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Quantitative *KRAS* ctDNA Dynamics Predict Early Recurrence After Neoadjuvant Therapy and Surgery in Pancreatic Cancer

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Abstract

Early recurrence remains prevalent in pancreatic ductal adenocarcinoma (PDAC) despite multimodality treatment. Circulating tumor DNA (ctDNA) is an emerging prognostic biomarker showing promise in detecting minimal residual disease (MRD). Using a high-sensitivity digital droplet PCR (ddPCR) assay, we evaluated *KRAS*-mutant ctDNA as a marker of MRD associated with early recurrence (<12 months) in patients with localized PDAC receiving neoadjuvant chemotherapy (NAC), surgery, and adjuvant chemotherapy (AC). *KRAS* G12D, G12V, and G12R mutations found in cell-free DNA were detected and quantified with maximum variant allele frequency (mVAF). Of 130 enrolled patients, 55 completed NAC and resection. ctDNA was detected a median of 7.6 months before imaging-confirmed recurrence. Postoperative detection *KRAS* ctDNA was independently associated with worse recurrence-free survival (RFS) (aHR 3.30, 95% CI 1.33–8.21, p=0.010), and ctDNA clearance after NAC and surgery was independently associated with improved RFS (aHR 0.23, 95% CI 0.06–0.90, p=0.035). Median cohort mVAF was 0.03%; patients with mVAF above the median had shorter RFS (12.8 vs. 26.3 months) and more frequent early recurrence (p=0.027). ctDNA-positive patients who received AC remained with worse outcomes than ctDNA-negative patients, suggesting persistent chemotherapy resistance. These data indicated that persistent *KRAS* ctDNA after NAC and surgery reflects MRD and support sensitive postoperative ctDNA testing to stratify high risk patients for early recurrence, guiding quantitative, longitudinal monitoring. Future studies in adaptive treatment settings may further extend these findings toward ctDNA-guided clinical decision-making.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death and has a 5-year survival of 13%.[1–3] Despite advances in perioperative chemotherapy, recurrence rates remain at 70-80% within 2 years.[4–9] Assessing treatment response remains challenging in PDAC management, with occult micrometastatic disease often present but undetectable by conventional imaging, limiting assessment of treatment response until clinical recurrence.[10] Currently, carbohydrate antigen 19-9 (CA19-9) is the only serum biomarker routinely used but is limited by false positives with jaundice and false negatives in Lewis antigen-negative patients.[11] Early recurrence within one year represents a major challenge in PDAC; therefore, identifying at-risk patients is critical for postoperative surveillance and may enable earlier intervention, yet sensitive measures are currently lacking.[6,12]

Circulating tumor DNA (ctDNA) is an emerging prognostic biomarker showing promise in measuring minimal residual disease (MRD).[13,14] First described in hematological malignancies, MRD assessment has recently gained attention in solid tumors, with recent studies showing associations with progression-free survival and overall survival across multiple cancers.[15–17] However, in PDAC, the prognostic significance of ctDNA as a quantitative measure of MRD for identifying patients at risk of early recurrence remains incompletely defined.[18–20]

KRAS mutations are present in approximately 90% of PDAC cases as a primary driver, making *KRAS*-mutant ctDNA a practical target for analyses.[21–23] We have previously shown that detection of *KRAS* ctDNA using next-generation sequencing (NGS) is associated with progression-free survival; additionally, we showed that *KRAS* ctDNA detection by digital droplet PCR (ddPCR) is highly sensitive and dynamic throughout PDAC treatment, capturing signals missed by NGS.[24–27] Accordingly, this study evaluates *KRAS* ctDNA using a highly sensitive ddPCR assay

as a dynamic and quantitative measure of MRD associated with early recurrence in the postoperative setting with potential to inform ctDNA-guided treatment.

Results

Patient Demographics

In total, 130 patients were enrolled from October 2020 through December 2024. Patients undergoing NAC and surgery were included for analysis of postoperative ctDNA. Those who did not undergo neoadjuvant chemotherapy (n=23), did not ultimately undergo curative-intent surgery (n=48), or did not have an available blood draw for post-resection testing (n=4) for any reason were excluded. Reasons for not undergoing NAC or resection are outlined in **Table S1** while a CONSORT diagram illustrating patients included for analysis can be found in **Figure S1**. The final cohort of patients who underwent both NAC and surgery included 55 patients contributing 197 total blood samples (**Table 1; Figure 1**). Samples were collected for ddPCR analysis from 50 patients at diagnosis (90.0%), 53 patients after NAC (96.3%), 55 patients after resection (100%), and 43 patients after adjuvant chemotherapy (AC; 78.2%). The median age at diagnosis was 68 years (IQR 57–79) with 50.9% female and 81.8% Caucasian. Most tumors were located in the head or uncinate process (70.9%), and radiographically borderline resectable according to National Comprehensive Cancer Network (NCCN) imaging criteria (58.2%).[28] Most patients had stage IB disease at diagnosis (60.0%). The median length of NAC was 6 (IQR 3-6) cycles of NAC over 2.6 (IQR 2.3–3.4) months. Patients most frequently received mFOLFIRINOX for NAC (69.1%), and those who also underwent AC after resection (78.2%) most frequently received mFOLFIRINOX or gemcitabine and nab-paclitaxel (49.1% or 27.3%, respectively). Most underwent open pancreatoduodenectomy (74.5%) with margin-negative resection (96.4%). Median follow-up was 25.1 months from time of diagnosis and 14.6 months from date of surgical resection. *KRAS*-mutant

ctDNA was detectable in 58.8% of patients at diagnosis (30/51), 58.5% after NAC (31/53), 56.4% after surgery (31/55), and 43.2% after AC (16/37).

