Novel Use of ctDNA to Identify Muscle-invasive and Non-organ-confined Upper Tract Urothelial Carcinoma

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Abstract #4587

Introduction and Background

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 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 invasive and non-organ-confined UTUC.

Methods

Patients with high-grade cTa-T3 UTUC without radiographic evidence of metastatic disease undergoing up-front radical nephroureterectomy (RNU) were prospectively accrued for pre- and post-operative plasma collection.

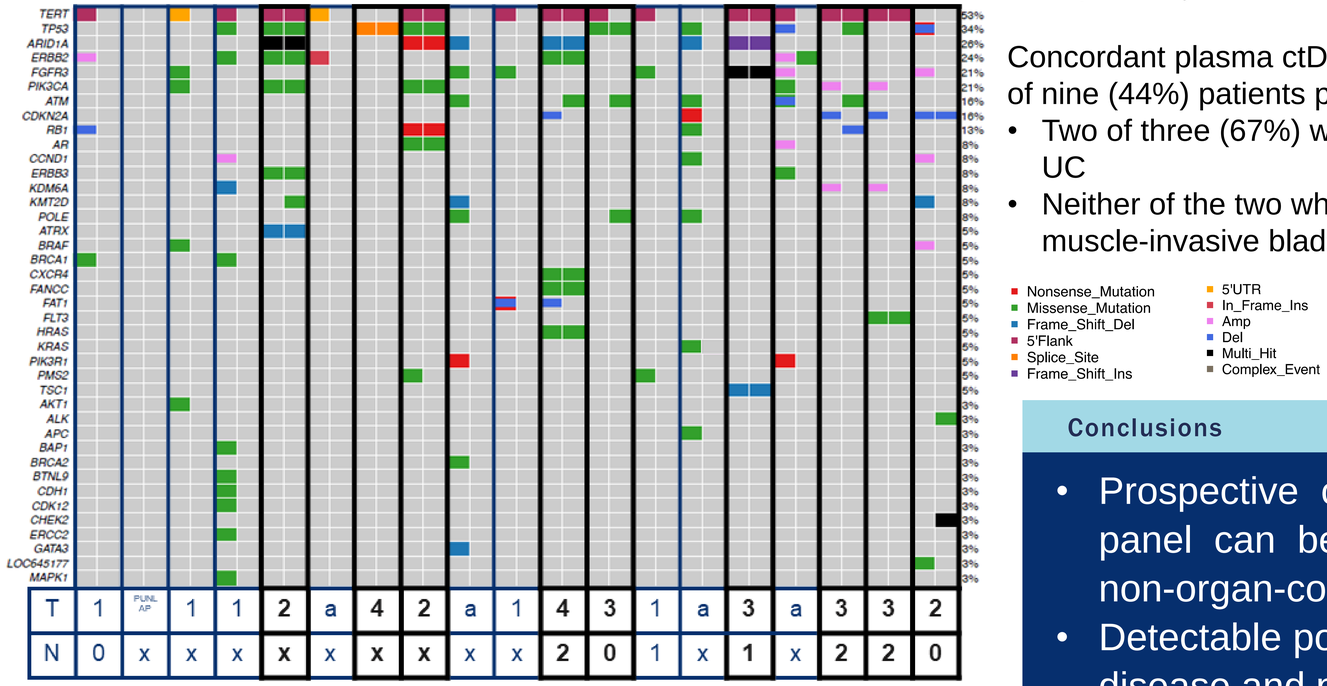
Blood was collected preoperatively on the day of surgery, and plasma and buffy coat were processed for extraction of cell-free DNA and genomic DNA, respectively. FFPE samples from RNU were used for tissue genomic DNA extraction. Targeted next-generation sequencing (NGS) was used for variant profiling via PredicineCARE™, a pancancer panel of 152 known actionable genetic alterations.

ctDNA positivity was defined as the presence of plasma cell-free DNA variants concordant with tissue-based variants.

Results

NGS successfully detected cell-free DNA in all 19 UTUC patients.

- 468 alterations were detected in 103 genes.
  - 74% SNVs, 25% CNVs, and 1 FGFR3-TACC3 fusion
- Urothelial tumor tissue alterations: TERT promoter (74%), TP53 (58%), FGFR3 (53%), myc amplification (53%), and ATM (42%)
- Plasma ctDNA alterations: TERT promoter (42%), TP53 (42%), PIK3CA (37%), ATM (32%) and CD274 (26%)



Nine patients (47%) had detectable plasma ctDNA alterations concordant with tumor-specific variants using the targeted NGS panel.

- All patients with detectable preoperative ctDNA had advanced staging (≥pT2 or ≥pN1) and lymphovascular invasion on final pathology
- → sensitivity 90%

- No patients with pTis/a/1 and pN0 had detectable concordant ctDNA mutations
→ specificity 100%

Concordant plasma ctDNA was detected in four of nine (44%) patients postoperatively.

- Two of three (67%) who developed metastatic UC
- Neither of the two who developed non-muscle-invasive bladder cancer recurrences

Table 1. Baseline clinicopathologic information and surgical pathology (N=19)

Age, mean (range)	69.4 (42-87)
Caucasian	19 (100%)
Male	13 (68%)
Location	
Renal pelvis	6 (32%)
Ureter	6 (32%)
Both	7 (37%)
Laterality	
Left	13 (68%)
Right	6 (32%)
Pathologic Grading	
Low Grade	4 (21%)
High Grade	15 (79%)
Multifocality	
Unifocal	11 (58%)
Multifocal	8 (42%)
T Stage	
PUNLAP, Ta, T1, Tis	10 (53%)
T2	3 (16%)
>T2	6 (32%)
N Stage	
N0 or Nx	14 (74%)
N+	5 (26%)
Positive margins	3 (16%)

Conclusions

- Prospective ctDNA analysis using a targeted NGS panel can be used to predict muscle-invasive and non-organ-confined UTUC preoperatively.
- Detectable postoperative ctDNA may indicate residual disease and predate clinical recurrence.