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# Prognostic significance of genetic variants in *GLUT1* in stage III non-small cell lung cancer treated with radiotherapy

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## Abstract

**Background:** To examine the impact of polymorphisms of glucose transporter 1 (*GLUT1*) gene on the prognosis of patients with stage III non-small cell lung cancer (NSCLC) who received radiotherapy.

**Methods:** Five single nucleotide polymorphisms (SNPs) (rs4658C>G, rs1385129G>A, rs3820589A>T, rs3806401A>C and rs3806400C>T) in *GLUT1* gene were evaluated in 90 patients with pathologically confirmed stage III NSCLC. A total of 21 patients were treated with radiotherapy alone, 25 with sequential chemoradiotherapy, and 44 with concurrent chemoradiotherapy. The association of the genetic variations of five SNPs with overall survival (OS) and progression-free survival (PFS) was analyzed.

**Results:** Two SNPs (rs1385129 and rs3806401) were significant risk factors for OS. Three SNPs (rs1385129, rs3820589 and rs3806401) were in linkage disequilibrium. In Cox proportional hazard models, GAA haplotype was a good prognostic factor for OS (hazard ratio [HR] = 0.57, 95% confidence interval [CI]: 0.39–0.81, p = 0.002) and PFS (HR = 0.68, 95% CI: 0.47–0.99, p = 0.043), compared to variant haplotypes. The GAA/GAA diplotype was observed in 46.7% of patients; these patients showed significantly better OS (HR = 0.38, 95% CI: 0.22–0.65, p < 0.001) and PFS (HR = 0.51, 95% CI: 0.31–0.85, p = 0.009) compared to those with other diplotypes.

**Conclusions:** These results suggest that polymorphisms of *GLUT1* gene could be used as a prognostic marker for patients with stage III NSCLC treated with radiotherapy.

**KEYWORDS**
GLUT1, non-small cell lung cancer, polymorphisms, radiotherapy

## INTRODUCTION

Lung cancer is the most common cancer and the leading cause of cancer-related deaths.[1] Non-small cell cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer; approximately 20% of these patients have stage III disease at diagnosis.[2] The treatment of stage III NSCLC has evolved from radiotherapy (RT) alone to sequential chemoradiotherapy (CRT) and concurrent CRT; the reported five-year overall survival (OS) rates are in the range of 10%–15%.[3] The staging system for NSCLC has been revised for more accurate prediction of survival outcomes; however, this system cannot provide clues for individualized treatment within the same stage group.

Metabolic reprogramming is an emerging hallmark of cancer.[4] Increased glycolysis under normoxic conditions, known as the Warburg effect, is a characteristic feature of cancer cells.[5–7] Cancer cells exhibit increased uptake of glucose as a compensatory mechanism against less efficient production of adenosine triphosphate by glycolysis compared to oxidative phosphorylation. Increased glycolytic metabolites play a pivotal role in the macromolecular biosynthesis and

organelles required for cell growth and proliferation.[5,6] The mechanism of increased glucose uptake by cancer cells involves specific glucose transporters; among these, glucose transporter 1 (GLUT1) is the most widely studied.[8] GLUT1 overexpression was shown to enhance proliferation, invasion, and migration of malignant cells.[9] Moreover, GLUT1 overexpression is known to be related to poorer outcomes in the context of various cancers including NSCLC.[10,11]

The GLUT1 is encoded by the solute carrier family 2, facilitated glucose transporter member 1 (*SLC2A1*) gene, located at 1p34.2. It is plausible that its genetic variations may affect glucose uptake and the consequent glycolytic metabolism in cancer cells, which may impact the post-treatment prognosis of cancer patients. However, the impact of *GLUT1* gene polymorphism on the prognosis of cancer patients treated with RT has not been reported. In a recent study, *GLUT1* genetic variations were found to be predictive biomarkers for NSCLC treated with surgery.[12]

Therefore, we investigated the clinical implications of the genetic variations of *GLUT1* gene on the survival outcomes of patients with stage III NSCLC treated with RT.

