

Concordances assessment between MET-positive circulating tumor cells and disease progression in patients with EGFR-mutated NSCLC



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Background

The use of EGFR-tyrosine kinase inhibitors (TKIs) has shown significant efficacy in treating non-small cell lung cancer (NSCLC) that carries an activating mutation in the epidermal growth factor receptor (EGFR). However, a **significant challenge in achieving long-term disease remission in clinical practice arises from the development of acquired resistance, specially, MET dysregulation**. Previously, we identified that monitoring MET-positive circulating tumor cells (CTC) could provide the information for predicting disease progression in hormone receptor positive metastatic breast cancer patients [1]. In this study, we investigated the concordance between MET-positive CTCs and disease progression in EGFR-mutated NSCLC patients.

Materials and Methods

Study design

- In this prospective, partially blind, single-center study, two hundred thirty-five patients with EGFR-mutated non small cell lung cancer (NSCLC) were enrolled during their standard treatment course at Samsung Medical Center (SMC), Seoul, Republic of Korea, between June 2022 and December 2023.
- Peripheral blood were collected in cell-free DNA blood collection tubes (Streck, La Vista, NE, USA) repeatedly from the patients during hospital visits.
- Disease progression was evaluated from the radiography images based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) guideline [2].
- Progression-free survival (PFS) was defined as the time from blood collection to radiological disease progression or death from any cause.

CTC enrichment and enumeration

- CTCs were isolated using GenoCTC® (Genobio Corp, Seoul, Republic of Korea), an immune magnetophoretic CTC isolation device, using the previously published method [3].
- Briefly, Each 4 ml blood sample was incubated with reagents for 30 minutes using MET-positive CTC isolation kits (Genobio Corp) according to the manufacturer's instruction. After incubation, the samples were loaded onto the GenoCTC® device for CTC isolation.
- Cells were stained using the GenoCTC profiling kit (Genobio Corp), then visualized and analyzed using the BioView DeNovo system (BioView Inc., Israel), an automated imaging and analysis platform.
- CTCs were defined as DAPI-positive, CK-18-positive, and CD45-negative cells.

Statistical analysis

- All data analyses were conducted using R Studio (v1.4.1103). A p-value of less than 0.05 was considered statistically significant. Categorical data were analyzed using the chi-squared test or Fisher's exact test. Concordance analysis was performed by determining the cutoff value based on the best Youden index from the ROC curve.

