Bespoke circulating tumor DNA assay for the detection of minimal residual disease in esophageal adenocarcinoma patients

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Background

- Over half of Esophageal Adenocarcinoma (EAC) patients that are treated with curative intent relapse.[1]
- In clinical practice, risk stratification is limited to TNM staging,[2] which highlights the need for additional patient stratification methods for EAC.
- Circulating tumor DNA (ctDNA) following surgical resection is prognostic across different tumor types.[3] However, the sensitivity and specificity of tumor-naive ctDNA panels are limited in the minimal residual disease (MRD) setting.
- EAC is known to be a low shedding tumor type,[4] thus, a personalized, tumor-informed approach for ctDNA analysis is ideal for MRD detection after treatment and for providing prognostic value in EAC patients.

Methods

- Using the prospectively collected multi-center UK OCCAMS dataset, we identified patients (n = 20) with pre- and post-surgical plasma samples (n = 52).
- Mutational profiles derived from tumor tissue were used to design assays targeting patient-specific somatic variants (Signatera™ bespoke multiplex-PCR NGS assay) **(Figure 1).**
- The personalized assays were used to determine the presence of ctDNA in the plasma samples of EAC patients.

Figure 1. Signatera™ Molecular Protocol

Sequence tumor tissue to identify unique signature of tumor mutations

Custom design and manufacture personalized mPCR assay for each patient targeting clonal mutations found in tumor

Use personalized assay to test patient's blood for presence of circulating tumor DNA (ctDNA)

Patient specific, bespoke multiplex-PCR NGS assays detect ctDNA with high sensitivity and specificity and can be used for recurrence monitoring in patients with esophageal adenocarcinoma

Figure 2. Overview of patient ctDNA and clinical profiles (n = 20)

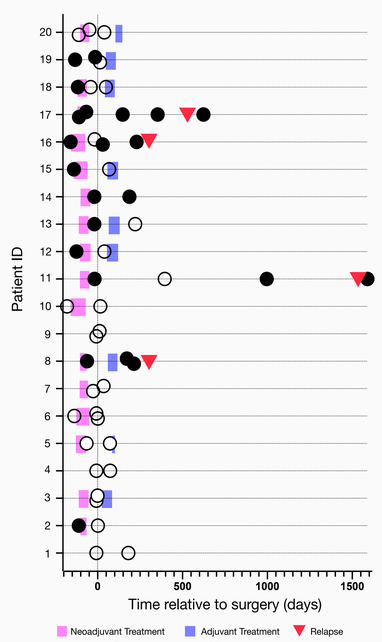

Figure 2: Post-operative ctDNA analysis detected clinical relapse in 4 patients with a median lead time of 335 days with a sensitivity of 100% and a specificity of 94%. Minimal residual disease post-surgery was detected down to a mean variant allele frequency of 0.001%.

Table 1. Demographics and Clinical Data of the Patient Cohort (n = 20)

Gender	Male: 17; Female: 3	Age (years)	Median 62.8 (range: 48.9 - 80.8)
T Stage	T1: 3; T2: 5; T3: 12	Procedure	EMR: 3; Surgery: 17
N Stage	N0: 9; N1: 6; N2: 2; N3: 1; Nx: 2	Mandard Score	TRG1: 4; TRG2: 0; TRG3: 4; TRG4: 7; TRG5: 2; NA: 3
Neoadjuvant Chemotherapy	Yes: 17, No: 3	Siewert Classification	Type 1:9; Type 2: 5; Type 3: 3; NA: 3

Table 1: The cohort consisted of 20 patients with a median age of 62.8 (48.9 – 80.8) years, of which 85% (17/20) were male and were T1-T3 at diagnosis. Of 20 patients, 17 (85%) were treated with neoadjuvant chemo-therapy and 3 (15%) also received radiotherapy.

Figure 3. Serial ctDNA profiles of patients with clinical relapse (n = 4)

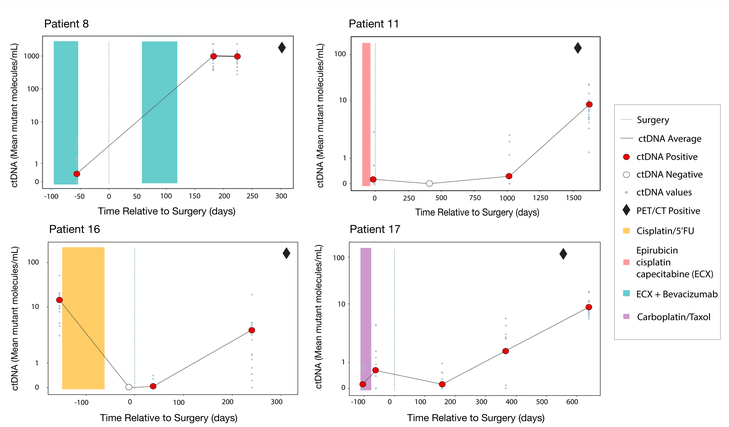

Figure 3: Representation of the patients' disease course, applied treatments and serial ctDNA analysis.

Figure 4. Comparison of percent ctDNA positive patients at pre-surgical timepoint with A) Stage and B) Relapse

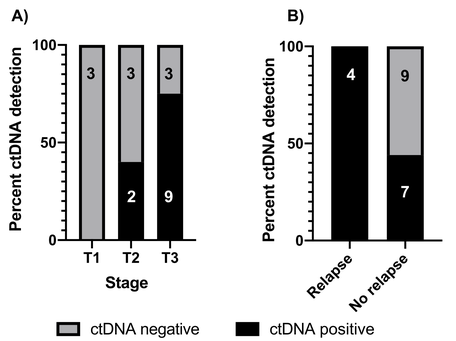

Figure 4: A) Pre-surgical ctDNA detection was observed to be higher at stage T3 compared to stage T2 (p <0.0001). **B)** All patients (100%) that had ctDNA detected pre-surgically experienced relapse (p <0.0001).

References

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