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Investigation of circulating free DNA as Independent Indicator of impending Recurrence in former Breast Cancer and Prognostic Marker in Metastatic Breast Cancer

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Nowadays, the investigation of circulating molecular markers in peripheral blood ("liquid biopsies") is of great importance because of the advantages like minimal invasive, reliable and reproducible. The cell free DNA (cfDNA) variables of cfDNA integrity (cfDI) and cfDNA concentration have displayed to be putative markers in cancer diagnosis and prognosis.

In PBC study, we here identified the potential of cfDNA variables, as diagnostic marker for recurrent BC patients before clinical confirmation. We have identified that recurrent patients had a significantly lower cfDI (median ALU cfDI = 0.52, median LINE1 cfDI = 0.39) compared to the group of non-recurrent patients (median ALU cfDI =0.62, median LINE1 cfDI = 0.54) ($P<0.0001$ for each). cfDI can distinguish patients with recurrence from non-recurrent patients with an AUC of 0.71 for ALU and 0.70 for LINE1. When cfDI of ALU and LINE1 were combined, the AUC reached 0.73. ALU cfDI had a hazard ratio of 3.69 (95% CI: 1.23 – 11.02). LINE1 cfDI had a similar hazard ratio of 3.74 (95% CI: 1.24 – 11.27). It confirmed that decreased cfDI was associated with an increased risk of breast cancer recurrence. In contrast, there were no cfDNA concentration differences of both ALU and LINE1 between two patient groups (ALU: P = 0.16; LINE1: P = 0.17)

In metastatic breast cancer (MBC) study, we compared cfDNA concentration and cfDI at baseline and after one cycle of therapy in metastatic breast patients. Generally, we observed a significantly increased cfDI (P = 1.21E-7 for ALU and P = 1.87E-3 for LINE1) and decreased cfDNA concentration (P = 1.17E-3 for ALU and P = 1.60E-2 for LINE1) in both repetitive DNA elements after one cycle of therapy. The overall survival was different based on the cfDI and cfDNA concentration at MBC patients at baseline and after one cycle of therapy. Hazard ratios (HR) for ALU and LINE1 cfDNA concentration were 1.59 (95% CI: 1.31-1.92) and 1.30 (95% CI: 1.17-1.45) at MBC1C patients which indicated a one more fold higher incidence of high cfDNA concentration patients compared to low cfDNA concentration patients. As for cfDI, the HR was 0.59 (95% CI: 0.42-0.84) and 0.51 (95% CI: 0.36-0.74) for ALU and LINE1 which indicated high cfDI was a protective factor of patients' survival.

When four cfDNA variables combined as a single marker, it can achieve a hazard ratio of 2.91 (95% CI: 1.85-4.58) for overall survival (OS) and 1.70 (95% CI: 1.21-2.39) for progress free survival (PFS) in MBCBL patients and 2.53 (95% CI: 1.77-3.62) for OS and 1.81 (95% CI: 1.25-2.63) for PFS in MBC1C patients. In comparison to circulating tumor cells (CTC) status determination, the integrate prediction error score of the cfDNA marker combination is lower in both OS and PFS. cfDNA marker combination were also shown to improve the prognostic power of the CTC status.

Taken together, these preliminary results indicated that cell-free DNA variables can not only be used as a potential diagnostic marker for primary breast cancer recurrence, but also a potential prognostic marker in MBC patients at baseline and during the systematic therapy.