Detection of ctDNA in Relation to Recurrence

After surgery, *KRAS* G12D was the most frequently detected *KRAS* mutation (**Figure 2a**). Of 27 patients with radiographic recurrence, recurrence was multisite (57.2%), single distant (32.2%), or locoregional (10.6%), with did not differ by *KRAS* ctDNA status (**Figure 2b**). Most distant recurrences occurred in the liver (20.0%) and lung (14.6%). ctDNA detection post-resection was not significantly associated with clinical characteristics (Supplemental Table 2).

Of 55 patients who received NAC followed by curative-intent resection, 27 recurred (49.1%) over a median of 9.9 months, with median RFS of 21.8 months. *KRAS* ctDNA detection was evaluated relative to timing of radiographic recurrence. Among 27 patients who recurred, 19 had detectable *KRAS* ctDNA after surgery, after completion of AC, or both (70.3%), including seven who were ctDNA-positive at both timepoints (36.8%). Overall, postoperative ctDNA preceded recurrence in 18 patients (66.7%); eight patients who recurred (29.6%) remained ctDNA-negative throughout, and one patient had ctDNA detected only after radiographic recurrence. Among patients with detectable ctDNA, median lead time from first detection to recurrence was 7.6 months (range 2.6–32 months; **Figure 2c**).

ctDNA Dynamics and Recurrence-Free Survival

After NAC and surgery, 31 of 55 patients (56.4%) were ctDNA-positive. In multivariable Cox regression, *KRAS* ctDNA detection was independently associated with shorter RFS (aHR 3.33, 95% CI 1.34–8.26, p=0.009; **Figure 3a**) in multivariable Cox regression. CA19-9 was not independently predictive.

We next evaluated whether ctDNA dynamics affected RFS. Among 30 patients with detectable ctDNA at diagnosis, 13 achieved ctDNA clearance (undetectable after NAC and resection) while 17 had persistent ctDNA. In patients who were ctDNA-positive at diagnosis, clearance was associated with improved RFS (aHR 0.23, 95% CI 0.06–0.90, p=0.035; **Figure 3b**); CA19-9 was not significantly associated with RFS. Recurrence occurred in 4/13 patients who cleared ctDNA (three within 12 months), compared with 10/17 of patients without full clearance (seven within 12 months).

Quantitative ctDNA Burden in Early Recurrence and Adjuvant Chemotherapy

We then sought to assess RFS differences based on quantitative tumor burden via mVAF. Median postoperative mVAF in the cohort of patients receiving NAC and surgery was 0.03% (range 0.01–3.33%; IQR 0.00–0.265%). Patients above median mVAF had significantly shorter VAF (median 12.8 vs 26.3 months, log rank p=0.039; **Figure 4a**) and more frequent early recurrence within 12 (13/26 vs 6/29, p=0.027; **Figure 4b**). While patients without early recurrence showed lower mVAF through treatment, those experiencing early recurrence sustained higher mVAF (**Figure 3c**).

As AC is shown to improve outcomes in resected PDAC, we next tested whether ctDNA detection remained prognostic when AC is utilized.[29] Of 43 patients who received AC over a median of 2.3 months, median RFS was not reached while median RFS in the ctDNA-positive group receiving AC was 15.5 months. RMST quantified differences in RFS within the first 12 months after resection, finding that ctDNA-positive patients after resection still experienced worse outcomes despite AC; over a 12-month horizon, ctDNA-positive patients spent an average of 1.6 fewer months recurrence-free compared with ctDNA-negative patients (9.7 months vs 11.3 months, p=0.025; **Figure 5a**). Clearance of ctDNA following AC was limited in patients with

detectable ctDNA following NAC and surgery. A minority of patients who were ctDNA-positive after NAC and surgery became ctDNA negative after AC (38.1%), whereas ctDNA-negative patients after NAC and surgery largely maintained their negative status (81.8%; **Figure 5b**).

Discussion

High early recurrence rates in PDAC make the MRD setting an important area of interest.[5] Because CA19-9 is limited as a standalone indicator, there arises a need for additional molecular markers capable of sensitive risk stratification.[10,11,30] This study builds upon our prior work evaluating *KRAS* ctDNA and overall survival by extending analysis to recurrence in the postoperative setting with quantitative assessment of ctDNA dynamics. We report that higher mVAF and lack of ctDNA clearance following NAC and curative-intent resection are associated with worse RFS and increased early recurrence risk within one year of surgery. These findings support high sensitivity assessment for *KRAS* ctDNA detection as a method for measuring MRD and molecular response.

