Combining Two Liquid Biopsy Tests Enables More Precise Recurrence Risk Stratification After Resection of Colorectal Oligometastases

Findings from PRECISION, a Prospective Multicenter Study Using Comprehensive Genomic Profiling (CGP) and Molecular Residual Disease (MRD) Testing

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National Cancer Center Japan

Highlights

- We conducted PRECISION, a prospective multicenter study analyzing circulating tumor DNA (ctDNA) through blood tests (liquid biopsy) performed before and after surgery in patients with surgically resectable distant metastases of colorectal cancer, such as liver and lung metastases.
- Comprehensive genomic profiling (CGP) testing of preoperative blood samples detected ctDNA in 114 of 118 patients (96.6%), of whom 75 (63.6%) carried a poor-prognosis genomic profile associated with worse outcomes. Molecular residual disease (MRD) testing of blood samples drawn 4 weeks after surgery detected MRD in 34 of 109 operated patients (31%).
- Patients with both a preoperative poor-prognosis profile and postoperative MRD positivity had an approximately 13-fold higher risk of recurrence (hazard ratio 13.28) compared with patients with neither finding.
- Combining these two liquid biopsy tests performed before and after surgery enabled more precise recurrence risk stratification than either test alone, suggesting a path toward individualized postoperative adjuvant chemotherapy.
- This study was published in *ESMO Open*, the official journal of the European Society for Medical Oncology (ESMO).

Overview

Dr. Shin Kobayashi, Chief of the Department of Hepatobiliary and Pancreatic Surgery and Director of Perioperative Treatment Development Promotion Office, and Dr. Yoshiaki Nakamura, the visiting researcher — both at National Cancer Center Hospital East (Director: Toshihiko Doi; Kashiwa, Chiba), part of National Cancer Center Japan (President: Hiroyuki Mano; Chuo-ku, Tokyo) — led a research group that conducted PRECISION, a prospective multicenter study combining preoperative comprehensive genomic profiling (CGP) [Note 1] testing with postoperative molecular residual disease (MRD) [Note 2] testing in patients with resectable colorectal oligometastases.

In this study, circulating tumor DNA (ctDNA)[Note 3] in blood samples from 118 patients was analyzed

at two time points: before surgery and 4 weeks after surgery. Patients who had both a preoperative poor-prognosis profile and postoperative MRD positivity were clearly stratified as the group with the highest risk of recurrence, compared with patients who had neither finding. The study was published in *ESMO Open*, the official journal of the European Society for Medical Oncology (ESMO), on Month XX, 2026.

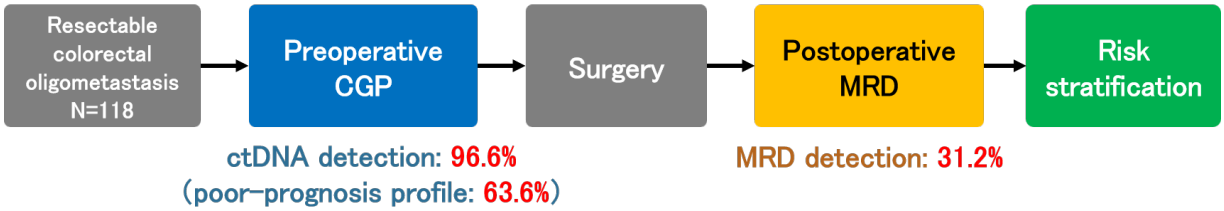
Background

Colorectal cancer [Note 4] is the third most commonly diagnosed cancer and the second leading cause of cancer-related death worldwide. Even when the disease has spread to distant sites such as the liver, lungs, or peritoneum (“distant metastases”), surgical resection is actively pursued when cure may be achievable. International clinical guidelines recommend perioperative (preoperative and/or postoperative) drug therapy in addition to surgery; however, while several phase III trials have shown improved recurrence-free survival (RFS), no improvement in overall survival (OS) has been confirmed, highlighting the need for reliable biomarkers [Note 5] that enable individualized perioperative treatment.

ctDNA－ cancer-derived DNA circulating in the blood － is a promising, minimally invasive biomarker for assessing cancer status. Our research group has previously reported that, among patients with resectable colorectal oligometastases, detecting a pathogenic variant in any of BRAF, KRAS, SMAD4, PIK3CA, or TP53 (“poor-prognosis profile”) on preoperative blood-based comprehensive genomic profiling (CGP) testing of 74 genes is associated with worse prognosis.

