Editorial
Diagnostic Genetics

Ann Lab Med 2024;44:119-121
https://doi.org/10.3343/alm.2023.0391
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Mi-Ae Jang, M.D., Ph.D.
Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Next-Generation Sequencing-Based Molecular Profiling Using Cell-Free DNA: A Valuable Tool for the Diagnostic and Prognostic Evaluation of Patients With Gastric Cancer

Gastric cancer (GC) is a global health challenge. With an estimated 1,089,103 new cases and 768,793 deaths in 2020, GC is the fifth most common type of cancer and the fourth leading cause of death worldwide [1]. Several molecular biomarkers for the treatment of GC, such as *ERBB2* (also known as *HER2*) amplification and microsatellite instability (MSI)-high status, are applied in clinical practice [2]. *ERBB2* is the first validated predictive biomarker for drug therapy and is overexpressed in 10%–20% of GC cases [3], and ERBB2-positive patients are candidates for trastuzumab treatment [4]. MSI-high is associated with a better prognosis and is a negative predictive marker for perioperative or adjuvant chemotherapy [5]. With the discovery of more molecular markers, molecular cancer DNA profiling has become a standard approach in oncology in the era of targeted therapy. However, traditional biopsy for molecular workup is an invasive procedure and is not always feasible [5].

Liquid biopsy for the analysis of cell-free DNA (cfDNA) from non-solid biological materials, including blood, urine, saliva, ascites, and pleural fluid samples, can be used to identify patients with specific tumor mutations more quickly and in a minimally invasive manner. Therefore, liquid biopsy may serve as an alternative to tissue biopsy [6, 7]. Increasing evidence suggests cfDNA may be a biomarker for diagnosis, prognosis, recurrence monitoring, and the identification of targetable alterations to predict sensitivity or resistance to GC treatments [8-10]. Table 1 lists ongoing clinical trials using liquid biopsy in the field of GC registered in ClinicalTrials.gov (https://clinicaltrials.gov/, accessed October 2, 2023). The ASCEND-Gastric study (NCT05224596) will evaluate the sensitivity and specificity of a combined cfDNA and protein biomarker-based assay for GC detection in participants at various clinical stages. Another study investigating the prognostic role of liquid biopsy in patients with locally advanced GC is underway (NCT04943406). Patients with a resectable tumor and below stage IV disease will be enrolled in this study, and liquid biopsies of peritoneal lavage fluid and plasma will be analyzed on multiple occasions, i.e., before curative gastrectomy, at hospital discharge, three months after surgery/at the completion of adjuvant therapy, and at disease recurrence, and overall and disease-free survival determined. In addition, next-generation sequencing (NGS)-based cfDNA assays to evaluate cfDNA positivity as a biomarker for monitoring minimal residual disease after radical gastrectomy (NCT05029869) are ongoing (Table 1). More multicenter studies and prospective evaluations in large clinical trials are necessary for the integration of liquid biopsy into GC diagnosis for precise clinical treatment.

In this issue of *Annals of Laboratory Medicine*, Kim, *et al*. [11] report the characteristics of somatic genomic alterations in patients diagnosed as having advanced or metastatic GC based on

Table 1. Ongoing clinical trials using liquid biopsy for somatic mutation detection in gastric cancer

Study No.	Study type	Status	Start date	Conditions	Primary outcome measure
NCT06036563	O	N/R	Sep 2023	Common cancers	Diagnostic accuracy of cfDNA for screening and differentiating common cancers, including gastric cancer, in participants compared with a reference histological test
NCT06028724	O	R	May 2023	Solid tumors	Prevalence of clinically useful mutations in solid tumors, including gastric cancer by a next-generation sequencing-based cfDNA method
NCT05366881	O	R	May 2022	Multiple types of cancer	Differentiation between cancer and non-cancer signals from patients and controls based on cfDNA analysis using a genome-wide methylome enrichment platform
NCT05227261	O	R	Apr 2022	Common cancers of the lung, breast, liver, colorectum, and stomach	Positive/negative predictive values of blood cfDNA in early cancer detection
NCT05347524	O	R	Mar 2022	Gastric cancer with peritoneal metastasis	Sensitivity and specificity of cfDNA methylation-based assay for detecting peritoneal metastasis of gastric cancer
NCT05513144	O	R	Dec 2021	Advanced ERBB2-negative gastric cancer	Molecular changes over the course of disease progression may serve as a prognostic marker for diagnosis and treatment response
NCT05027347	O	R	Oct 2021	Early-stage gastric cancer	Sensitivity and specificity of a cfDNA assay for detecting early-stage gastric cancer
NCT05029869	O	R	Oct 2021	Gastric cancer after gastrectomy	Sensitivity of a cfDNA assay for monitoring minimal residual disease
NCT05059444	O	R	Sep 2021	Early-stage solid tumors treated	Detection of distant recurrence-free intervals in individuals treated for early-stage solid tumors
NCT05224596	O	R	Jan 2021	Gastric cancer	Sensitivity and specificity of a cfDNA methylation-based assay for detecting gastric cancer
NCT04253106	I	R	Nov 2020	Hereditary diffuse gastric cancer	Percentage of patients with somatic mutations or methylation profiles using liquid biopsy
NCT04484636	I	R	Oct 2020	Gastrointestinal cancer	Measurement of genomic profiles
NCT04943406	O	R	May 2020	Locally advanced gastric cancer	Overall and disease-free survival based on ctDNA positivity in peritoneal lavage and peripheral blood of patients with locally advanced gastric cancer
NCT03957564	I	R	May 2019	Gastric cancer, gastro-esophageal junction cancer	Detection of circulating tumor cells and cfDNA before and after neoadjuvant chemotherapy and surgery