The independent association between RFS and ddPCR detection of *KRAS* ctDNA in patients receiving NAC and achieving R0 resection may imply residual disease missed by imaging, reflecting microscopic tumor burden despite NAC and resection.[31,32] Additionally, ctDNA is detectable several months prior to clinical recurrence, and may be an early indicator of residual disease associated with subsequent disease progression. Previously, we showed ctDNA detection by NGS was prognostic following NAC and resection; however, sensitivity was limited with only 31% of patients being NGS-positive after treatment; a follow-up study confirmed that ddPCR captures relevant signals missed by NGS.[24,26] The high sensitivity of ddPCR to detect *KRAS* ctDNA is evidenced here by the 56.4% rate of detection after NAC and surgery in our cohort,

which is likely to enhance risk stratification and assessment of treatment response compared with imaging alone.[33]

KRAS ctDNA detection and clearance remain independently prognostic even after adjustment for CA19-9 as a covariate. This suggests that detectable ctDNA despite treatment may imply higher risk for recurrence and provides information beyond CA19-9, which was not prognostic in our cohort. This is consistent with our previous work using NGS detection of ctDNA which noted its prognostic value for progression-free survival and lack of association in CA19-9, supporting the use of ctDNA testing along with current methods of risk stratification.[24]

Additionally, we demonstrate that *KRAS* ctDNA clearance is independently associated with improved RFS, suggesting that changes in ctDNA may reflect the extent which treatment reduces tumor burden. These findings support previous findings of ctDNA as a dynamic biomarker during treatment.[24,25,33] Quantitative differences in mVAF further stratify risk beyond detection alone, as patients above median mVAF experienced worse RFS and more frequent early recurrence. Continuous mVAF measures may therefore identify highest-risk patients, providing granularity greater than binary detection, given that ddPCR enables absolute quantifcation.[34–37]

We observed that the mVAF trajectories in patients experiencing early recurrence sustained at a higher level both at diagnosis and after multimodality treatment than patients without early recurrence, suggesting that a high baseline that fails to decline through standard-of-care treatment may therefore indicate presence of a greater MRD burden compared to patients with lower mVAF. Along with our results demonstrating the importance of ctDNA clearance, these data indicate that persistent ctDNA after treatment may serve as a dynamic, clinically meaningful endpoint for identifying high-risk patients beyond baseline measurements.

Even among patients who received AC following NAC and resection, those who were ctDNA-positive after resection experienced worse outcomes, suggesting that ctDNA detection after NAC and resection may capture a population at elevated risk of recurrence despite receiving standard AC. Furthermore, we found that the majority of patients with detectable postoperative ctDNA remained persistently ctDNA-positive even after AC, which may reflect residual disease insufficiently addressed by standard-of-care multi-agent chemotherapy regimens that may be addressed by targeted therapies. Recent and ongoing trials, including Alliance A021806, are evaluating the optimal timing of systemic therapy in resectable PDAC by comparing perioperative and adjuvant approaches.[38,39] In parallel, our findings raise the possibility that standard AC may be insufficient for patients with detectable postoperative ctDNA who may represent a group with persistent residual disease and higher risk of recurrence. ctDNA may be a tool to identify patients who possibly benefit from alternative therapeutic strategies to inform more individualized postoperative management. However, the limited number of ctDNA-positive patients who did not receive AC in our cohort constrained our ability to compare outcomes between adjuvant-treated and untreated patients within this subgroup. Future studies with larger cohorts will more robustly evaluate whether AC sufficiently modifies outcomes among patients with ctDNA-positive disease.

KRAS is the driving mutation in over 90% of PDAC cases.[40] Our finding that persistent *KRAS*-mutant ctDNA is associated with inferior RFS support growing interest in *KRAS*-directed therapeutic strategies. Emerging *KRAS* inhibitors, including daraxonrasib, have demonstrated success in clinical trials.[41–45] Our findings suggest that patients with persistent *KRAS*-mutant ctDNA following treatment may be a molecularly high-risk group with residual disease despite standard therapies. Especially given the median 7.6-month lead time between ctDNA detection and imaging-confirmed recurrence observed in our study, sensitive detection could serve as a tool

to inform clinical decision-making for increased surveillance, *KRAS*-targeted therapies, or other adjuvant trial enrollment while monitoring efficacy of such treatments. ctDNA-informed trial enrollment is an approach that has been explored in other gastrointestinal malignancies, and sensitive postoperative *KRAS*-mutant ctDNA testing may further guide the use of emerging *KRAS*-directed treatments.[46,47] While additional future studies are needed to further support the incorporation of ctDNA as an integral biomarker, the lead time and independent prognostic value of *KRAS*-mutant ctDNA in this work raise the possibility that ctDNA could be a feasible strategy for identifying a population that derive the greatest benefit from these interventions. . As most patients in this cohort underwent open pancreatoduodenectomy (74.5%), a procedure associated with substantial perioperative morbidity, early recurrence carries particular significance. These data raise the possibility that ctDNA may help identify patients less likely to durably benefit from resection, warranting further study in preoperative risk stratification.