## METHODS

### Patients

This study included 90 patients with pathologically confirmed NSCLC who were treated with curative RT with or without chemotherapy. Among the patients with lung cancer who were treated between November 2010 and May 2018, those who met the following criteria were enrolled: clinical stage III disease based on the AJCC eighth staging system[13]; total radiation dose received: ≥54 Gy; no surgical resection performed after concurrent CRT without evidence of disease recurrence; and availability of blood sample stored in the National Biobank of Korea-KNUH. This study was approved by the Institutional Review Board of the Kyungpook National University Chilgok Hospital (approval No. KNUCH 2019-01-025) and the requirement for informed consent was waived in consideration of the retrospective nature of this study.

### SNP selection and genotyping

We selected SNPs of *GLUT1* gene and performed genotyping for the selected SNPs as described in the previous paper.[12] To identify potentially functional polymorphisms in GLUT1, we first searched the public single nucleotide polymorphism (SNP) database of the National Institutes of Health (http://www.ncbi.nlm.nih.gov/SNP) for all SNPs in *GLUT1* gene with minor allele frequency ≥0.05, based on the HapMap JPT data. Next, using the FuncPred utility for prediction of functional SNPs and the TagSNP utility for linkage disequilibrium (LD) tag SNP selection in the SNPinfo web server (https://snpinfo.niehs.nih.gov), five SNPs in *GLUT1* (rs4658C>G, rs1385129G>A, rs3820589A>T, rs3806401A>C, and rs3806400C>T) were identified after excluding those in LD ($r^2 \geq 0.8$). Genomic DNA was extracted from peripheral blood lymphocytes using blood QuickGene DNA whole blood kit S (Fujifilm). Genotyping was performed using the MassARRAY iPLEX assay (SEQUENOM Inc.). For genotype validation, approximately 5% of the cohort samples were randomly selected for repeat genotyping performed by a different investigator using a restriction fragment length polymorphism assay; the results were 100% concordant.

### Statistical analysis

The distribution of genotypes according to the clinicopathologic factors were compared using Pearson's $x^2$ test or Fisher's exact test. Hardy–Weinberg equilibrium was tested by comparing the observed and expected genotype frequencies using a goodness-of-fit $x^2$ test with 1 degree of freedom. The LD status among SNPs was determined using HaploView version 4.2.[14] LD blocks were inferred based on the definition proposed by Gabriel et al.[15] The haplotype frequencies were estimated based on a Bayesian algorithm using the Phase program (Phase version 2.1.1).[16]

OS and progression-free survival (PFS) were calculated from the start of RT to the date of event or the last follow-up using the Kaplan–Meier method. Between-group differences with respect to survival outcomes were assessed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariate Cox proportional hazards models after adjusting for age, tumor histology, clinical TNM stage, and treatment modality. All statistical analyses were performed using R statistics (version 4.0.0, The R Foundation for Statistical Computing). *p*-values <0.05 were considered indicative of statistical significance.

## RESULTS

### Patient characteristics

The median age was 68 (range: 45–85) years; 77 patients (85.6%) were male. The histological types were squamous cell carcinoma in 55 (61.1%), adenocarcinoma in 24 (26.7%), large-cell carcinoma in one (1.1%), and unspecified non-small cell carcinoma in 10 (11.1%) patients. The Eastern Cooperative Oncology Group performance status was 0–1 in 79 patients and 2 in 11 patients. Clinical stage was IIIA in 39 (43.3%), IIIB in 40 (44.4%), and IIIC in 11 (12.2%) patients. The treatment modalities were RT alone in 21 (23.3%) patients, sequential CRT in 25 (27.8%) patients, and concurrent CRT in 44 (48.9%) patients. Median values of total equivalent doses in 2-Gy fractions were 66 (range: 58.5–70.0) Gy in the RT group, 66 (range: 53.1–71.6) Gy in the sequential CRT group, and 66 (range: 58.4–70.0) Gy in the concurrent CRT group ($p = 0.193$). The most commonly used chemotherapeutic agents were paclitaxel/cisplatin in both sequential (11/25, 44.0%) and concurrent (41/44, 93.2%) groups.

