

RNA-Based Circulating Tumor Cell Signatures for Localized Prostate Cancer

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Background: Prostate biopsies are an essential part of risk stratification for localized prostate cancer, but are associated with undergrading and understaging. We recently showed that a digital RNA expression signature of circulating tumor cells (CTCs) predicts subclinical dissemination of prostate cancer identified at the time of radical prostatectomy. Thus, molecular CTC signatures may improve the accuracy of risk stratification may predict response to radiation therapy. Here, we evaluated a CTC molecular signature in prostate cancer patients receiving external beam radiation therapy (EBRT) in the context of a prospective clinical trial and assessed for correlations with baseline clinicopathologic features.

Methods: Patients enrolled in a prospective randomized clinical trial comparing proton beam therapy (PBT) and intensity modulated radiation therapy (IMRT) were consented to an optional companion CTC biomarker study. Eligible patients had a diagnosis of low or intermediate risk prostate cancer and were planned for treatment with EBRT (either PBT or IMRT) without concurrent hormonal therapy. 65 patients donated 20 mL blood prior to initiation of EBRT, and a subset of patients donated blood during the last week of EBRT and 3 months after completion of EBRT. CTCs were isolated using the CTC-iChip negative selection microfluidic device, and quantitation of CTC RNA expression was performed for a panel of 8 prostate-lineage genes using a highly sensitive multiplex droplet digital PCR assay. Using previously trained algorithms for digital RNA CTC signatures in localized prostate cancer, a CTC-L score was calculated for each time point. Pre-treatment CTC-L scores were compared to baseline clinicopathologic characteristics. Longitudinal trends in CTC-L scores were assessed in a subset of patients.

Results: Molecular CTC analyses were performed prospectively in 65 prostate cancer patients enrolled in a randomized clinical trial comparing PBT and IMRT. 28 patients (43%) had low risk and 37 (57%) had intermediate risk disease. Baseline CTC-L scores were not significantly correlated with clinical T-stage or Gleason score, but patients with a pre-treatment PSA ≥ 10 ng/mL had a significantly higher CTC-L score compared to those with a PSA < 10 ng/mL ($P=0.01$). Among intermediate risk patients, 3/37 (8%) had a CTC-L score above a threshold previously associated with increased risk for microscopic dissemination beyond the prostate; 0/28 low risk patients scored above this threshold. Out of 31 patients with longitudinal data available, 61% exhibited a decreased or stable CTC-L score upon completion of EBRT, while 39% exhibited an increase in CTC-L score at the end of therapy.

Conclusion: Analysis of a digital RNA CTC signature in the blood may improve the accuracy of risk stratification in localized prostate cancer. Long-term follow up is necessary to determine whether molecular CTC signatures correlate with clinical outcomes after radiation therapy.

Conflict of Interest Statement: MGH has applied for patent protection for the CTC-iChip

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