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Original article

Neoadjuvant and adjuvant chemotherapy use in upper tract urothelial carcinoma

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Abstract

Objective: To determine trends in neoadjuvant and adjuvant chemotherapy use for upper tract urothelial cancer and assess its effects on survival.

Materials and methods: We identified all patients diagnosed with upper tract urothelial cancer who underwent surgical treatment in the SEER-Medicare database from 2002 to 2011. We collected and analyzed patient demographic, clinical, and pathologic characteristics. We strictly defined neoadjuvant and adjuvant chemotherapy and studied patients who met such criteria. Multivariable Cox proportional hazards models identified were used to identify independent predictors of overall and cancer-specific survival.

Results: A total of 3,432 patients met inclusion criteria, and their median age was 77 years. Overall, 86.4% of patients underwent surgery alone, 1.8% received neoadjuvant chemotherapy plus surgery, and 11.8% underwent surgery and adjuvant chemotherapy. Neoadjuvant chemotherapy use increased during the study period. Gemcitabine, carboplatin, cisplatin, and paclitaxel were the most commonly used agents. Cancer-specific survival at 5 years was 65.0% (95% CI: 63.2%–66.8%). Cox proportional hazards modeling controlling for sex, race, year of diagnosis, location, and pathologic stage revealed that higher pathologic nodal stage, tumor size >3 cm, increased age, and carcinoma in situ predicted for worse survival.

Conclusion: Age, nodal stage, and tumor size >3 cm predict for worse cancer-specific survival. Neoajduvant chemotherapy is underused.

Keywords: Upper tract urothelial cancer; Chemotherapy; Neoadjuvant; Nephroureterectomy; Upper tract transitional cell carcinoma; SEER-medicare

1. Introduction

Upper tract urothelial cancer (UTUC) is defined as disease involving the ureter or renal urothelium, and it accounts for 5% to 10% of urothelial cancers, with approximately 6,000 new cases diagnosed annually in the United States [1]. UTUC portends a worse prognosis than urothelial cancer arising from the bladder, and potential explanations for this difference include the thinner ureteral or renal pelvic wall, a later stage at diagnosis, added difficulty in screening and biopsy, or less expertise in treatment [2]. Given the inherent risk of recurrence and progression, this disease can be quite challenging to treat, making urothelial cancer among the most costly cancer per patient in terms of diagnosis, treatment, and subsequent surveillance [3]. There is a large degree of overlap between bladder and upper tract cancers, as up to 20% of patients with UTUC present with concurrent bladder cancer, and delayed recurrence in the bladder in small series has been encountered in up to 50% of cases [4,5].

Although the standard treatment for UTUC is nephroureterectomy, evidence has steadily been growing regarding both neoadjuvant and adjuvant chemotherapy to have a role in treatment [6]. Firstly, the positive results from neoadjuvant cisplatin-based chemotherapy trials in bladder cancer suggest that these drug regimens could also improve the survival of patient with UTUC [7,8]. Indeed, evidence is growing of a potential survival advantage and pathologic response to chemotherapy for UTUC [9–14]. Secondly, there are numerous population-based [15,16] single-institutional [17,18] and multi-institutional [12] studies

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showing poor survival for muscle-invasive, node-positive or nonorgan-confined UTUC, suggesting the significant need for systemic therapy options in these patients. Thirdly, Lane et al. [19] demonstrated that more than 50% of patients presenting with UTUC have chronic kidney disease, which worsens after nephroureterectomy, precluding postsurgical cisplatin-based chemotherapy for most patients. This argues strongly in favor of neoadjuvant, rather than adjuvant chemotherapy in UTUC. The European guidelines group for the management of UTUC is awaiting further evidence from prospective trials before including a definitive recommendation for chemotherapy in the adjuvant or neoadjuvant setting [6].