**TABLE 1** Survival rates according to clinical factors

| Variables | No. of patients | Overall survival | | Progression-free survival | |
|---|---|---|---|---|---|
| | | 2YSR | *p*-value | 2YSR | *p*-value |
| Age (years) | | | | | |
| ≤68 | 46 (51.1%) | 60.7% | 0.011 | 14.3% | 0.919 |
| >68 | 44 (48.9%) | 25.0% | | 17.4% | |
| Sex | | | | | |
| Male | 77 (85.6%) | 36.4% | 0.011 | 15.9% | 0.762 |
| Female | 13 (14.4%) | 84.6% | | 16.7% | |
| Histology | | | | | |
| Adenocarcinoma | 24 (26.7%) | 79.2% | 0.001 | 16.4% | 0.258 |
| Others | 66 (73.3%) | 30.0% | | 15.8% | |
| Treatment modality | | | | | |
| RT alone | 21 (23.3%) | 19.1% | <0.001 | 5.9% | 0.010 |
| CRT | 69 (76.7%) | 50.6% | | 18.5% | |
| Stage | | | | | |
| IIIA | 39 (43.3%) | 43.3% | 0.453 | 17.6% | 0.142 |
| IIIB | 40 (44.4%) | 45.0% | | 19.2% | |
| IIIC | 11 (12.2%) | 36.4% | | 0.0% | |

Abbreviations: 2YSR, two-year survival rate; CRT, chemoradiation; RT, radiotherapy.

**TABLE 2** Information for five SNPs of GLUT1 gene and the association with survival outcomes

| | CR (%) | MAF | HWE-*p* | W/W | W/V | V/V | *p*-values for OS[a] | | | *p*-values for PFS[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CO | DO | RE | CO | DO | RE |
| rs4658C>G | 97.8 | 0.364 | 0.530 | 37 | 38 | 13 | 0.754 | 0.316 | 0.491 | 0.598 | 0.661 | 0.131 |
| rs1385129G>A | 97.8 | 0.216 | 0.949 | 54 | 30 | 4 | 0.013 | 0.003 | 0.711 | 0.284 | 0.157 | 0.752 |
| rs3820589A>T | 97.8 | 0.102 | 0.285 | 70 | 18 | 0[b] | 0.314 | 0.314 | NA | 0.123 | 0.123 | NA |
| rs3806401A>C | 97.8 | 0.188 | 0.526 | 59 | 25 | 4 | 0.005 | <0.001 | 0.655 | 0.521 | 0.385 | 0.813 |
| rs3806400C>T | 96.7 | 0.069 | 0.490 | 75 | 12 | 0[b] | 0.285 | 0.285 | NA | 0.575 | 0.575 | NA |

Abbreviations: CO, codominant model; CR, call rate; DO, dominant model; HWE-*p*, *p*-value for Hardy–Weinberg equilibrium; MAF, minor allele frequency; NA, not available; OS, overall survival; PFS, progression-free survival; RE, recessive model; V, variant allele; W, wild allele.

[a]Results of multivariate Cox proportional hazard models after adjusting for age, tumor histology, clinical TNM stage, and treatment modality.

[b]Since there were no patients with V/V genotype, the *p*-values of codominant and dominant models were identical for rs3820589 and rs3806400.

## Clinical factors and survival outcomes

The median follow-up period was 21 (range: 3–109) months. OS rates at two- and five-years were 43.2% and 17.4%, respectively. PFS rates at two- and five-years were 15.9% and 14.5%, respectively. The results of univariate analysis showing clinical predictors of survival outcomes are presented in Table 1. Age, sex, histological type, and treatment modality were significant prognostic factors for OS. Treatment modality was the only prognostic factor for PFS.

## GLUT1 polymorphisms and survival outcomes

All the five SNPs were in Hardy–Weinberg equilibrium. None of the five SNPs showed a significant association with clinical factors including age, sex, histological type, stage, or treatment modality, with the exception of rs3820589A>T. As for rs3820589, the AT genotype was associated with higher stage than AA genotype ($p = 0.032$), with no association with other factors.

Among the five SNPs studied, the rs1385129G>A and rs3806401A>C were significant prognostic factors for OS under both codominant and dominant models. The association of each SNP with survival outcomes is summarized in Table 2. Figure S1 shows the OS curves according to the genotypes of each SNP.

