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Monitoring Treatment Response and Metastatic Relapse in Advanced Bladder Cancer by Liquid Biopsy Analysis

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Abstract

Of the patients undergoing radical cystectomy, 20–80% experience relapse. Minimally invasive methods for early detection of metastatic relapse after cystectomy and for monitoring ongoing therapy are urgently needed to improve individualised follow-up and treatment. Therefore, we evaluated the use of circulating tumour DNA (ctDNA) in plasma and urine to detect metastatic relapse after cystectomy and measure treatment efficacy. We exome sequenced tumour and germline DNA from patients with muscle-invasive bladder cancer and monitored ctDNA in 370 liquid biopsies throughout the disease courses by 84 personalised digital droplet polymerase chain reaction assays targeting 61 genes. Patients were prospectively recruited between 2013 and 2017. Patients with metastatic relapse had significantly higher ctDNA levels compared with disease-free patients ($p < 0.001$). The median positive lead time between ctDNA detection in plasma and diagnosis of relapse was 101 d after cystectomy (range 0–932 d). Early detection of metastatic relapse and treatment response using liquid biopsies represents a novel, highly sensitive tool for monitoring patients, supporting clinicians, and guiding treatment decisions.

Patient summary: Measurement of tumour-specific mutations in plasma and urine may be a powerful tool to monitor response during treatment and identify early signs of metastatic disease.

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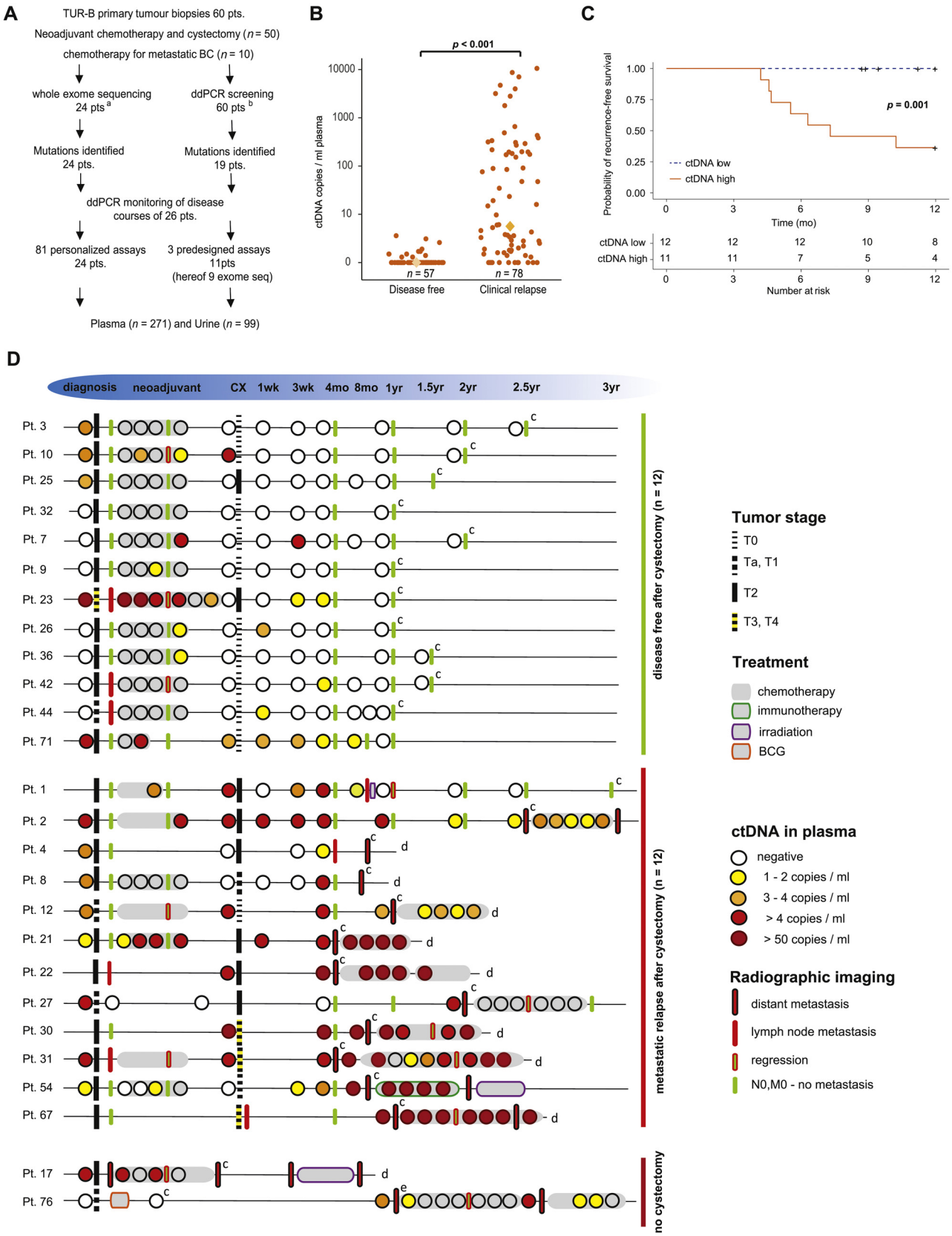

Fig. 1 – Patient overview and results of liquid biopsy analyses. (A) Patient enrolment and analyses performed. Predesigned assays were used to screen 60 tumour biopsies for hotspot mutations in *PIK3CA* and *FGFR3*. In total, 19 patients had at least one hotspot mutation in *PIK3CA* and *FGFR3*. Tumour and germline DNA from 24 selected patients was exome sequenced (nine with a hotspot mutation and 15 without), and 81 personalised assays against cancer driver mutations were designed. The cfDNA in longitudinally collected plasma and urine samples from 26 patients (24 exome sequenced and two included due to positive screening without sequencing) was analysed by ddPCR. (B) Levels of ctDNA in disease-free patients and in patients with