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Circulating and urine tumor DNA dynamics predict minimal residual disease and guide adjuvant therapy in locally advanced upper tract urothelial carcinoma (CURATE-UTUC): A multicenter prospective longitudinal cohort study

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Background

Locally advanced upper tract urothelial carcinoma (UTUC; ≥pT2/N+) has high recurrence rates despite adjuvant therapy. CURATE-UTUC evaluated circulating/urinary tumor DNA (ctDNA/utDNA) dynamics to predict minimal residual disease (MRD) and optimize adjuvant management.

Methods

This multicenter prospective cohort enrolled 78 patients (2022-2024) with pT2-4/N+ non-metastatic UTUC post-nephroureterectomy, initiating adjuvant therapy within 3 months. Serial plasma/urine samples were collected preoperatively (T0), post-op month 1 (T1), post-cycle 2 therapy (T2), end-of-treatment (T3), and quarterly thereafter (T4-T6). Tumor-informed MRD assays used surgical specimen whole-exome sequencing. Primary endpoint was radiologic/cystoscopic recurrence. Analyses included Kaplan-Meier and Cox regression.

Results

At median 15-month follow-up (95%CI 11.7–18.3), 43.6% (34/78) recurred. Liquid biopsy detected relapse with 94.1% sensitivity (32/34), identifying MRD 106 days earlier than clinical recurrence (median). T1 ctDNA+ predicted extravesical recurrence (HR 8.6, 95%CI 3.2–22.9; P<0.001), while utDNA+ signaled intravesical relapse (HR 3.9, 1.1–14.8; P=0.041). By T2, ctDNA+ patients had 40.9-fold higher extravesical recurrence risk (HR 40.9, 9.5–176.3; P<0.001), and utDNA+ predicted intravesical recurrence (HR 17.3, 3.6–83.4; P<0.001). Multivariable analysis confirmed T1 biomarker+ (HR 3.2, P=0.034), T2 ctDNA+ (HR 28.5, P<0.001), and nodal involvement (HR 3.3, P=0.013) as independent predictors of systemic relapse. T2 utDNA+ independently predicted intravesical recurrence (HR 17.3, P<0.001). Biomarker performance was consistent across adjuvant modalities (chemotherapy vs. immunotherapy).

Conclusions

Longitudinal ctDNA/utDNA monitoring enables early recurrence detection and risk stratification in locally advanced UTUC, identifying MRD >3 months before clinical progression. Dual-liquid biopsy may guide adjuvant therapy optimization, warranting validation in interventional trials.

Clinical trial identification

NCT05595408.

Legal entity responsible for the study

The authors.

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Disclosure

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