Circulating tumor DNA (ctDNA) dynamics in liver-limited metastatic colorectal cancer (mCRC) patients resected after first-line systemic treatment

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Abstract Presentation # 3544

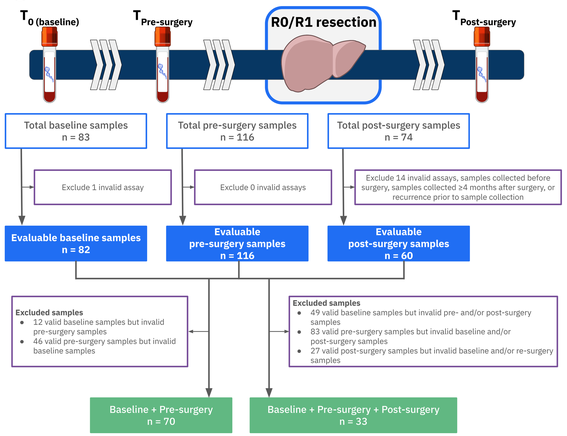
INTRODUCTION

Liver-limited disease (LLD) occurs in 20-30% of metastatic colorectal cancer (mCRC) patients. Although 20-30% of patients who undergo resection can achieve a long-term overall survival benefit from liver surgery, most patients relapse during the first two years after hepatectomy. ctDNA is a promising tool in detecting the presence of minimal residual disease (MRD) after resection of colorectal liver metastases and a reliable prognostic tool for recurrence. ctDNA and its dynamics may also serve as a prognostic tool in patients candidate to liver resection following upfront chemotherapy.

METHODS

mCRC patients (N=116) with initially unresectable LLD and R0/R1 resected after upfront chemotherapy were selected from three Italian academic centers. Blood samples were collected prospectively at baseline (T_0), pre-surgery (T_{PrS}) and post-surgery (T_{PoS}). T_0 samples were evaluable for 82 patients, T_{PrS} for 116 and T_{PoS} for 60. T_{PoS} samples were collected between 0-4 months post-surgery. Biobanked plasma samples were analyzed with the Tempus xM MRD assay (xM), a tumor-naïve ctDNA MRD assay that integrates methylation and genomic variant classifiers to deliver a binary MRD call blinded to clinical outcomes. Relapse-free survival (RFS) is assessed, defined as the time from the index date (date of resection of liver metastases for pre-surgery MRD status or date of T_{PoS} sample collection for post-surgery MRD status) to the date of recurrence or death from any cause within 24 months. A patient is classified as censored if they do not have a recurrence, or are still alive after 24 months, or lost to follow-up. Reported p-values were obtained using the Wald test, applying a one-sided significance level of 5%.

Figure 1. Workflow



Sample collection/surgery timeline and inclusion/exclusion criteria for patient cohort.

SUMMARY

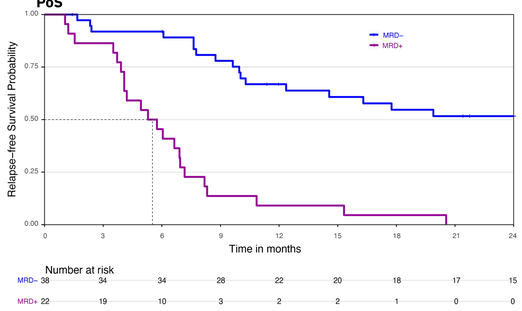
- xM demonstrates remarkable performance in predicting clinical recurrence and correlation to relapse-free survival (RFS) at T_{PoS} in LLD mCRC patients resected after upfront systemic therapy
- Longitudinal methylation dynamics, measured by PTFM (Predicted Tumor Fragments per Million), were predictive of longer RFS for patients with PTFM at the 25th percentile compared to those with PTFM at the 75th percentile, even after adjusting for ACT status (HR=1.82, p<0.001)

RESULTS

Table 1. Cohort Characteristics for T_{PoS}

	Overall, n=60	MRD status at T_{PoS}	
		MRD+, n=22	MRD-, n=38
Age at enrollment			
Mean (SD)	58.22 (11.09)	61.64 (11.19)	56.24 (10.69)
Median	59	59.5	57
IQR	53.00 - 65.25	55.00 - 72.25	50.25 - 64.50
Min / Max	29 / 79	39 / 79	29 / 76
Sex			
Female	25 (41.7%)	9 (40.9%)	16 (42.1%)
Male	35 (58.3%)	13 (59.1%)	22 (57.9%)
MSI-High status			
Positive	1 (1.7%)	0 (0.0%)	1 (2.6%)
Negative	57 (95.0%)	21 (95.5%)	36 (94.7%)
RAS status			
Positive	16 (26.7%)	4 (18.2%)	12 (31.6%)
Negative	44 (73.3%)	18 (81.8%)	26 (68.4%)
BRAF mutation status			
Positive	1 (1.7%)	1 (4.5%)	0 (0.0%)
Negative	59 (98.3%)	21 (95.5%)	38 (100.0%)
Adjuvant chemotherapy			
No	24 (40.0%)	12 (54.5%)	12 (31.6%)
Yes	36 (60.0%)	10 (45.5%)	26 (68.4%)
Median follow-up (in months)	11.3	7.3	18.8

Figure 2. Association between MRD status and RFS at T_{PoS}



	MRD-, n = 38	MRD+, n = 22
Median RFS*, in months (95% CI)	NA (10.29, NA)	5.52 (3.91, 6.94)
HR[a] (95% CI), MRD+ vs MRD- (Ref.)	6.66 (3.31, 13.39)	

*Median RFS unadjusted for treatment with ACT
[a] HR after adjusting for ACT status

T_{PoS} MRD status was associated with RFS with the MRD- group experiencing longer median RFS (mRFS) than MRD+ (HR = 6.7, mRFS >24 months vs. 5.5 months, p<0.001), adjusting for ACT status. Overall n=60.