In addition, the state in which trace amounts of cancer-derived ctDNA remain detectable in the blood even after macroscopically complete surgical resection of the tumor is called “molecular residual disease (MRD).” Previous research has shown that MRD assessment at 4 weeks after surgery is the most useful for deciding whether to administer postoperative adjuvant chemotherapy; however, a certain proportion of patients with a negative MRD result still experienced recurrence, revealing the limitation that MRD assessment at a single time point alone is insufficient for adequate risk stratification. Our research group therefore hypothesized that combining preoperative comprehensive genomic profiling (CGP) testing with MRD testing at 4 weeks after surgery could enable more precise risk stratification and individualized treatment, and set out to examine the feasibility of this approach (Figure 1)

Figure 1. PRECISION study design

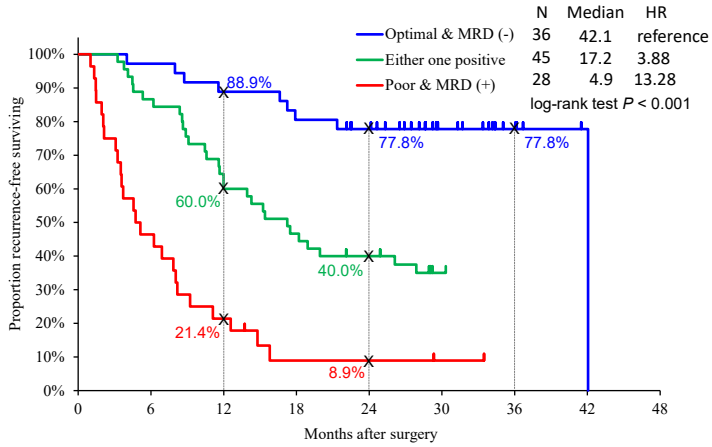


Results (Methods and Findings)

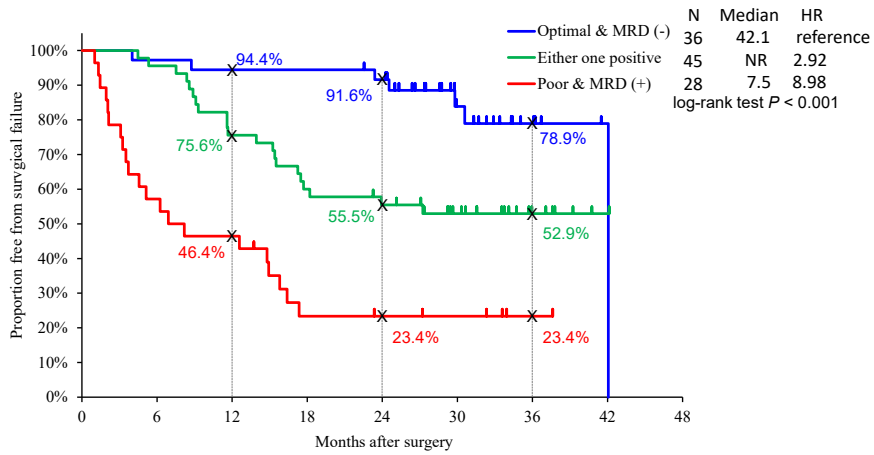
This prospective, multicenter, observational study enrolled 118 treatment-naive patients with resectable colorectal oligometastases between March 2021 and October 2022. Comprehensive genomic profiling (CGP) testing of 74 genes was performed before surgery, and molecular residual disease (MRD) testing was performed 4 weeks after surgery. ctDNA was detected at enrollment in 114 of 118 patients (96.6%), exceeding the prespecified threshold of 80% and demonstrating the feasibility of preoperative ctDNA-based CGP testing. Of these, 75 patients (63.6%) carried a pathogenic variant in BRAF, KRAS, PIK3CA, SMAD4, or TP53, meeting the definition of a "poor-prognosis profile." Among the 109 patients who underwent surgery, MRD was detected at 4 weeks after surgery in 34 patients (31.2%). On multivariable analysis, both a preoperative poor-prognosis profile and postoperative MRD positivity were independently and significantly associated with shorter RFS (hazard ratio [HR]: 3.28 and 4.07, respectively) and time to unresectable recurrence (TUR) (HR: 2.76 and 3.05, respectively). Furthermore, patients with both a preoperative poor-prognosis profile and postoperative MRD positivity had the worst prognosis of all groups across every endpoint examined — RFS (HR: 13.28), TUR (HR: 8.98), and OS (HR: 9.21) — compared with patients with neither finding (Figure 2). Patients with neither finding had the most favorable prognosis, with a 2-year recurrence-free survival rate of 77.8% and a 3-year overall survival rate of 93.0%.