This study is limited by its single-institution design and modest sample size among patients receiving NAC followed by resection. While median follow-up time for the entire cohort was 25 months, the shorter post-resection follow-up (15 months) may limit capture of later recurrences, though our primary endpoint was early recurrence within 12 months. Additionally, ddPCR was selected as the ctDNA detection method due to high sensitivity; however, as a targeted approach, it cannot capture the all possible genomic alterations possibly present and detectable using broader sequencing methods such as NGS.[33] Larger, multicenter cohorts would establish generalizability.

We demonstrate that *KRAS*-mutant ctDNA may serve as a highly sensitive, independently prognostic biomarker for identifying MRD and predicting early recurrence in pancreatic cancer. In this study, quantitative and dynamic ctDNA captured by molecular clearance after NAC and surgery were significantly associated with RFS. These findings suggest that persistent ctDNA

detection may warrant additional clinical surveillance, potentially identifying patients who may derive additional benefit from targeted therapies.

Methods

Study Design and Patient Enrollment

Adult patients with newly diagnosed, localized PDAC with intent to undergo NAC were prospectively enrolled at Northwestern Medicine sites between October 2020 and December 2024 as part of an observational single arm phase II trial designed to evaluate ctDNA as a biomarker in PDAC (NCT04616131). For this study, patients completing both NAC and surgery with blood samples analyzed using ddPCR after resection were included while those not completing the full course of treatment (NAC and surgery) were excluded (**Figure S1a**). AC was routinely recommended and considered on a case-by-case basis for all patients, consistent with current standard practice.[8] Patients received mFOLFIRINOX or gemcitabine/nab-paclitaxel regimens according to tolerability and clinician judgement. All cases underwent multidisciplinary tumor board discussion and were managed according to institutional standards of care at Northwestern Medicine. This study was approved by the Northwestern University Institutional Review Board (NMHC IRB #21-012) and performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines as reported in adherence to Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines.[48,49] Written informed consent was obtained from all participants prior to study enrollment.

Sample Collection and Processing

Peripheral blood samples were collected from patients at diagnosis, following NAC, 2–6 weeks after resection, and after AC as applicable. All post-resection samples in this cohort underwent ddPCR testing for *KRAS*-mutant ctDNA. Samples were drawn into EDTA tubes and

immediately spun for plasma, which was then isolated within 4 hours of collection and stored at -80°C until DNA extraction.

Cell-free DNA was extracted using the QIAamp Circulating Nucleic Acid Kit #55114 (Qiagen N.V., Venlo Netherlands) in the Northwestern Medicine Surgical Oncology Translational Research Laboratory.

Digital Droplet PCR

Extracted cell-free DNA was analyzed using the QX200 Droplet Reader System. Samples were probed for the three most common *KRAS* mutations in PDAC: codon 12 exon 2 glycine substitutions for aspartic acid (G12D), valine (G12V), and arginine (G12R).[41] Each ddPCR reaction was performed in 22μL total volume containing 8μL of plasma-derived DNA, with positive and negative controls included. Droplets were generated using the QX200 Droplet Generator and sealed at 180° with the PX1 PCR Plate Sealer. The C1000 Touch Thermal Cycler was used for PCR amplification with plates subsequently read on the QX200 reader. Analysis was performed using QuantaSoft software (Bio-Rad Laboratories, Inc., Hercules, CA; RRID: SCR_008426). Fluorescence threshold of 3,000 was used to classify positivity. Variant allele frequency (VAF) was used to quantify mutational burden, defined as the proportion of mutated droplets relative to the total droplet concentration (mutated plus wild type). Mutant *KRAS* above the assay limit of detection of 1×10^{-7} ng was considered ctDNA-positive, which corresponds to approximately 0.01% VAF. All assays were performed by personnel in the Northwestern University Circulating Tumor Cell Core Facility.

Statistical Analysis

R (v4.5.1) was used for all analyses and data visualization with two-sided $p<0.05$ considered statistically significant. Descriptive statistics summarized demographic and clinical characteristics overall and by ctDNA detection. Differences were assessed using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables. The primary outcome of this study was recurrence-free survival (RFS), measured from the date of surgery to the date of recurrence identified, death, or last contact.

Early recurrence was defined as recurrence within 12 months of surgery. The primary molecular endpoints of this study were detection of *KRAS*-mutant ctDNA and VAF. In samples containing multiple mutations, maximum VAF (mVAF) was defined as the highest VAF among G12D, G12V, and G12R. Lead time was defined as the interval between first postoperative ctDNA detection and radiographic confirmation of recurrence. Multivariable analysis was performed using Cox proportional hazards regression with covariates selected for clinical relevance; adjusting for age, gender, clinical stage at diagnosis, and CA19-9 (>37 U/mL).[24] Results were reported as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). RFS was compared by ctDNA detection and clearance, with clearance defined as detectable ctDNA at diagnosis which became undetectable post-treatment.