The information of clinical trials was obtained from http://clinicaltrials.gov (accessed on October 2, 2023).
Abbreviations: O, observational; I, interventional; R, recruiting; N/R, not yet recruiting; cfDNA, cell-free DNA.

NGS-based cfDNA analysis using the Oncomine Pan-Cancer Cell-Free Assay (Thermo Fisher Scientific, Waltham, MA, USA) and AlphaLiquid 100 kit (IMBdx, Seoul, Korea). In this study of 81 patients with GC, 64.2% of patients (52/81) had tier I or II mutations, of whom 45 patients had mutations in genes amenable to potential targeted therapy and are in clinical trials. *ERBB2* amplification was detected in 4.9% of patients (4/81). Among other biomarkers showing potential for targeted therapy, *TP53* mutation (38.3%, 31/81) and *FGFR2* amplification (6.2%, 5/81) were the most frequently detected. The study showed that NGS-based cfDNA analysis provides accurate and reliable information on somatic genomic alterations in patients with GC and may replace tissue biopsy as a diagnostic and prognostic tool.

Liquid biopsy is currently applied in clinical practice [12, 13]. While tissue biopsy is an important method for detecting somatic mutations, the development of cfDNA assays and their implementation in clinical practice should be recognized as a valuable option for patients who do not have adequate tissue quantities for mutation testing or who refuse or are unable to undergo tissue biopsy. In particular, NGS-based molecular cfDNA profiling may be a valuable tool for the diagnostic and prognostic assessment of patients with GC, allowing a broader use of currently approved targeted therapies and ensuring proper treatment for each patient.

AUTHOR CONTRIBUTIONS

Jang MA wrote the manuscript and approved the final manuscript.

https://doi.org/10.3343/alm.2023.0391

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. International Agency for Research on Cancer, WHO. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer, https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf (Updated on Sep 2023).
2. National Comprehensive Cancer Network. Gastric Cancer: National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Version 2.2023. August 29, 2023.
3. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020;396:635-48.
4. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:1005-20.
5. Pietrantonio F, Miceli R, Raimondi A, Kim YW, Kang WK, Langley RE, et al. Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. J Clin Oncol 2019;37:3392-400.
6. Telekes A and Horváth A. The role of cell-free DNA in cancer treatment decision making. Cancers (Basel) 2022;14:6115.
7. Zhong Y, Xu F, Wu J, Schubert J, Li MM. Application of next generation sequencing in laboratory medicine. Ann Lab Med 2021;41:25-43.
8. Huffman BM, Aushev VN, Budde GL, Chao J, Dayyani F, Hanna D, et al. Analysis of circulating tumor DNA to predict risk of recurrence in patients with esophageal and gastric cancers. JCO Precis Oncol 2022;6:e2200420.
9. Grizzi G, Salati M, Bonomi M, Ratti M, Holladay L, De Grandis MC, et al. Circulating tumor DNA in gastric adenocarcinoma: future clinical applications and perspectives. Int J Mol Sci 2023;24:9421.
10. Lengyel CG, Hussain S, Trapani D, El Bairi K, Altuna SC, Seeber A, et al. The emerging role of liquid biopsy in gastric cancer. J Clin Med 2021;10.
11. Kim B, Kim Y, Cho J, Lee K. Identification of potential genomic alterations using pan-cancer cell-free DNA next-generation sequencing in patients with gastric cancer. Ann Lab Med 2023;44:164-73.
12. Cho SM, Lee HS, Jeon S, Kim Y, Kong SY, Lee JK, et al. Cost-effectiveness analysis of three diagnostic strategies for the detection of EGFR mutation in advanced non-small cell lung cancer. Ann Lab Med 2023;43:605-13.
13. Shin S, Woo HI, Kim JW, M D YK, Lee KA. Clinical practice guidelines for pre-analytical procedures of plasma epidermal growth factor receptor variant testing. Ann Lab Med 2022;42:141-9.

Corresponding author: Mi-Ae Jang, M.D., Ph.D.
Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
E-mail: miaeyaho@gmail.com

Key Words: Biomarkers, Cell-free nucleic acids, Disease-free survival, Genomics, High-throughput nucleotide sequencing, Liquid biopsy, Prognosis, Stomach neoplasms