Results

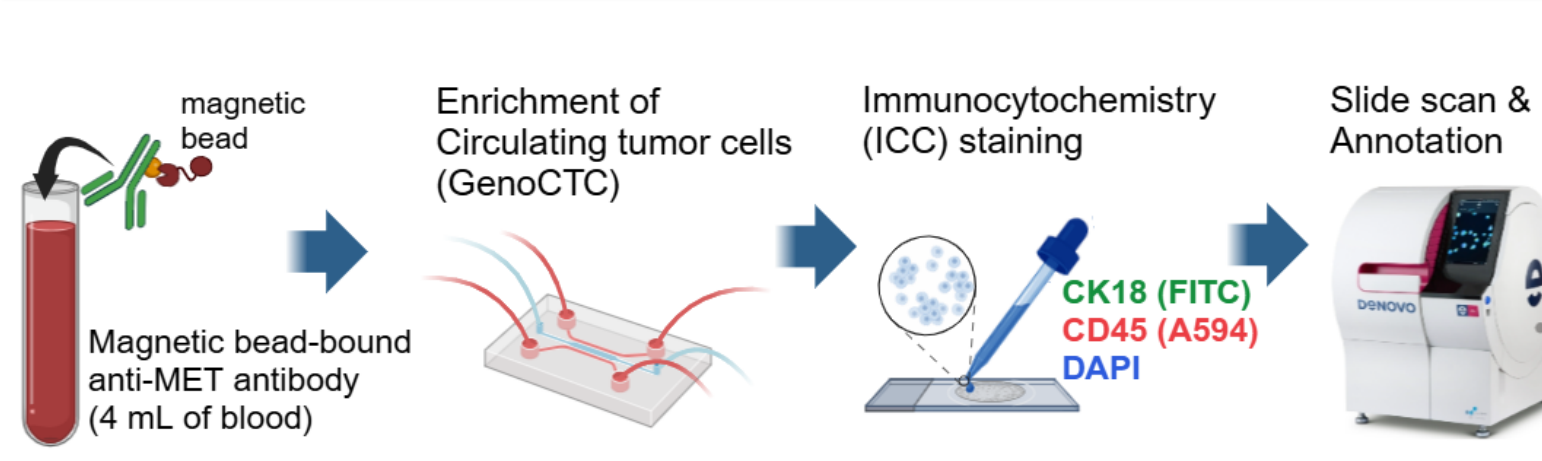


Figure 1. Schematic diagram of CTC enrichment and enumeration

Table 1. Patient demographic and clinical characteristics

	SUM	MET+CTC		p-value
		High (≥8)	Low (<8)	
Age at diagnosis				
<60	102 (43.4)	23 (51.1)	79 (41.6)	0.32
≥60	133 (56.6)	22 (48.9)	111 (58.4)	
Sex				
Male	96 (40.9)	18 (40.0)	78 (41.1)	1.00
Female	139 (59.1)	27 (60.0)	112 (58.9)	
Histology				
Adenocarcinoma	232 (98.7)	45 (100.0)	187 (98.4)	1.00
Squamous cell carcinoma	2 (0.9)	0 (0.0)	2 (1.1)	
Others	1 (0.4)	0 (0.0)	1 (0.5)	
Stage				
I,II	40 (17.2)	8 (18.2)	32 (16.9)	1.00
III,IV	193 (82.8)	36 (81.8)	157 (83.1)	
Unknown	2			
ECOG				
0	93 (39.6)	17 (37.8)	76 (40.0)	0.91
1	140 (59.6)	28 (62.0)	112 (58.9)	
2	2 (0.9)	0 (0.0)	2 (1.1)	
Smoking				
Never	153 (65.1)	31 (68.9)	122 (64.2)	0.68
Current/Former	82 (34.9)	14 (31.1)	68 (35.8)	
EGFR mutation				
Exon 21 L858R	99 (42.1)	19 (42.2)	80 (64.2)	1.00
Exon 19 del	136 (57.9)	26 (57.8)	110 (35.8)	
Line of therapy				
1	166 (70.9)	23 (51.1)	143 (75.7)	0.002
2	37 (15.8)	14 (31.1)	23 (12.2)	
≥3	31 (13.2)	8 (17.8)	23 (12.2)	
Treatment				
Chemotherapy	16	3 (6.7)	13 (6.9)	0.49
EGFR-TKI	212	40 (88.9)	172 (91.5)	
Others	4	2 (4.4)	3 (1.6)	