Figure 2 Comparison of survival time according to the poor-prognosis profile and MRD

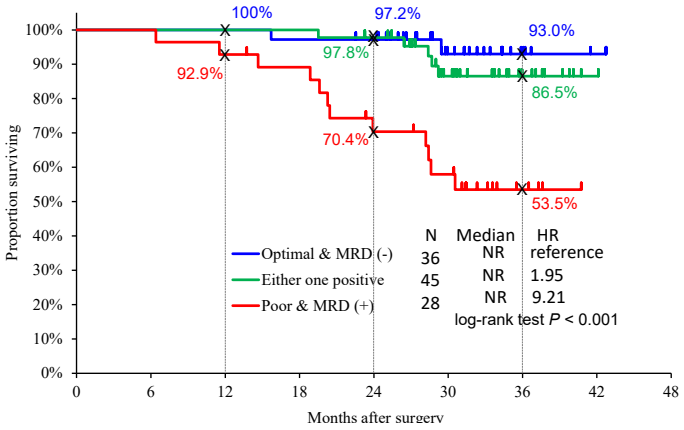
A: RFS (recurrence-free survival)



B: TUR (time to unresectable recurrence)



C: OS (overall survival)



Outlook

Risk stratification combining CGP and MRD testing is expected to enable more precise, individualized treatment for patients with resectable colorectal oligometastases. As this study involved a relatively small number of patients and was a non-randomized observational study, the findings are exploratory and should be regarded as hypothesis-generating.

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Glossary

Note 1: Comprehensive Genomic Profiling (CGP)

A test that comprehensively analyzes variants across multiple cancer-related genes using blood or tissue samples. In this study, 74 genes were analyzed using ctDNA detected in preoperative blood samples.

Note 2: Molecular Residual Disease (MRD)

A state in which trace amounts of cancer-derived DNA (ctDNA) remain detectable in the blood even after macroscopically complete surgical removal of the tumor. It is gaining attention as a marker that can identify recurrence risk earlier than imaging studies can.

Note 3: Circulating Tumor DNA (ctDNA)

Fragmented DNA released into the bloodstream when cancer cells die. Blood testing (liquid biopsy) can be used to assess genomic alterations and recurrence risk.

Note 4: Colorectal cancer

A cancer arising in the colon or rectum. It is among the most common cancers in Japan in terms of both incidence and mortality.

Note 5: Biomarker

A measurable indicator — such as a test parameter (blood pressure, heart rate, electrocardiogram, cognitive testing, etc.) or a biological substance (protein, metabolite, gene, etc.) — used to predict the presence of a disease or changes in its status, progression, or response to treatment.

Related Press Releases

- June 10, 2020 — CIRCULATE-Japan, a New Project Toward Personalized Cancer Care Through Liquid Biopsy, Launched — World's Largest Physician-Led International Clinical Trial Targeting Molecular Residual Disease Begins (in Japanese) https://www.ncc.go.jp/jp/information/pr_release/2020/0610/index.html
- January 24, 2023 — Liquid Biopsy Confirmed Useful for Assessing Recurrence Risk After Colorectal Cancer Surgery — World's Largest Prospective Study Aims to Individualize Postoperative Adjuvant Chemotherapy (in Japanese) https://www.ncc.go.jp/jp/information/pr_release/2023/0124/index.html
- September 17, 2024 — Liquid Biopsy Confirmed Useful for Deciding on Adjuvant Therapy After Resection of Colorectal Liver Metastases — Published in Annals of Oncology (in Japanese) https://www.ncc.go.jp/jp/information/pr_release/2024/0917_3/index.html
- September 17, 2024 — CIRCULATE-Japan GALAXY Confirms Effectiveness of Liquid Biopsy in Predicting Recurrence Risk and Post-operative Treatment Efficacy in Colorectal Cancer — Published in Nature Medicine — https://www.ncc.go.jp/en/information/press_release/2024/0917_1/index.html
- June 12, 2026 — World-First Investigation of an Early Preemptive Treatment Strategy for Patients at High Risk of Colorectal Cancer Recurrence Using Liquid Biopsy — A Phase III Trial in ctDNA-Positive Patients (ALTAIR) (in Japanese) https://www.ncc.go.jp/jp/information/pr_release/2026/0612/index.html
- July 7, 2026 — Exploratory Analysis Identifies Patient Groups Expected to Benefit from Adjuvant Therapy After Resection of Colorectal Liver Metastases Using Liquid Biopsy — Published in JAMA Oncology (in Japanese) https://www.ncc.go.jp/jp/information/pr_release/2026/0707/index.html
- September 15, 2026 — Proposing a New Framework for Cancer Treatment Development Using Liquid Biopsy — Toward Accelerating New Treatment Development Through a Molecular Residual Disease (MRD) Registry (in Japanese) https://www.ncc.go.jp/jp/information/researchtopics/2026/0915/index.html

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