantly lower for patients who remained on endoscopic management ($P = .02$), CSS (Fig. 3B) is not

significantly different between patients who remained on endoscopic management and those who eventually received surgical management.

COMMENTS

Using propensity score analysis to control for baseline differences, our study aimed to identify survival differences between endoscopic and surgical management for patients diagnosed with nonmuscle-invasive, low-grade UTUC as their first malignancy. We found that patients receiving upfront surgical management had significantly improved OS and CSS, and accordingly endoscopic management was an independent predictor of all-cause and cancer-specific mortality. The significant improvement in OS and CSS seen with upfront surgical management was not immediately noticeable, as the survival curves between groups remained similar during the first 24 months. However, at approximately 24 to 36 months from diagnosis, both OS and CSS began to decline more rapidly in the endoscopic management arm (Fig. 1).

To further explore reasons for the increased cancer-specific and overall mortality with initial endoscopic management, we examined patients who initially received endoscopic management and underwent delayed surgical intervention (53% of the endoscopic management group). Although OS was significantly improved for these patients compared to those remaining on endoscopic management alone, CSS was not significantly different (Fig. 3). This suggests that the apparent OS benefit seen with patients receiving delayed surgical intervention may be a result of inherent selection bias. Patients who were healthier went on to subsequent surgery. However, those patients receiving delayed surgical management after initial endoscopic management had significantly lower CSS when compared to the matched cohort of patients receiving upfront surgical management, with curves continuing to diverge between 24 and 36 months from diagnosis (Fig. 2B). These results suggest that the delays in surgical management negatively impact patient survival.

The inferior CSS seen with endoscopic management in our study may be a result of limitations of endoscopic surveillance to detect progression of low-grade UTUC. Although there is limited available literature regarding disease progression during endoscopic surveillance of UTUC, data exist for low-risk bladder cancer surveillance and can be viewed as a similar disease profile. Patients with low-risk, noninvasive bladder cancer have been found to rarely progress to muscle invasion, but those who progress during surveillance have a higher risk of disease-specific mortality.¹⁵ Furthermore, patients who progress to muscle-invasive disease during surveillance have similar survival to patients with initial presentation of muscle-invasive bladder cancer.¹⁶ The failure of endoscopic surveillance in low-risk bladder cancer to provide a survival benefit suggests that endoscopic surveillance regimens may not be effective at detecting disease progression in a timely manner such that intervention can alter survival outcomes. Similarly, repeated endoscopic surveillance for low-grade UTUC may not be effective at detecting disease progression, as evidenced by patients with low-grade UTUC who have been found to progress to metastatic disease during endoscopic management.¹⁷

Also contributing to the inferior survival of patients diagnosed with UTUC treated with endoscopic management may be the diagnostic limitations in UTUC. As grade of cancer is closely related to tumor stage for UTUC, an accurate pathologic diagnosis is critical to appropriate management.^{18,19} Currently, modalities to diagnose UTUC include selective urine cytology, ureteroscopic biopsy, and cross-sectional imaging. One study reviewing the efficacy of positive urine cytology in patients undergoing definitive surgical management found the sensitivity and positive predictive value for high-grade disease to be 56% and 54%, respectively.²⁰ Ureteroscopic biopsy has diagnostic limitations as well, with high-grade UTUC biopsy demonstrating positive predictive value of 60% to 67% for muscle invasion,^{19,21} and understaging occurring in 22% of cases.²² Although the presence of hydronephrosis is a predictive factor for higher-stage disease, imaging lacks resolution to correctly identify the depth of cancer invasion unless UTUC is invading surrounding organs.^{23,24} As such, patients who were initially endoscopically diagnosed with low-grade disease may harbor high-grade elements that would be found on complete pathologic examination of the extirpated specimen, but not during subsequent endoscopic surveillance.

Although we find that surgical management provides superior OS and CSS for UTUC patients, there is a limited but important role of endoscopic management in the treatment of low-risk UTUC. With median-estimated OS for the entire cohort of 72 months, similar to previous studies of UTUC,²⁵ patients with a diagnosis of UTUC have substantial competing risks of mortality. This is likely a result of environmental (eg, smoking, occupational exposures) and genetic (eg, Lynch syndrome) factors involved in the development of UTUC that are linked to other malignancies as well as risks of noncancer-related death.^{26,27} Thus, as in prostate cancer,²⁸ aggressive management with upfront surgery for all patients with low-risk UTUC may result in overtreatment. For very elderly patients and those with significant comorbidities, the potential improvement in CSS with surgical over endoscopic management may be outweighed by competing causes of mortality. And so, for these patients, particularly those with less than 36-month estimated OS at the time of low-risk UTUC diagnosis, endoscopic management represents the best treatment alternative.