Quantitative tumor burden was assessed by categorizing patients as above or below median mVAF. Kaplan-Meier curves and respective log-rank tests assessed RFS between groups while Fisher's exact test compared differences in the proportion of patients in each group experiencing early recurrence. A spaghetti plot was used to show median trajectory of mVAF over the course of treatment by early recurrence status. Restricted mean survival time (RMST) analysis was performed over a 12-month time horizon to estimate absolute differences in RFS between ctDNA detection groups in patients who received AC, reported as median RFS within the first 12 months.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and confidentiality considerations but are available from the corresponding author on reasonable request.

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Author Contributions

AC conceptualized and design the study. CS, KS, MC, DV, AH, AC, VR, AW, JM, IT, NR, MK, and QZ acquired, analyzed, and interpreted the data. CS drafted the manuscript. Statistics were performed by CS, QZ, KS, and AC. KV, AC, VR, AW, IT, NR, MK, PU, MP, LD, and YV provided administrative, technical, and material support. AC obtained funding and supervised this work. All authors critically revised the manuscript for intellectual content.

Competing Interests

All authors declare no financial or non-financial competing interests.

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Table 1. Baseline clinical and demographic characteristics of study cohort.

	Total/Median (Percent/IQR)
N	55 (100%)
Age	68 (57-79)
Sex	
Female	28 (50.9%)
Male	27 (49.1%)
Race/Ethnicity	
Asian	3 (5.45%)
Black or African American	1 (1.82%)
Caucasian	45 (81.8%)
Hispanic or Latino	4 (7.27%)
Other	2 (3.64%)
Primary Tumor Location	
Body/tail	12 (21.8%)
Head/uncinate	39 (70.9%)
Neck	4 (7.27%)
Follow-up from Diagnosis (months)	25.07 (18.7-37.6)
Follow-up from Resection (months)	14.62 (9.13-25.9)
CA19-9 at Diagnosis (U/mL)	117 (31-340)
CA19-9 After Resection (U/mL)	20 (10-32)
Vascular Involvement	
Arterial	18 (32.7%)
Venous	47 (85.4%)
Radiographic Stage	
Resectable	22 (40.0%)
Borderline resectable	32 (58.2%)
Locally advanced	1 (1.81%)
Preoperative AJCC Stage	
IA	9 (16.4%)
IB	33 (60.0%)
II	7 (12.7%)
III	6 (10.9%)
NAC Regimen	
FOLFIRINOX	38 (69.1%)

Gemcitabine + Nab-Paclitaxel	16 (29.1%)
Other	1 (1.82%)
Cycles of NAC	6 (3-6)
Surgical Procedure	
Open pancreatoduodenectomy	41 (74.5%)
Open subtotal pancreatectomy	9 (16.3%)
Laparoscopic or robotic subtotal pancreatectomy	5 (9.1%)
Underwent Adjuvant Chemotherapy	
Yes	43 (78.2%)
No	12 (21.8%)
Adjuvant Chemotherapy Regimen	
FOLFIRINOX	27 (62.8%)
Gemcitabine + Nab-Paclitaxel	15 (34.9%)
Gemcitabine alone	1 (2.32%)
ctDNA Detection at Diagnosis	
No	21 (38.2%)
Yes	30 (54.5%)
No available draw	4 (7.27%)
ctDNA Detection after NAC	
No	22 (40.0%)
Yes	31 (56.4%)
No available draw	2 (3.64%)
ctDNA Detection after Resection	
No	24 (43.6%)
Yes	31 (56.4%)
No available draw	0 (0.00%)
ctDNA Detection after Adjuvant Therapy	
No	17 (30.9%)
Yes	15 (27.2%)
No available draw	11 (20.0%)
No adjuvant chemotherapy	12 (21.8%)

Figure 1. Swimmer plot of patients in cohort, specifying relative timings of ctDNA testing, NAC, resection, recurrence, and death. Beginning of timeline is pre-NAC (diagnosis) ctDNA testing or time of diagnosis if testing was unavailable.

