Tumor-agnostic detection of circulating tumor dna in patients with advanced pancreatic cancer using targeted dna methylation sequencing and cell-free dna fragmentomics

Abstract Submitter: Oddmund Nordgard, Norway*

Co-Authors: Morten Lapin, Kjersti Tjensvoll, Karin Hestnes Edland, Satu Oltedal, Herish Garresori, Bjørnar Gilje, Saga Ekedal, Trygve Eftestøl, Jan-Terje Kvaløy, Filip Janku

*Stavanger University Hospital

Abstract

BACKGROUND:

Circulating tumor DNA (ctDNA) can be detected in the circulation of patients with many types of solid cancers, including pancreatic cancer. The most established methods for ctDNA detection are based on tumor-specific genetic alterations, whereas newer methods based on epigenetic features and fragmentomics have emerged as novel targets.

OBJECTIVE: In this study, we investigated whether DNA methylation and cell-free DNA (cfDNA) fragmentation patterns could be leveraged to improve ctDNA detection in patients with advanced pancreatic cancer.

METHODS: ctDNA detection was performed in a cohort (n=33) of patients with advanced pancreatic cancer using DNA methylation and cfDNA fragment features (fragment lengths and 4-mer 5’ end motifs). Machine learning models estimating ctDNA levels were built for each individual detection method and a combination of the methods. The detection of ctDNA in patient samples, correlation with previously reported mutation-based detection, and ability to predict clinical outcomes using the machine learning models were assessed.

RESULTS:

All machine learning models estimated ctDNA levels in the plasma of patients which significantly differed from those of healthy individuals (P<0.001). Using the highest estimated levels in plasma samples from healthy volunteers as cutoffs for ctDNA positivity, ctDNA was detected in 26 (79%), 22 (67%), 22 (67%), and 18 (55%) of the 33 patients using the methylation, fragment length, end motifs and combined models, respectively. All models strongly associated with known mutation-based ctDNA levels, yet some patient samples that were negative for ctDNA by mutation analysis had ctDNA detected using the tumor-agnostic approaches. Univariable Cox regression demonstrated that ctDNA estimates by all models were associated with increased hazard ratios (HR, all P<0.001) for both progression-free survival (PFS) and overall survival (OS). Multivariable Cox regression analysis demonstrated that estimated ctDNA levels were also an independent predictor of both PFS (HR = 1.9, P<0.001) and OS (HR = 2.7, P<0.001).

CONCLUSION:

Methylation and fragmentomics-based machine learning models could be used to estimate ctDNA levels in patient samples, as these highly correlate with traditional mutation-based ctDNA detection. High ctDNA levels estimated using these models were associated with reduced PFS and OS in patients with advanced pancreatic cancer.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.