Novel Use of ctDNA to Identify Locally Advanced and Metastatic Upper Tract Urothelial Carcinoma

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Upper tract urothelial carcinoma (UTUC) is an aggressive cancer for which use of neoadjuvant chemotherapy (NAC) is limited by suboptimal clinical staging prior to nephroureterectomy. Detection of circulating tumor DNA (ctDNA) has been associated with locally advanced and nodally metastatic urothelial carcinoma of the bladder and may help identify UTUC patients who would benefit from NAC.

Here we examine the feasibility and utility of plasma ctDNA detection in the diagnosis of high-risk and non-organ-confined UTUC.

Introduction and Background

Patients with high-grade cTa-T2 UTUC without radiographic evidence of metastatic disease undergoing up-front radical nephroureterectomy (RNU) were prospectively accrued.

Blood was collected preoperatively on the day of surgery, and plasma and buffy coat were processed for extraction of cell-free DNA. FFPE samples from RNU were used for tissue genomic DNA extraction. Next-generation sequencing (NGS) was used for variant profiling.

Detection of cancer variants with a mutation allele frequency (MAF) ≥ 0.25% and hotspot variants with a MAF down to 0.1% were reported for plasma samples targeted by a NGS panel. Variants with MAF ≥ 5% and hotspot variants with a MAF down to 2% were reported for FFPE samples.

NGS successfully detected cell-free DNA in all 15 accrued UTUC patients.

- Urothelial tumor tissue alterations: TERT promoter (62%), TP53 (38%), FGFR3 (31%), ERBB2 (25%), ARID1A (19%), and PIK3CA (19%).

- Plasma ctDNA alterations: TERT promoter (47%), TP53 (30%), ARID1A (20%), ERBB2 (20%), FGFR3 (20%), and PIK3CA (17%).

Results

Five patients (33%) had detectable plasma ctDNA alterations concordant with tumor-based genotypes using the targeted NGS panel.

- All patients with detectable preoperative ctDNA had advanced staging (≥pT2 or ≥pN1) and lymphovascular invasion → sensitivity 71.4%
- No patients with pTis/a/1 and pN0 had detectable concordant ctDNA mutations → specificity 100%

Discussion

Detection of circulating tumor DNA (ctDNA) using targeted next-generation sequencing has the potential to improve clinical staging in patients with UTUC.

Conclusion

Prospective ctDNA analysis using a targeted NGS panel is a feasible nonsurgical approach to predict high-risk UTUC and has the potential to identify patients that may benefit from NAC.