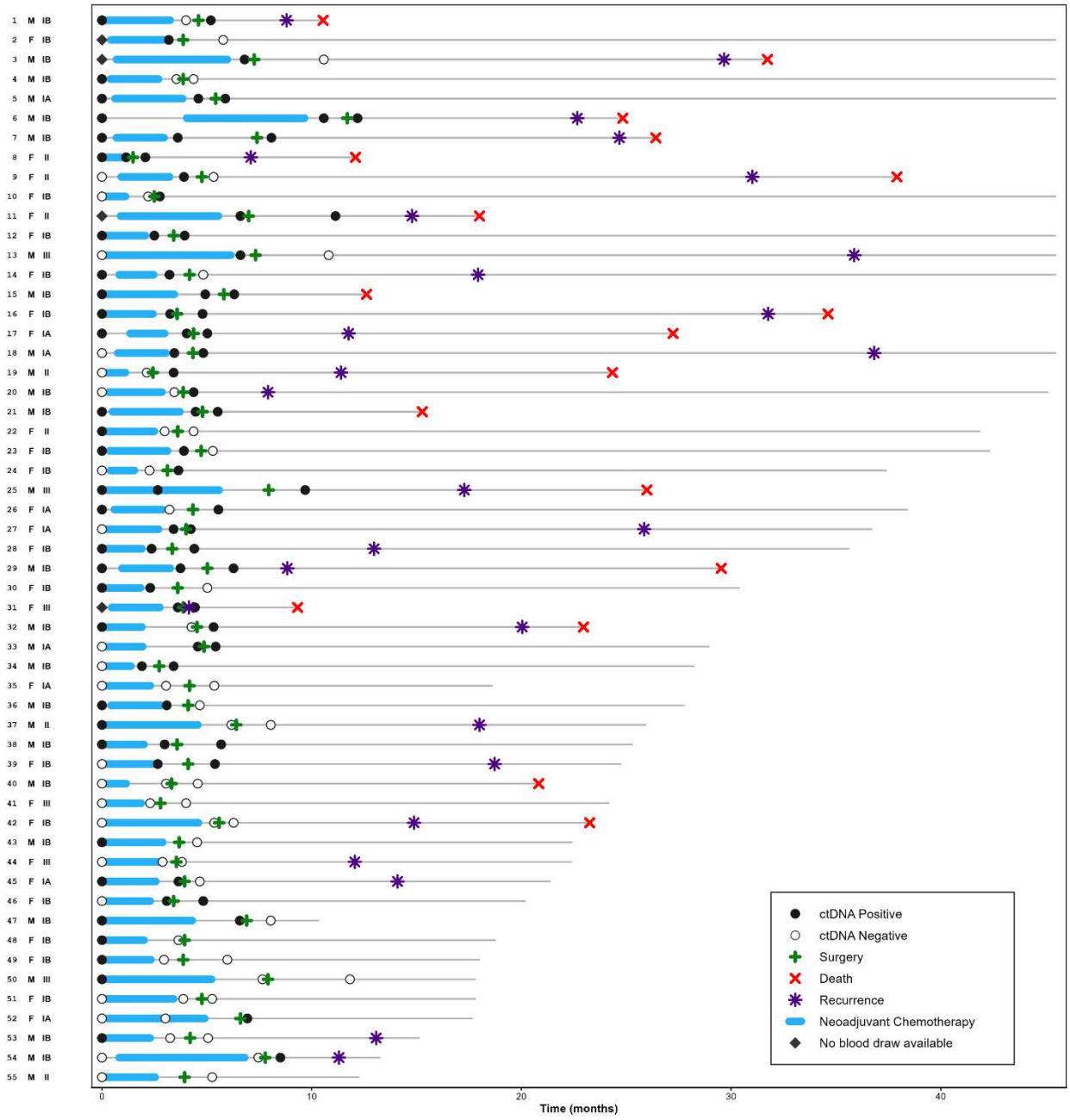


Figure 2. *KRAS*-mutant ctDNA detected among NAC-treated and resected PDAC cohort.

(a) Oncoplot of *KRAS* mutations identified by ddPCR across all patients in cohort; (b) Patterns of recurrence by postoperative ctDNA status; (c) Lead time plot illustrating ctDNA detection at resection and/or during surveillance/ after adjuvant chemotherapy in relation to radiographic recurrence in patients who recurred.

