Impact of Primary Tumor Location on Survival from the European Organization for the Research and Treatment of Cancer Advanced Urothelial Cancer Studies

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Purpose: The prognostic relevance of primary location of urothelial carcinoma on survival has been poorly investigated.

Materials and Methods: We used prospectively collected data from 3 European Organization for the Research and Treatment of Cancer advanced urothelial carcinoma studies, including 30924 (methotrexate, vinblastine, doxorubicin and cisplatin vs high dose methotrexate, vinblastine, doxorubicin and cisplatin), 30986 (methotrexate, carboplatin and vinblastine vs gemcitabine and cisplatin in patients who were not candidates for cisplatin) and 30987 (gemcitabine and cisplatin-paclitaxel vs gemcitabine and cisplatin in candidates for cisplatin). Patients were grouped by primary tumor location as those with bladder cancer or upper tract urothelial carcinoma. Progression-free and overall survival was tested by tumor location using Cox proportional hazard regression stratified by study and treatment using 2-sided $\alpha = 0.05$.

Results: Of the 1,039 patients 878 (85.3%) and 161 (14.7%) had bladder cancer and upper tract urothelial carcinoma, respectively. Patients with bladder cancer had better performance status and were more likely to be male ($p = 0.008$ and <0.074, respectively). By a median followup of 4.8 years (IQR 4.0–6.7) 733 patients had died and 925 had experienced disease progression. Overall and progression-free survival did not differ significantly between bladder and upper tract urothelial carcinoma cases ($p = 0.3$ and 0.7, respectively), even after adjusting for the effects of Bajorin risk group by each tumor location. When upper tract urothelial carcinoma was considered separately, patients with primary ureteral tumors had better overall survival than patients with primary bladder cancer (OR = 0.74, $p = 0.047$). However, this association did not remain significant after adjusting for Bajorin risk group ($p = 0.05$).

Abbreviations and Acronyms

BCa = bladder cancer

EORTC = European Organization for the Research and Treatment of Cancer

GC = gemcitabine and cisplatin

HD = high dose

MCAVI = methotrexate, carboplatin and vinblastine

M-VAC = methotrexate, vinblastine, doxorubicin and cisplatin

OS = overall survival

PFS = progression-free survival

RNU = radical nephroureterectomy

UC = urothelial carcinoma

UTUC = upper tract urothelial carcinoma

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Conclusions: Primary tumor location had no impact on progression-free or overall survival in patients with locally advanced or metastatic urothelial carcinoma treated with platinum based combination chemotherapy.

Key Words: urinary bladder neoplasms; urothelium; urologic neoplasms; drug therapy, combination; mortality

Upper and lower tract UC share many similarities, which has led physicians to extrapolate treatment decisions for the relatively rare entity UTUC from the more prevalent BCa. However, differences in biological, molecular and anatomical characteristics support that these entities are different.[1] This has led to the development of independent, distinct guidelines for UTUC and BCa.[2–4] Comparison of next generation sequencing of UTUC with BCa identified similar mutations in the 2 cancer types but at different frequencies with 4 unique molecular and clinical subtypes indicating a potential need for unique management strategies.[5,6]

At this time there is limited evidence of the survival impact of these differences on oncologic outcomes such as sensitivity to standard therapy. A few retrospective studies have investigated the impact of tumor location on survival outcomes with different conclusions.[7–10] A specific question that remains unstudied is the differential impact of UC tumor location on the response to systematic therapies. As most UC studies included approximately 10% to 20% of UTUC cases, some data seemed to suggest that primary UTUC was less responsive to platinum based chemotherapy than primary BCa.

In the current study we combined data from the 3 EORTC phase III trials 30924,[11] 30986[12] and 30987.[13] These trials investigated different platinum based combination chemotherapy approaches in patients with advanced/metastatic UC who had primary BCa or UTUC. We hypothesized that patients with UTUC would be less responsive and have higher progression and mortality than patients with BCa. Our aim was to assess the impact of primary tumor location on survival outcomes in patients with primary metastatic or unresectable UC.

MATERIALS AND METHODS

Patient Characteristics

Patients included in study were treated in 3 EORTC phase III studies, including 30924,[11] 30986[12] and 30987.[13] EORTC 30924 included patients diagnosed with measurable distant metastases or unresectable UC of the urinary tract with no prior systematic cytotoxic or biological treatment and a WHO performance status of 0 or 1.[11] Patients were randomized 1:1 between HD M-VAC administered every 2 weeks with granulocyte colony-stimulating factor vs classic M-VAC.

EORTC 30986 included patients diagnosed with histologically proven UC with unresected positive lymph nodes, distant metastases or unresectable primary UC.[12] No previous systemic treatment had been administered. All patients had to be ineligible for platin based chemotherapy, defined as WHO performance status 2 and/or impaired renal function. Patients were randomly assigned to gemcitabine/carboplatin or MCAVI.

EORTC study 30987 included patients diagnosed with histologically confirmed, stage IV, locally advanced UC (T4b, any N or any T, N2-3) or metastatic UC of the urinary tract.[13] Patient performance status was WHO 0 or 1. Patients were randomly assigned to paclitaxel, cisplatin and gemcitabine or GC.

Ineligible patients and patients with a tumor at sites other than the upper urinary tract or bladder (ie urethral tumors) were excluded from study, leaving 1,039 of the original 1,127 (92.2%) in the studies for analysis.

End Points and Outcome Measures

Two end points were considered as defined in the original study protocols, including OS and PFS. These end points were calculated from the date of randomization to the date of death or the last visit. Events were death of any cause or the first event (death or progression). Primary tumor location was defined as UTUC, stratified by location as pyelocaliceal, ureter or BCa.

Statistical Analyses

We statistically compared OS and PFS by primary tumor location using Cox regression analysis stratified for the effect of treatment arm in each trial (6 strata) using a 2-sided significance level of 0.05. Heterogeneity of effect was tested by a Cox model with treatment arm in the trial and its interaction with tumor location as a covariate. Analyses included ureteral and pyelocalyceal UTUC combined and separate. The HR with the 95% CI is shown in a forest plot. Survival curves adjusted for the effects of Bajorin risk groups[14] obtained from the Cox model are also presented as sensitivity analyses, in addition to unadjusted Kaplan-Meier estimates.

RESULTS

Description of Included Patients

Figure 1 shows the patient selection process of the EORTC 30924, 30986 and 30987 studies.[11–13] Of the 1,127 patients included in all 3 trials 88 diagnosed with a primary urethral tumor were excluded from analysis. This left 878 patients (84.5%) with BCa, 61 (5.9%) with ureteral UTUC and 100 (9.6%) with pyelocaliceal UTUC. Table 1 lists patient characteristics stratified by primary tumor location. No significant difference was noted in Bajorin risk