Among the five SNPs, three SNPs (rs1385129G>A, rs3820589A>T and rs3806401A>C) were in LD. Thus, we assessed the associations of the haplotypes of the three SNPs with survival outcomes. Four types of haplotype phase were inferred (Table S1). The survival curves of each haplotype are shown in Figure S2. In multivariate analyses, patients with the GAA haplotype showed significantly better OS

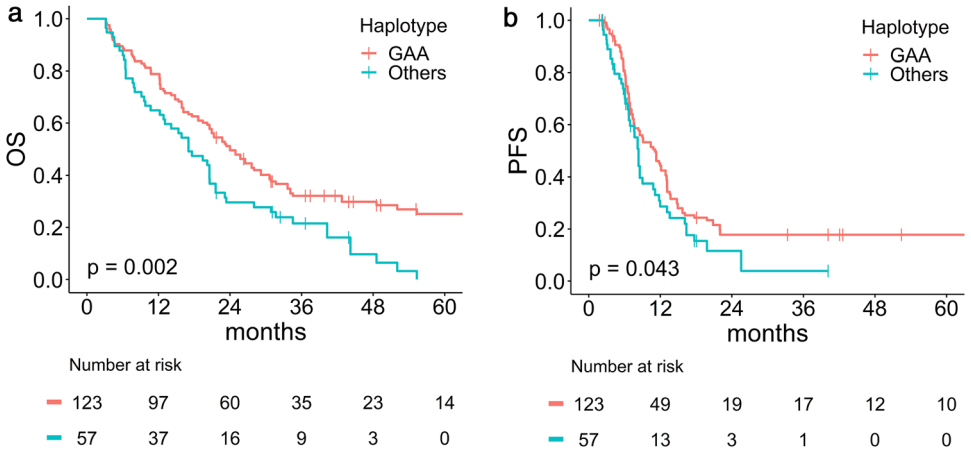


**FIGURE 1** Kaplan–Meier plots for (a) overall survival and (b) progression-free survival according to the haplotypes of three SNPs (rs1385129G>A, rs3820589A>T, and rs3806401A>C). *p*-values are from the multivariate Cox proportional hazards model

**TABLE 3** Multivariate analyses of the prognostic factors for overall survival and progression-free survival

| | | Overall survival | | Progression-free survival | |
|---|---|---|---|---|---|
| | | **HR (95% CI)** | ***p*-value** | **HR (95% CI)** | ***p*-value** |
| Haplotype | | | | | |
| Age | ≥68 vs. <68 | 1.63 (1.04–2.58) | 0.034 | 1.01 (0.64–1.61) | 0.967 |
| Histology | Adenocarcinoma vs. others | 0.49 (0.31–0.77) | 0.002 | 0.82 (0.55–1.24) | 0.356 |
| Stage | IIIB vs. IIIA | 1.61 (1.08–2.40) | 0.019 | 1.47 (0.97–2.22) | 0.067 |
| | IIIC vs. IIIA | 2.90 (1.61–5.23) | <0.001 | 2.47 (1.33–4.58) | 0.004 |
| Treatment | RT alone vs. CRT | 2.53 (1.63–3.95) | <0.001 | 2.59 (1.63–4.10) | <0.001 |
| Genotype | GAA vs. others | 0.57 (0.39–0.81) | 0.002 | 0.68 (0.47–0.99) | 0.043 |
| Diplotype | | | | | |
| Age | ≥68 vs. <68 | 1.80 (0.95–3.40) | 0.071 | 1.10 (0.58–2.09) | 0.773 |
| Histology | Adenocarcinoma vs. others | 0.49 (0.26–0.92) | 0.026 | 0.85 (0.48–1.49) | 0.562 |
| Stage | IIIB vs. IIIA | 1.66 (0.95–2.88) | 0.073 | 1.60 (0.89–2.86) | 0.116 |
| | IIIC vs. IIIA | 2.46 (1.07–5.62) | 0.033 | 2.39 (1.00–5.70) | 0.049 |
| Treatment | RT alone vs. CRT | 2.63 (1.40–4.92) | 0.003 | 2.64 (1.38–5.08) | 0.004 |
| Genotype | GAA/GAA vs. others | 0.38 (0.22–0.65) | <0.001 | 0.51 (0.31–0.85) | 0.009 |

Abbreviations: CI, confidence interval; CRT, chemoradiation; HR, hazard ratio; RT, radiotherapy.