Table 2. Post-surgery (T_{PoS}) clinical performance

	Recurrent	Non-Recurrent	Total
MRD+	22	0	22
MRD-	17	21	38
Total	39	21	60
Sensitivity	56.4% (95% CI: 39.6%, 72.2%)		
Specificity	100% (95% CI: 83.9%, 100%)		
PPV	100% (95% CI: 84.6%, 100%)		
NPV	55.3% (95% CI: 38.3%, 71.4%)		

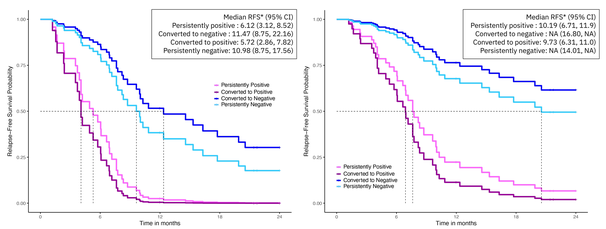
The xM assay demonstrated a clinical sensitivity of 56.4% and a clinical specificity of 100% in post-surgery patients (n=60).

Figure 3. Prognostic impact of ctDNA dynamics (MRD status change) on RFS from T_{PrS} to T_{PoS}

MRD Status Change	N	HR [b] (95% CI)	Median RFS* (95% CI)
Persistently positive	9	Reference	5.29 (3.91, 15.32)
Converted to negative	13	0.18 (-0.54, 0.9)	NA (9.63, NA)
Converted to positive	12	1.45 (0.77, 2.14)	5.90 (1.55, 8.19)
Persistently negative	20	0.26 (0.02, 0.5)	16.31 (7.63, NA)

[b]adjusting for ACT status
*Median RFS unadjusted for treatment with ACT

No ACT



ACT

Patients who were persistently positive by methylation calls (n=20) or converted to negative (n=13) from T_{PrS} to T_{PoS} experienced longer RFS (mRFS 16.3 months and >24 months respectively). Those who remained persistently positive (n=9) or converted to positive (n=12) had a mRFS of 5.3 and 5.9 months respectively. Overall n=54.

Plots show comparisons of mRFS* in patients without adjuvant chemotherapy (ACT; left) versus with ACT (right).

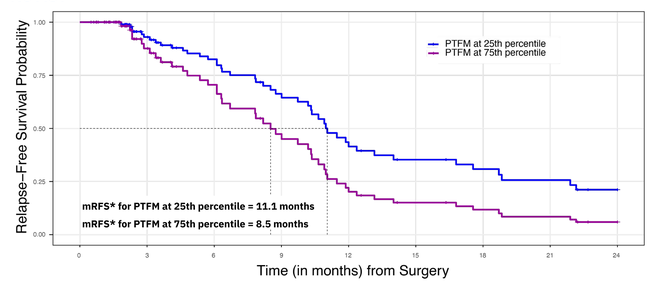
*mRFS is the median RFS unadjusted for treatment with ACT

Table 3. Summary measures of predicted tumor fragments per million (PTFM) across time points (T_0, T_{PrS}, T_{PoS})

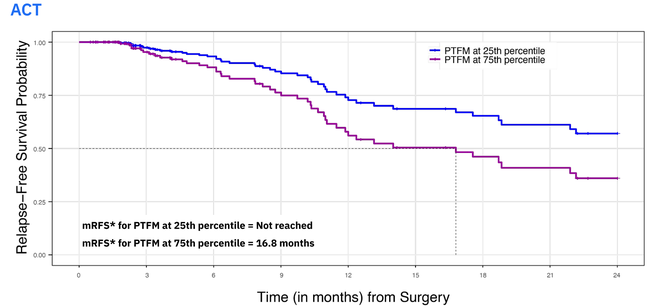
Timepoint	n	Range (min - max)	Mean	Median	Q1 / Q3
Baseline (T_0)	82	124.1 - 500078.0	138686.9	110460.0	45057.1 / 228424.8
Pre-surgery (T_{PrS})	116	27.2 - 363193.0	8265.3	258.4	140.0 / 639.2
Post-surgery (T_{PoS})	60	47.4 - 59940.6	3394.3	254.5	163.6 / 872.0

Figure 4. Impact of longitudinal PTFM measure on RFS

No ACT



ACT



RFS is assessed in a Cox model with PTFM as a time-varying covariate and ACT status as a fixed covariate. Patients without T_{PoS} samples were excluded from the analysis. After adjusting for ACT status, predicted RFS for patients with PTFM at the 25th percentile over all time was longer than predicted RFS for those with PTFM at the 75th percentile, (HR=1.82, p<0.001).

*mRFS is the median RFS unadjusted for treatment with ACT

ACKNOWLEDGMENTS

We thank Victoria Chiou for critical discussions of this work and Dana DeSantis from the Tempus Science Communications team for poster development.

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