This study is not without limitations. The observational database study design restricts the level of detail that may be obtained in a single or multicenter retrospective study. Details regarding adequacy of the initial biopsy and clinical decision-making for management (endoscopic, endoscopic with delayed surgical, vs surgical intervention) would refine allocation to treatment groups. Additionally, the endoscopic management group in this study is heterogenous with no standardized approach to surveillance and intervention, which introduces bias. However, given that this group received repeated endoscopic interventions without extirpation, this broadly represents patients receiving endoscopic management in real practice. As claims-based data were used, clinical assumptions were made to refine the treatment groups. The most notable assumption involves including patients who received surgical interventions within 90 days of endoscopic interventions in the surgical management group. The assumption was based on guideline recommendations to repeat upper tract evaluation at 90 days after endoscopic diagnosis.^{6,7} Although the divergence of the surgical management group and the delayed surgery group (Fig. 2B) suggests that the distinction of 90 days after endoscopic diagnosis is consistent with patient outcomes, the use of claims-based data may include inaccuracies that cannot be completely eliminated.

Although propensity score-matched subset was generated from the upfront surgical management group, there are inherent biases of surgical selection between endoscopic and surgical intervention that could not be completely accounted. The patients who received endoscopic management, and more importantly those who remained on endoscopic management, were likely less healthy than those who received surgical management, and this underlying difference in morbidity may not be adequately accounted for in the matching algorithms. Finally, as SEER-Medicare data were used for this study, our results cannot be applied to patients younger than 65 years of age. Such patients may have fewer competing causes of mortality, and thus be at increased risk for disease recurrence or progression.

CONCLUSION

For nonmuscle-invasive, low-grade UTUC, endoscopic management provides similar early (first 24 months) OS and CSS to upfront surgical management. However, after this period of time, survival curves diverge with significantly inferior OS and CSS for patients who received endoscopic management. For patients who eventually underwent surgical intervention after initial endoscopic management, CSS remains significantly inferior to those who received upfront surgical management, and CSS remains similar to those who remain on endoscopic management only. When considering endoscopic management for UTUC, the survival detriment of this treatment alternative should be carefully weighed against competing causes of mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX: Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.urology.2016.05.033>.

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Figure 1. Kaplan-Meier estimated overall survival (**A**) and cancer-specific survival (**B**) curves for endoscopic management compared to matched subset of patients receiving surgical management.

Figure 2. Kaplan-Meier estimated overall survival (**A**) and cancer-specific survival (**B**) curves for initial endoscopic management with eventual surgical management compared to matched subset of patients receiving surgical management.

Figure 3. Kaplan-Meier estimated overall survival (A) and cancer-specific survival (B) curves for endoscopic management only compared to initial endoscopic management with eventual surgical management.

Table 1

Baseline clinical information for patients who received endoscopic management and the matched subset of patients who received surgical management

Variable	Endoscopic Management	2:1 Propensity Score-matched Subset of Surgical Management	P Value
Patients	151	302	—
Age at diagnosis (years)			.835
65–69	15.9%	13.2%	
70–74	19.9%	18.5%	
75–79	27.8%	28.8%	
80	36.4%	39.4%	
Gender			.787
Male	57.6%	58.9%	
Female	42.4%	41.1%	
Race			.528
White	91.4%	93.0%	
Other	8.6%	7.0%	
Marital status			.637
Married	57.0%	59.3%	
Single/Unknown	43.0%	40.7%	
Charlson comorbidity index			.867
=0	45.0%	44.7%	
=1	26.5%	29.8%	
=2	16.6%	14.9%	
3	11.9%	10.6%	
Year of diagnosis			.671
2004	13.2%	12.3%	
2005	15.2%	16.9%	
2006	13.9%	17.5%	
2007	21.9%	16.9%	
2008	15.9%	13.6%	
2009	19.9%	22.8%	