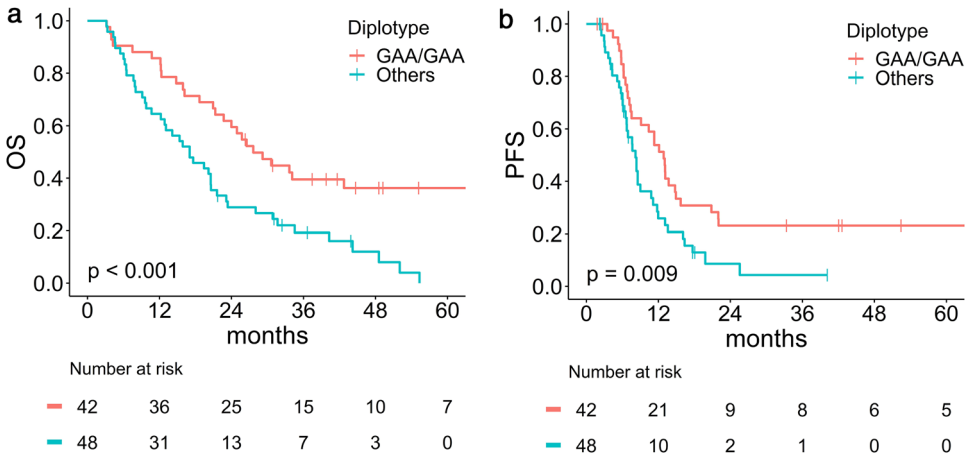


**FIGURE 2** Kaplan–Meier plots for (a) overall survival and (b) progression-free survival curves according to the diplotypes of rs1385129-rs3820589-rs3806401 haplotypes. *p*-values are from the multivariate Cox proportional hazards model

(HR = 0.57, 95% CI: 0.39–0.81, $p = 0.002$) and PFS (HR = 0.68, 95% CI: 0.47–0.99, $p = 0.043$) (Figure 1 and Table 3).

Among the seven types of diplotypes (Table S1), a homozygous pair of the GAA haplotype was the most common diplotype (46.7%). Survival curves of each diplotype

are shown in Figure S3. In multivariate analyses, patients with the GAA/GAA diplotype showed significantly better OS (HR = 0.38, 95% CI: 0.22–0.65, $p < 0.001$) and PFS (HR = 0.51, 95% CI: 0.31–0.85, $p = 0.009$) (Figure 2 and Table 3). The GAA/GAA diplotype was a favorable prognostic factor for OS in both adenocarcinoma (HR = 0.18, 95% CI: 0.04–0.76, $p = 0.020$) and squamous cell carcinoma (HR = 0.40, 95% CI: 0.20–0.79, $p = 0.008$), when analyzed in patients with each histological type of tumor (Tables S3 and S4).

## DISCUSSION

We evaluated the effect of *GLUT1* polymorphisms on the prognosis of patients with stage III NSCLC who were treated with RT with or without chemotherapy. Clinical factors including age, sex, histological subtype, and treatment modality were significant risk factors for OS in univariate analyses. On haplotype and diplotype analyses for the three SNPs with LD (rs1385129G>A, rs3820589A>T and rs3806401A>C), presence of wild-type haplotype of the three SNPs was an independent predictor of favorable OS and PFS.

GLUT1 overexpression is related to poor outcomes in various cancers including NSCLC.[10,11] In a study by Zhao et al[9]., GLUT1 significantly upregulated cyclin A, cyclin D1, cyclin E, cyclin dependent kinase 2 (CDK2), CDK4, CDK6, and matrix metalloproteinase 2, but downregulated p53 and p130 in NSCLC cell lines (A549 and LK2). In vitro assays showed that GLUT1 enhanced cell proliferation, invasion, and migration, but inhibited cell apoptosis. According to the authors, the effect of GLUT1 on the malignant phenotype of NSCLC was related to integrin β1/Src/focal adhesion kinase signaling. Guo et al.[17] conducted gene set enrichment analysis and found significant enrichment of 11 hallmark pathways (including, glycolysis, G2M checkpoint, mTORC1 signaling, and hypoxia) in lung adenocarcinoma with high GLUT1 expression. Therefore, it is plausible that functional polymorphisms in *GLUT1* gene may modulate the effect of GLUT1 on the prognosis of NSCLC.