Given the relative rarity of UTUC, single-center series and small cancer registries are unreliable in estimating nationwide use of these and other therapies. To that end, we studied therapies for UTUC in the SEER-Medicare population, representing 28% of all adults aged 65 years and older with a cancer diagnosis in the United States. We hypothesize that given the recent literature on the potential benefit of using neoadjuvant and adjuvant chemotherapy in UTUC, these would increase during the study period. Similarly, increasing use of neoadjuvant chemotherapy in bladder cancer could translate into more use for UTUC over the same period given the overlap in tumor histology and treating physicians for these 2 conditions [20]. Our other objective was to study the effect of these varied therapies on patient survival for clinically localized UTUC.

2. Materials and Methods

Using SEER-Medicare files from 2002 to 2011, we included all cases with a diagnosis of UTUC using International Statistical Classification of Diseases (ICD-9) codes: 189.1—malignant neoplasm of renal pelvis or 189.2—malignant neoplasm of ureter. Moreover, histology location codes were queried for C65.9 and C66.9 (ureter and renal pelvis). We limited the study group to those patients with at least 1 year of data and excluded those patients with extreme age, retaining those 65 to 95 years old. Patient enrollment in both Medicare Part A and B was required to capture all treatment modalities. Furthermore, we studied patients presenting with nonmetastatic disease, those who had received definitive surgical treatment, and those with complete pathologic information available in regard to tumor stage.

Of note, 16.8% of patients with upper tract cancer had already been diagnosed with one other primary tumor during our study period (Fig. 1). We included these patients to maximize the number of subjects in the cohort and maintain the generalizability of our results; however, in survival analysis, those patients with multiple cancer diagnoses were excluded to ensure accuracy of UTUC cause-specific mortality rates.

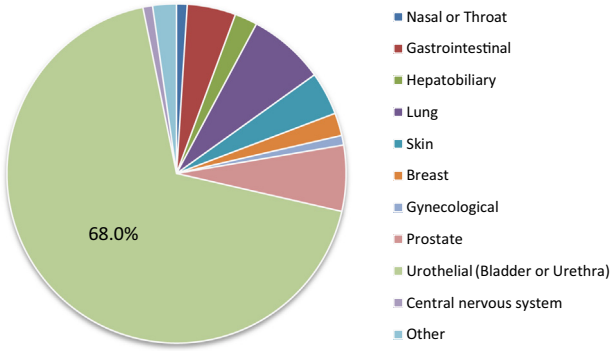

Fig. 1. Frequency of other cancers concomitant with upper tract urothelial cancers. (Color version of figure is available online.)

Patients who underwent definitive surgery were those whose Current Procedural Terminology codes matched appropriate histology coding for UTUC. Ultimately, total or partial ureterectomy, as well as nephroureterectomy, were considered definitive surgery. All approaches, whether robotic, laparoscopic, open, open + resection of ureteral orifice via endoscopy were included. A full list of codes is included in Appendix I. Charlson Comorbidity Index scores were derived from hospital and physician claims [21]. Chemotherapy use was queried using J codes, a full list included in Appendix II. Neoadjuvant chemotherapy patients were defined as those whose claim for surgery was within 180 days after the first chemotherapy claim. Alternatively, chemotherapy within 180 days after the surgery claim was categorized as recipients of adjuvant chemotherapy. Those with less than 4 chemotherapy claims or excessive number of claims on a single day were not included to exclude patients who did not receive a full course of chemotherapy or were miscoded.

Using the SAS 9.3 (Cary, NC) statistical program, we analyzed patient and pathologic characteristics using chi-square analysis, Kruskal-Wallis, or Wilcoxon signed-rank test where appropriate.Trends in treatment modalities over time were evaluated using the Cochran-Armitage Trend Test. Kaplan-Meier survival analysis and stratified log-rank test were used to compare overall survival stratified by the various treatment strategies. Overall survival was estimated as the time from diagnosis to death, and surviving patients were censored at the time of the last follow-up. A multivariable Cox proportional hazards model identified predictors of overall and cancer-specific survival. All tests were 2 tailed, and a threshold of $P < 0.05$ was considered significant for statistical analyses.

3. Results

Initially, over 10,000 patients were identified within the 2002 to 2011 SEER-Medicare database with a diagnosis of UTUC. Ultimately, 3,432 patients met inclusion criteria. The median age of the cohort was 77 years (interquartile range [IQR]: 72–82), with a median follow-up of 35