Potential clinical utility of circulating tumor DNA detected by digital PCR in a nationwide Danish cohort of high-risk colorectal cancer patients

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Background & objectives

Increasingly, circulating tumor DNA (ctDNA) is proposed as a tool for minimal residual disease (MRD) assessment, with the potential to guide postoperative treatment decisions. Low ctDNA levels immediately after surgery necessitate extremely sensitive detection methods. For potential clinical implementation, detection methods should feature short turnaround times (TATs) and low analysis costs. Compared to sequencing-based detection methods, digital PCR is low-cost, and features TATs of less than a day. Consequently, digital PCR is a good candidate for clinical implementation, though few large-scale studies have been published using this method. We aimed to assess the potential clinical utility of monitoring MRD using a tumor-informed digital PCR strategy for ctDNA detection in a large colorectal cancer cohort.

Methods

Stage II-III colorectal cancer patients (n=702) treated with curative intent were recruited from Danish surgical centers. Whole exome sequencing was conducted on matched tumor and buffy coat from all patients. After thorough clonality assessment, a mutational target was chosen for digital PCR analysis. Plasma samples (8mL) collected within 60 days after surgery, were investigated for ctDNA using digital PCR. Additionally, a subset of patients (n=229) had serial samples collected every three months analyzed for ctDNA.

Results

Postoperative ctDNA detection was highly correlated to recurrence (HR=10.4, 95%CI 7.1-15.4, P<0.001). The median time to recurrence was significantly shorter for postoperatively ctDNA positive patients (11 months, interquartile range (IQR) 5-12 months) compared to ctDNA negative patients (14 months, IQR 12-26 months, P<0.001), indicating a higher disease burden postoperatively in ctDNA positive patients. In a subset of patients with serial samples (n=214), ctDNA was similarly prognostic of recurrence (HR=39.6, 95%CI 20.8-75.5, P<0.001) and the ctDNA growth rates were correlated to survival after recurrence (HR=2.57, 95%CI 1.51-4.38, P=0.001).

Conclusion

These results from one of the largest ctDNA detection cohorts of stage II-III CRC patients demonstrate that our personalized digital PCR approach effectively detects MRD immediately after surgery. Additionally, our approach shows promise for serial ctDNA detection for recurrence surveillance applications. With digital PCR being a widespread and cost-effective method with short TATs, clinical implementation of ctDNA analysis may be more forthright using this method over cost-intensive sequencing-based methods.