2016

Underuse and Potential Detrimental Effect of Radiotherapy in the Management of Ureteral Cancer

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Abstract

Ureteral cancer is extremely rare, with only 3530 cases predicted in 2016. Therefore, published studies on ureteral cancers are limited to single-institution retrospective studies, which have not elucidated a clear recommendation on the best treatment modality. Large cancer databases such as the Surveillance, Epidemiology, and End Results program (SEER) are ideal for providing data for these rare cancers. Epidemiological studies using the SEER database with large sample sizes (13,800) found rising incidence of ureteral cancer over the past 30 years with worsened outcomes in older patients, males, and patients with regional/distant spread. However, to date, these studies have not used the available data in the SEER databases to stratify survival outcomes based on different treatment modalities. The purpose of this study is to assess the overall survival (OSS), cause-specific survival (CSS) and effect of intervention (surgery and postoperative radiotherapy) in patients with ureteral carcinoma.

Methods

The Surveillance, Epidemiology, and End Results (SEER) database is a national cancer database run by the National Cancer Institute that records all incident cases from 18 registries covering 28% of the US population. The SEER registries collect data on patient demographics, primary tumor site, disease extent, course of treatment and follow up. Data is de-identified and available for public use. Using the SEER database, we identified patients with pathologically confirmed primary tumor of renal pelvis and ureters using International Classification of Diseases codes ICD-O-3 codes 65.9 (renal pelvis) and 66.9 (ureter) who underwent attempted curative surgery for their diagnosis between 1995 and 2012. Exclusion criteria included in-situ disease, metastatic disease, preoperative radiotherapy, brachytherapy, or patients with incomplete information regarding tumor staging, treatment or outcomes. Localized disease was defined as “confined to the organ of origin without extension beyond the primary organ” while a tumor with regional extension were those with “direct extension to adjacent organs or structures or spread to regional lymph nodes” As a result of this inclusion criteria, a total of 6,057 patients were included for analysis. Categorical variables included histology, patient age at diagnosis, gender, race, year of diagnosis, primary site (renal pelvis vs. ureter), extent of disease (localized vs. regional), and use of adjuvant RT. Cause specific survival (CSS) was the primary endpoint. This was determined using specified cause of death from either ureteral or renal pelvis carcinoma and was measured from date of diagnosis until death. Overall survival (OS) was measured from the date of diagnosis to the date of death from any cause. Kaplan-Meier plot and Wilcoxon test were used to evaluate survival of patients in regards to radiation. In the next step, patients then stratified based on the stage to evaluate effects of adjuvant radiotherapy in each stage.

Results

6057 patients were identified with a mean age of 70.57±10.37SD, 64.88% were male, 61.32% had renal pelvic carcinoma and 38.68% had ureteral carcinoma, 2601 (42.94%) had localized tumor and 3456 (57.06%) had regional disease. The majority of cases were transitional cell carcinoma (96.67%), all patients underwent surgery and 217 (3.58%) received adjuvant RT. For the 5840 patients who only received curative surgery, 64.81% were male, 61.83% had renal pelvic carcinoma and 38.17% had ureteral carcinoma, 3611 (61.83%) had localized tumor and 2229 (38.17%) had regional disease. For the 217 patients who received adjuvant radiotherapy in addition to curative surgery 66.82% were male, 47.46% had renal pelvic carcinoma and 52.53% had ureteral carcinoma, 22 (10.14%) had localized tumor and 195 (89.86%) had regional disease. (table 1) CSS at 1, 2 and 5 years was 98%, 94.6% and 86.1% without adjuvant RT and 92.1%, 84.7% and 69.4% with adjuvant RT ($p<0.0001$) (figure1).

Given the large variation in disease stage between the subgroup of patients who received adjuvant RT and those who did not , we also analyzed survival stratified by disease stage. CSS for local disease at 1, 2 and 5 years was 98.8%, 97.5% and 91.5% without adjuvant RT and 90.7%, 85.3% and 85.3% with adjuvant RT. CSS for regional disease at 1, 2 and 5 years was 97.3%, 92% and 80.7% without adjuvant RT and 92.3%, 84.5% and 66.9% with adjuvant RT. (figures 2 and 3)

On multivariate analysis, older age, regional extension, and postoperative RT had a negative impact on both overall survival and cause-specific survival. Specifically, receiving postoperative RT had a hazard ratio of 2.16 with Confidence Interval of 1.63 to 2.85. Female sex was associated positively with OS but negatively with CSS. (table 2)

n (%) Mean ± SD	Total patients n=6057	Curative surgery n=5840 (96.42%)	Curative surgery + adjuvant radiotherapy n=217 (3.58%)
Sex			
Male	3930 (64.88%)	3785 (64.81%)	145 (66.82%)
Female	2127 (35.12%)	2055 (35.19%)	72 (33.18%)
Race			
Caucasian	5508 (90.94%)	5313 (90.98%)	195 (89.86%)
African-American	209 (3.45%)	201 (3.44%)	8 (3.69%)
Others	337 (5.56%)	323 (5.53%)	14 (6.45%)
Unknown	3 (0.05%)	3 (0.05%)	0 (0%)
Primary tumor site			
Renal pelvis	3714 (61.32%)	3611 (61.83%)	103 (47.46%)
Ureter	2343 (38.68%)	2229 (38.17%)	114 (52.53%)
Tumor stage			
Local	2601 (42.94$%)	3611 (61.83%)	22 (10.14%)
Regional	3456 (57.06%)	2229 (38.17%)	195 (89.86%)
Histology			
Transitional cell carcinoma	5855 (96.67%)	5651 (96.76%)	204 (94.01%)
Squamous cell neoplasms	89 (1.47%)	82 (1.4%)	7 (3.23%)
Epithelial neoplasms, not otherwise specified	31 (0.51%)	28 (0.48%)	3 (1.38%)
Adenocarcinoma	61 (1.01%)	58 (0.99%)	3 (1.38%)
Others	21 (0.35%)	21 (0.36%)	0 (0%)