The prognostic impact of polymorphisms of various cancer-related genes has been reported in NSCLC patients treated with RT.[18–20] However, the impact of *GLUT1* polymorphisms on the prognosis of patients with stage III NSCLC treated with RT has not been reported, even though metabolic reprogramming is a common phenomenon in NSCLC. Among the five SNPs (rs4658, rs1385129, rs3820589, rs3806401, and rs3806400) of the *GLUT1* gene, the rs1385129 and rs3806401 were associated with OS of patients with stage III NSCLC treated with RT in the current study, while rs4658 and rs3820589 were associated with OS in early-stage NSCLC treated with surgery in the study by Do et al.[12]

In genetic studies, phased data helps improve the statistical power by reducing the dimension of association tests.[21] Haplotype-based analysis showed a better performance than single SNP analysis with respect to discriminating the survival of NSCLC patients treated with RT and predicting radiation-induced skin toxicity in patients with breast cancer.[18,22] In the current study, a wild-type haplotype of rs1385129G-rs3820589A-rs3806401A was associated with better OS and PFS, even though individual SNPs of rs1385129 and rs3806401 were risk factors only for OS. Of note, the GAA/GAA diplotype was a predictor of good OS and PFS as compared to other diplotypes. Plateau of survival curves was observed only in patients with the GAA/GAA diplotype (Figure 2), even though the follow-up period was not long. These findings suggest that testing diplotypes of these three SNPs may help predict the prognosis of patients with stage III NSCLC.

The minor allele frequencies of five SNPs studied in the current study were similar to those reported in a Korean population (Table S2). In the current study, the minor allele frequencies of the three SNPs (rs1385129G>A, rs3820589A>T, and rs3806401A>C) were 15%–22%, and a GAA/GAA diplotype with all major alleles was observed in 46.7% of patients. This implies that approximately half of all NSCLC patients could be classified as having good prognosis based on haplotype analysis of these three SNPs. However, due to interethnic differences with respect to *GLUT1* polymorphisms (Table S2), our results need to be validated in different ethnic groups.

On the other hand, several studies have reported a difference in glucose metabolism between squamous cell carcinoma and adenocarcinoma. GLUT1 is more frequently overexpressed in squamous cell carcinoma than in adenocarcinoma.[11] *GLUT1* polymorphisms were associated with the prognosis of early-stage NSCLC undergoing surgical resection only for squamous cell carcinoma, not for adenocarcinoma.[12] However, in the current study, multivariate analyses showed the GAA/GAA diplotype was a significant good prognostic factor for OS in both adenocarcinoma and squamous cell carcinoma (Tables S3 and S4, Figure S4). The following evidence supports that *GLUT1* polymorphisms could be a predictive marker for adenocarcinoma as well as squamous cell carcinoma in stage III NSCLC treated with RT. Guo et al.[17] found that GLUT1 was significantly overexpressed in lung adenocarcinoma tissues compared with paired normal tissues, with a higher frequency in stage III patients than in stage I or II patients (27.9% for stage I vs. 33.3% for stage II vs. 46.5% for stage III, $p = 0.002$); in addition, overexpression of GLUT1 was associated with worse OS in the cohort sourced from public databases and in patients who underwent R0 resection at the authors' institution. Koh et al.[23] also reported GLUT1 overexpression in 50% of surgically resected lung adenocarcinoma; GLUT1 overexpression was related to worse OS.

This study has some limitations owing to the retrospective study design. Our results may have been affected by potential selection bias due to the small number of patients in various treatment groups. Moreover, we did not investigate the relationships between *GLUT1* polymorphisms and the expression level or functionality of GLUT1 protein.

In conclusion, among patients with stage III NSCLC who received RT with or without chemotherapy, those with

a homozygous pair of rs1385129G-rs3820589A-rs3806401A haplotype of *GLUT1* gene showed better survival outcomes compared to those with at least one variant haplotype. Our results suggest that testing the genotype of these three SNPs in addition to clinical factors may help identify subgroups that are at higher risk of poor outcomes. This is the first study to report the prognostic impact of *GLUT1* polymorphisms on the post-RT survival outcomes of patients with stage III NSCLC. Further investigations are warranted to validate our results.

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## CONFLICT OF INTEREST

The authors declare that there no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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