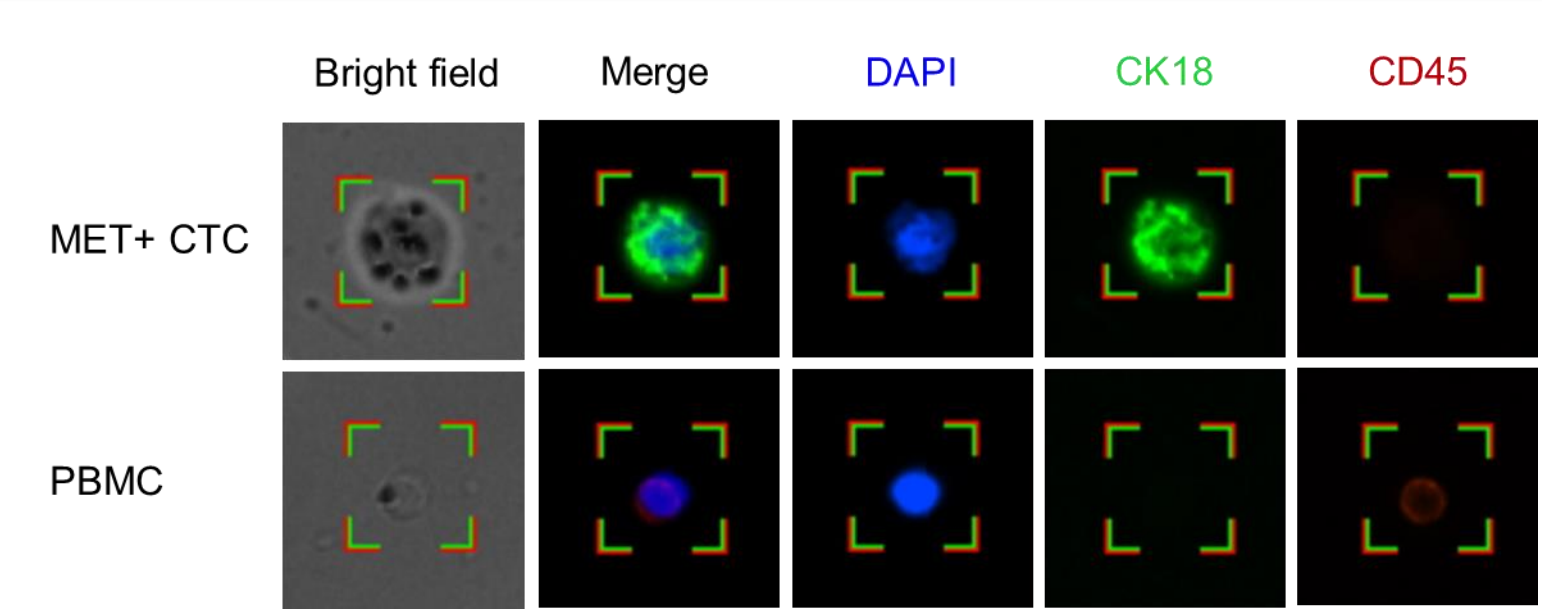


Figure 2. Representative images of MET-positive circulating tumor cell (MET+ CTC)