Table 1: Predictors of surgical and adjuvant radiotherapy usage in ureteral cancer

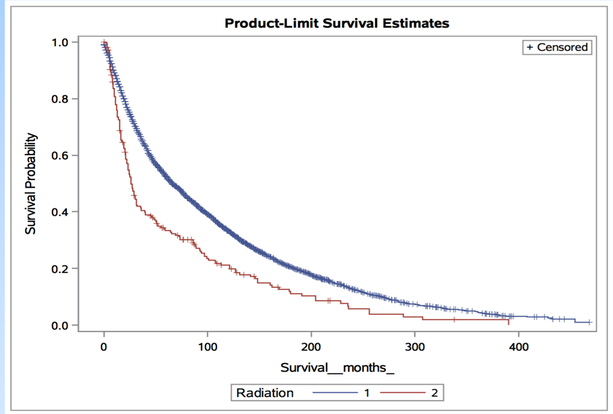

Figure 1: Kaplan-Meier plot of cause-specific survival stratified for all patients by adjuvant radiotherapy use. Blue line represents patients who only underwent surgery, red line represents patients who underwent surgery and radiotherapy

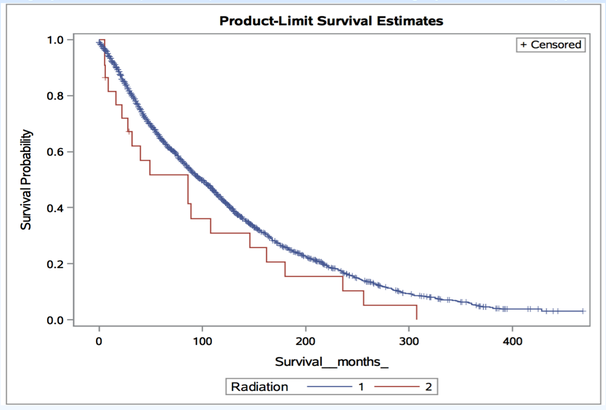

Figure 2: Kaplan-Meier plot of cause-specific survival for patients with localized disease stratified by adjuvant radiotherapy use. Blue line represents patients who only underwent surgery, red line represents patients who underwent surgery and radiotherapy

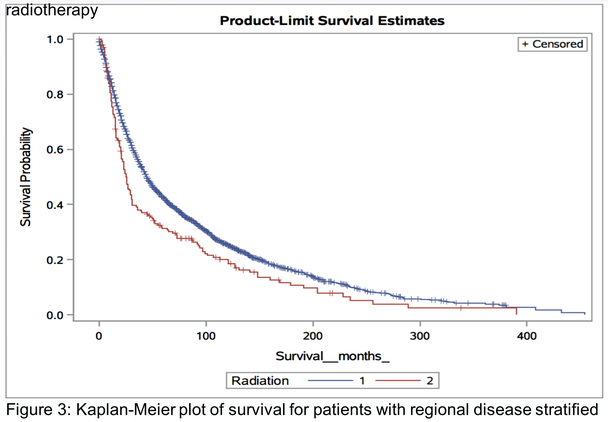

Figure 3: Kaplan-Meier plot of survival for patients with regional disease stratified by adjuvant radiotherapy use. Blue line represents patients who only underwent surgery, red line represents patients who underwent surgery and radiotherapy

	Overall Survival			Cause-Specific Survival		
	Hazard Ratio	95% Hazard Ratio Confidence Limits		Hazard Ratio	95% Hazard Ratio Confidence Limits	
Radiation: Yes	1.433	1.233	1.665	2.159	1.634	2.852
Gender: Female	0.877	0.823	0.935	1.200	1.044	1.378
Stage: Regional	1.529	1.436	1.627	2.020	1.746	2.338
Primary site: Renal Pelvis	0.977	0.918	1.040	1.202	1.041	1.388

Table 2: Multivariate analysis comparison of overall and cause-specific survival by prognostic factor

Conclusion

This is a large population-based study to look at the role of adjuvant RT in patients with ureteral carcinoma. In this nonrandomized population, adjuvant RT was used in a minority of patients and showed a detriment in both OS and CSS. After stratifying based on stage, adjuvant RT was still associated with decreased OS and CSS in both localized and regional disease. However, it is likely that post-op RT was used in cases where there were pathologic risk features showing high risks for recurrence, such as R1/R2 resections, larger tumors, lymph node positive disease, etc. Further elucidation of risk features and the role of RT in this rare disease warrant more investigation.

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