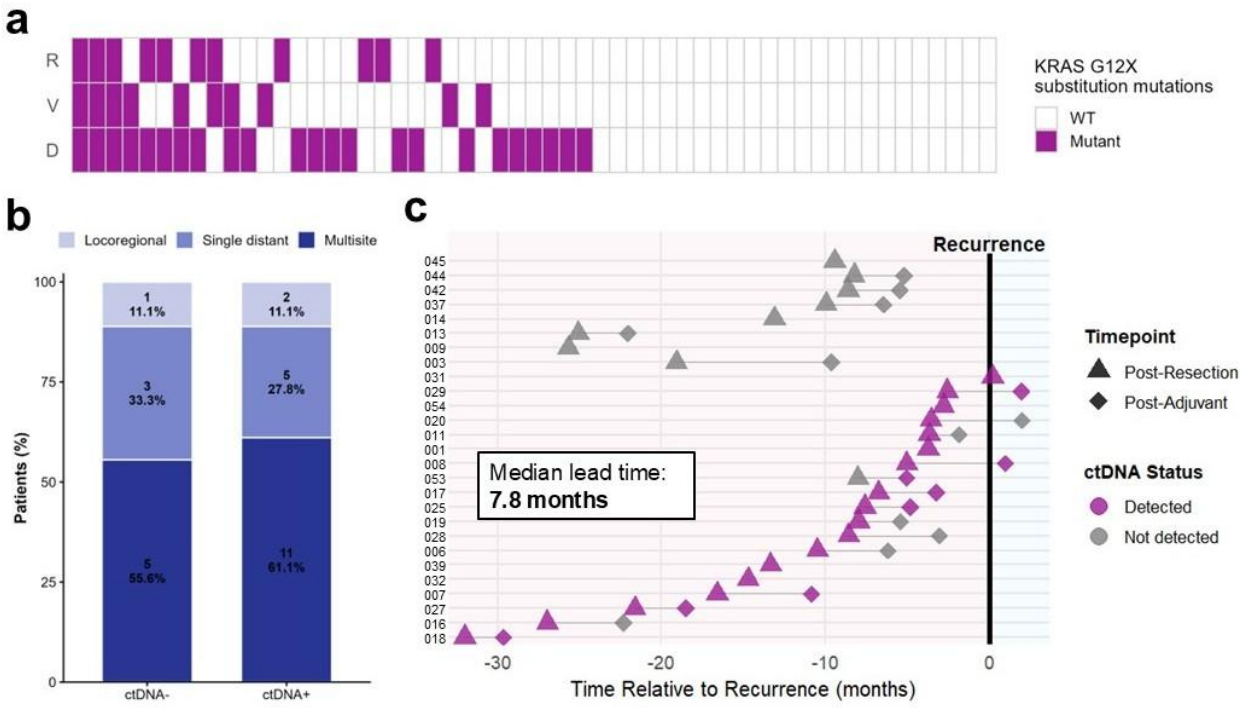


Figure 3. *KRAS* ctDNA detection and dynamics on recurrence-free survival. Forest plots depicting Multivariable Cox regressions showing adjusted hazard ratio with 95% CI to assess prognostic value of (a) detection of postoperative *KRAS* ctDNA by ddPCR and (b) clearance of ctDNA from diagnosis to post-treatment in patients who were ctDNA-positive at diagnosis. Each regression includes clinical stage, age, sex, and CA19-9 as covariates.

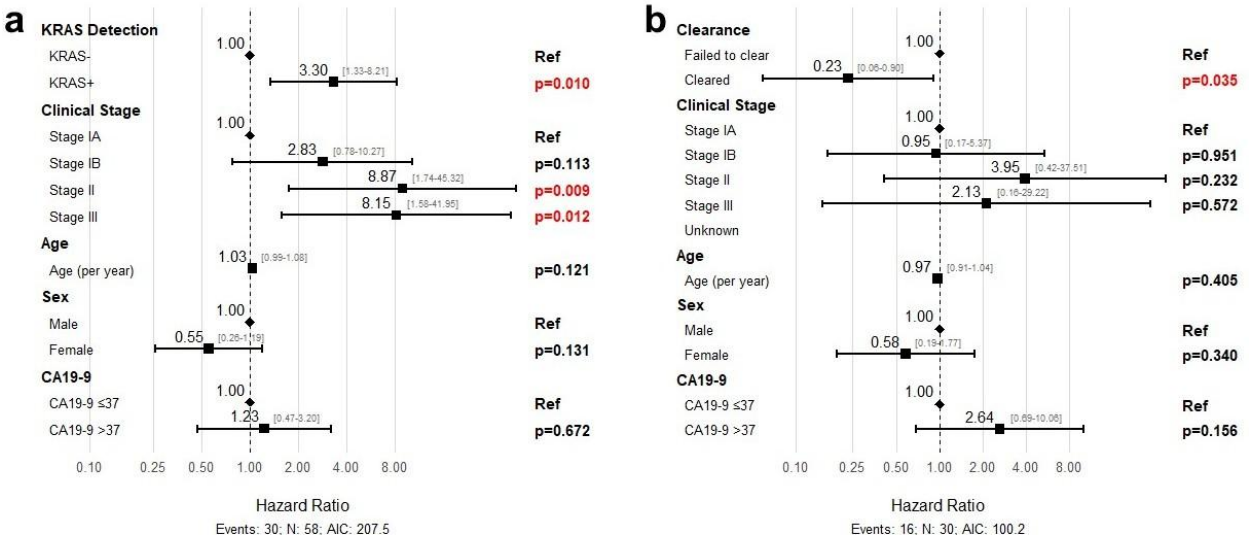


Figure 4. Quantitative evaluation of variant allele frequency. (a) Kaplan-Meier curve with log-rank test, split by above/below median mVAF (=0.03) and (b) proportion of early recurrences by median mVAF split; (c) spaghetti plot depicting mVAF trajectory from diagnosis to after NAC and resection by patients with and without early recurrence.