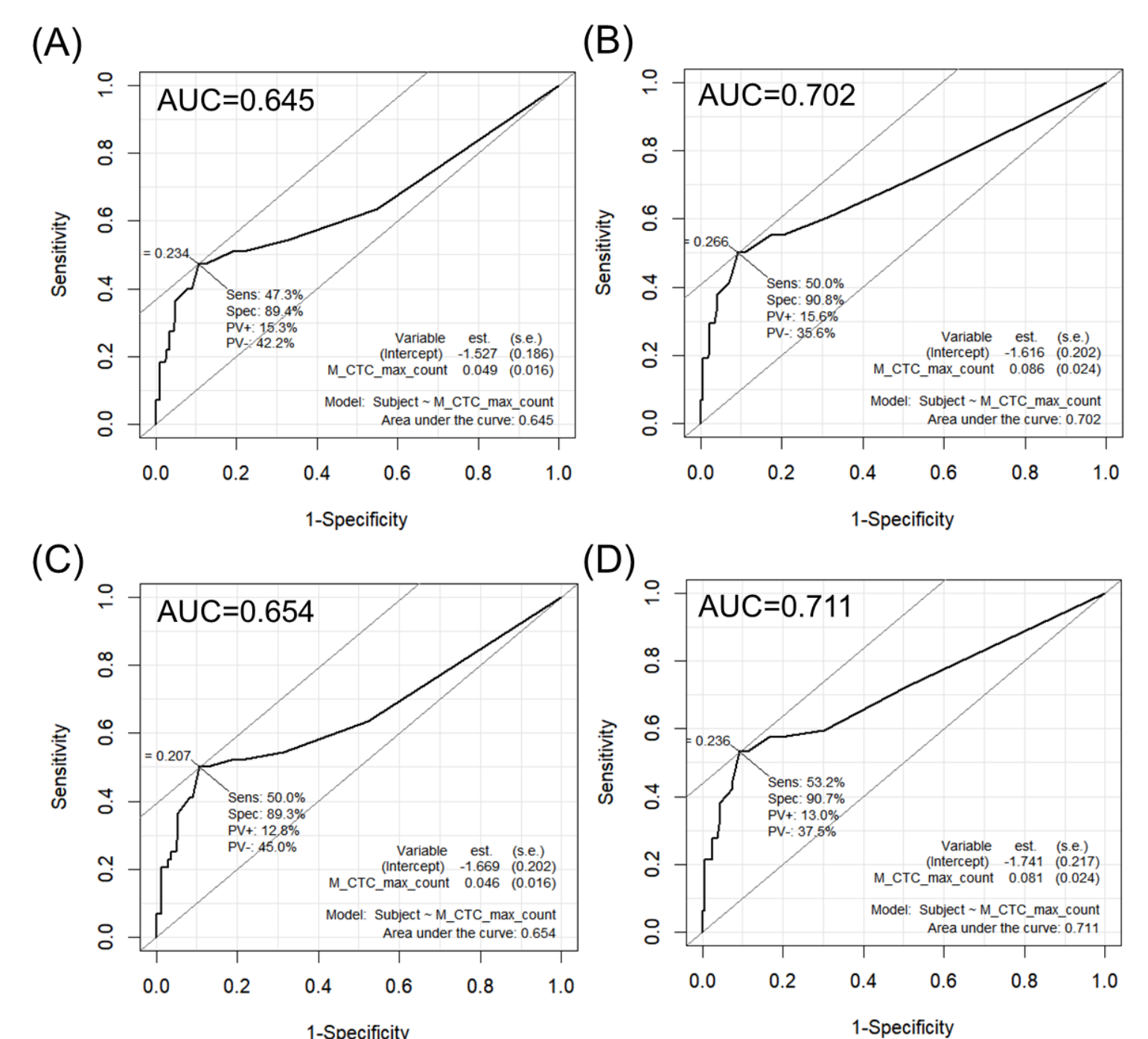


Figure 3. Receiver Operating Characteristic analysis based on the detection of MET+ CTCs and the presence of disease progression within 2 months (A, C) or 3 months (B, D) following CTC detection (A) and (B) show analyses for patients with EGFR common mutations, while (C) and (D) focus on those receiving EGFR-TKI therapy. CTCs, circulating tumor cells, AUC, Area under the curve

Table 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for detecting 8 or more MET+ CTCs and progression within 2 or 3 months.

	Progression within 2 months				Progression within 3 months			
	Total (n=235)		EGFR-TKI (n=212)		Total (n=235)		EGFR-TKI (n=212)	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Sensitivity	47.3	(33.6-61.2)	50.0	(34.6-65.4)	50.0	(36.6-63.4)	53.2	(38.1-67.9)
Specificity	89.4	(84.0-93.5)	89.3	(83.6-93.5)	90.8	(85.4-94.6)	90.7	(85.2-94.7)
PPV	57.8	(45.1-69.5)	55.0	(41.9-67.4)	64.4	(51.5-75.5)	62.5	(48.5-74.3)
NPV	84.7	(81.1-87.7)	87.2	(83.5-90.2)	84.4	(80.6-87.5)	87.0	(83.1-90.1)
Accuracy	79.6	(73.8-84.5)	81.1	(75.2-86.2)	80.5	(74.8-85.4)	82.3	(76.4-87.2)

CTCs, circulating tumor cells; CI, confidential interval

Conclusion

- Assessing disease progression within two months using MET-positive CTC detection showed moderate PPV with high specificity in the overall treatment cohort.
- This performance remained consistent for patients who received EGFR-TKI, suggesting that **MET-positive CTC might serve as an indicator for disease progression complementary to current imaging methods in EGFR-mutated NSCLC patients treated with EGFR-TKI**.

Acknowledgement & Disclosure

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References

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 [2] Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.
 [3] Micromachines (Basel). 2020 May 30;11(6):560. doi: 10.3390/mi11060560.

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