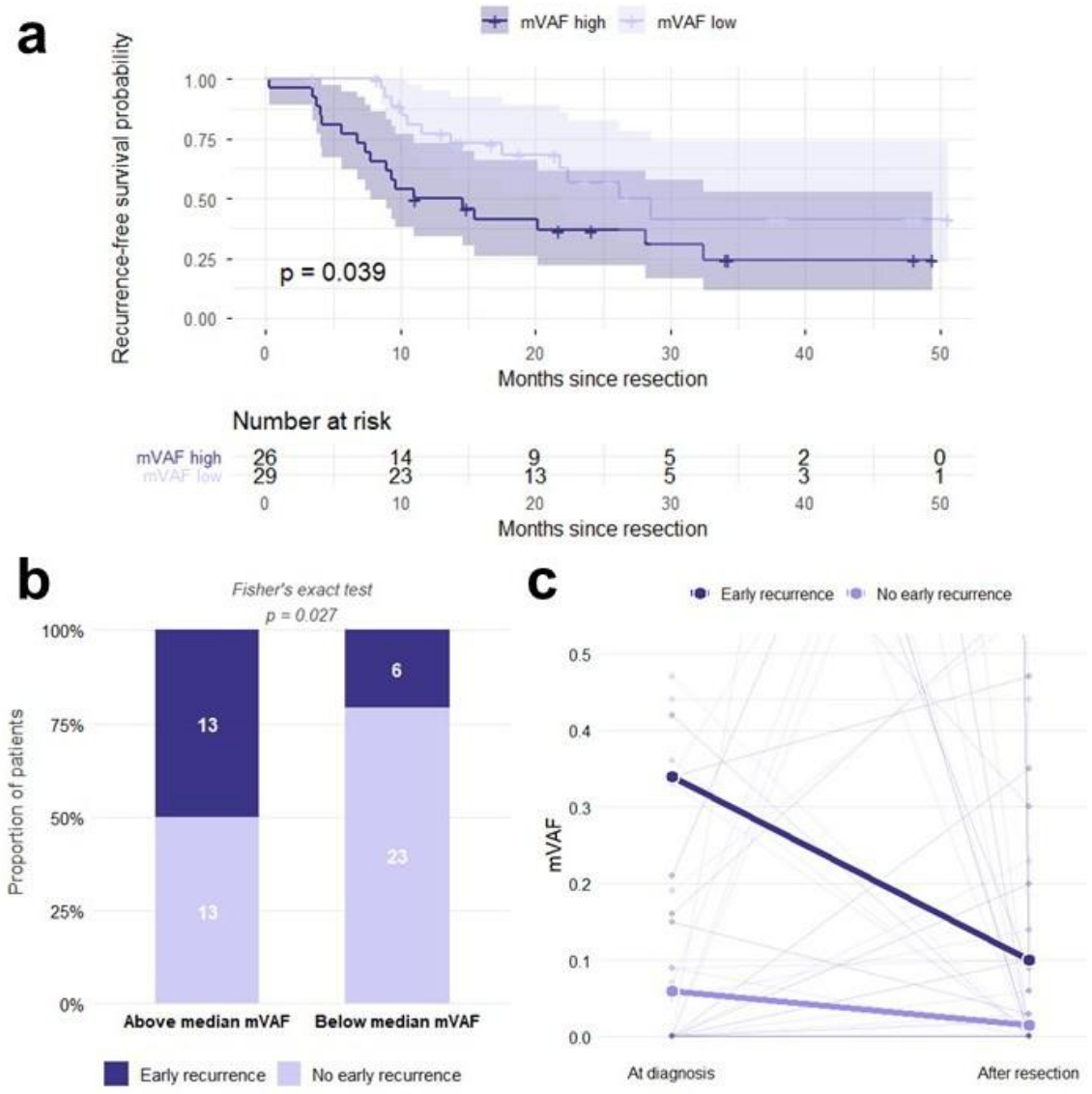
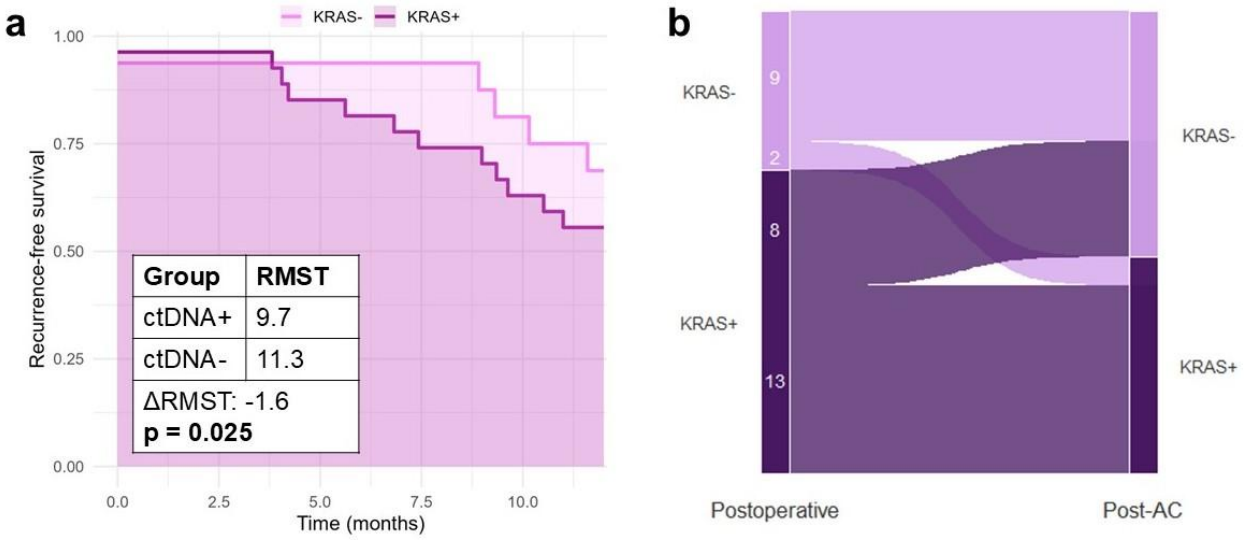


Figure 5. Assessment of ctDNA detectability in the adjuvant setting. (a) restricted mean survival time among patients receiving adjuvant chemotherapy by postoperative ctDNA status; (b) Sankey diagram showing postoperative to post-adjuvant ctDNA detection status.



Supplementary Files

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- Tables.docx
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