^{18}F-fluorodeoxyglucose Uptake with Expression of Excision Repair Cross-complementary Group 1 and Ribonucleotide Reductase Subunit M1 in Non-small Cell Lung Cancer

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Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is widely applied in non-small cell lung cancer (NSCLC). The standardized uptake value (SUV), a semi-quantitative index, plays an essential role in NSCLC for diagnosis, staging, and efficacy evaluation. It has been proposed that the SUV_{max} of tumors may correlate with the presence or absence of chemotherapy resistance-associated biomarkers based on studies that have displayed a close correlation between SUV_{max} and the expression levels of excision repair cross-complementary Group 1 (ERCC1)[1] and Tp53-induced glycolysis and apoptosis regulator.[2] FDG avidity of NSCLC and ERCC1 and ribonucleotide reductase subunit M1 (RRM1) levels have not been as extensively investigated. Based on these findings, we looked for correlations among metabolic parameters (SUV_{max}, metabolic tumor volume [MTV], and total lesion glycolysis [TLG]) and *ERCC1* and *RRM1* expression in patients with NSCLC, to investigate whether FDG uptake reflects the presence or absence of chemoresistance proteins (ERCC1 and RRM1) within tumor cells.

The study was approved by the Medical Ethics Committee of The Second Xiangya Hospital, Central South University, China. All individuals signed written informed consent. The cases of 89 patients with curatively resected Stage I or II adenocarcinoma or squamous cell NSCLC, for which paraffin-embedded tumor specimens and preoperative PET/CT scans were available, were enrolled. SUV_{max}, MTV, and TLG were calculated. PET/CT images were analyzed by experienced nuclear physicians blinded to the clinical history using a workstation (MEMRS Workstation 6.6, MedEX, Beijing, China). The maximum diameter of the tumor was measured on CT mediastinal windows. The SUV_{max} was automatically calculated by drawing regions of interest around the lung cancer nodules on the fused images. MTV was calculated using a fixed threshold SUV of 2.5. TLG was calculated as the product of MTV multiply SUV_{mean}.

Nuclear (ERCC1) and cytoplasmic (RRM1) expression of the biomarkers was measured with immunohistochemical staining. All immunostained sections were reviewed under a light microscope (Olympus, Japan) at ×400 magnification by an experienced pathologist, looking for cytoplasmic staining of RRM1 and nuclear staining of ERCC1. The ERCC1 and RRM1 concentrations in each case were estimated by a semi-quantitative H-score according to the intensity of staining. Spearman's correlation analysis was employed to confirm the relationship between different parameters. Binary logistic regression analysis with the optimum metabolic parameters was used to predict *ERCC1* and/or *RRM1* expression. Receiver operating characteristic (ROC) curves of the PET/CT metabolic parameters (SUV_{max}, MTV, and TLG) for the prediction of *ERCC1* and/or *RRM1* expression were generated to ascertain the cutoff value which yielded a maximum sensitivity and specificity. $P < 0.05$ indicated a statistically significant

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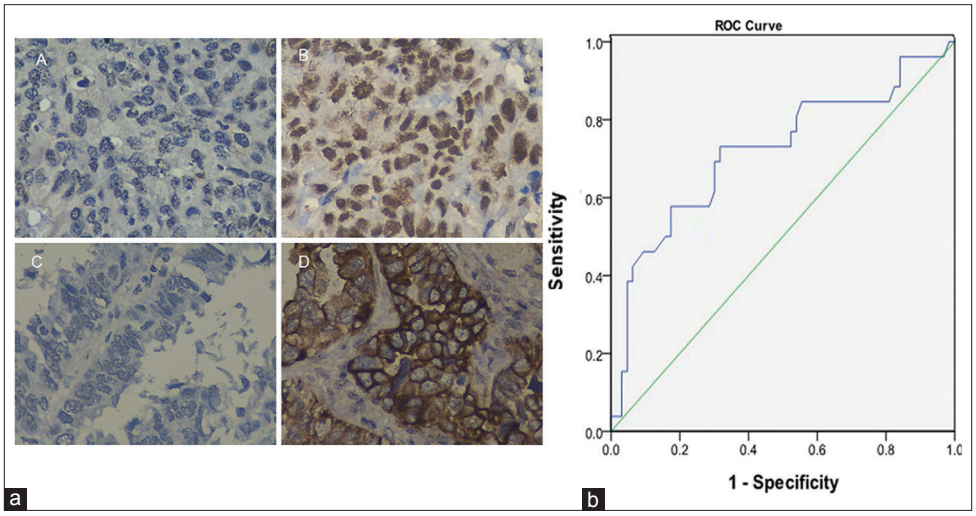

Figure 1: (a) Representative immunohistochemistry images: immunohistochemical stains for (A, negative; B, positive) ERCC1 and (C, negative; D, positive) RRM1 (original magnification ×400). (b) ROC curves of the SUV_{max} for the prediction of *RRM1* expression. Area under the curve: 0.719; 95% *CI*: 0.591–0.846; $P = 0.001$. A SUV_{max} ratio of 10.2 or lower suggests a NSCLC to be RRM1 negative with a sensitivity of 73.1% and specificity of 68.3%. ERCC1: Excision repair cross-complementary Group 1; RRM1: Ribonucleotide reductase subunit M1; *CI*: Confidence interval; SUV_{max}: Maximum standardized uptake value; NSCLC: Non-small cell lung cancer.

difference. Of the 89 cases, 67 (75.3%) were ERCC1 positive and 63 (70.8%) were RRM1 positive [Figure 1a]. No significant correlation was found between SUV_{max}, MTV, or TLG and the expression of ERCC1 ($P = 0.135$, 0.170, and 0.422). RRM1 expression correlated negatively with SUV_{max} ($r = -0.360$, $P = 0.001$), MTV ($r = -0.290$, $P = 0.006$), and TLG ($r = -0.315$, $P = 0.003$). Binary logistic regression analysis revealed SUV_{max} to be the optimal index reflecting the expression of RRM1. ROC curve analysis revealed that the area under curve is 0.719 with 95% confidence interval ranging from 0.591 to 0.846 ($P = 0.001$). ROC also demonstrated that the optimal cutoff value of SUV_{max} to predict RRM1 negativity was 10.2, which was associated with 73.1% sensitivity and 68.3% specificity [Figure 1b].

This study evaluated the correlation of two tumor markers of chemotherapy resistance in NSCLC with FDG PET/CT. Duan *et al*.[3] suggested a correlation between SUV_{max} and ERCC1 levels in NSLCLC, but when they used multiple stepwise regression analysis detected no robust correlation, so based on their study, it is still inconclusive whether SUV_{max} can be applied to determine ERCC1-related chemotherapy resistance. Our results were similar to their study. Our data also did not find any significant difference in FDG avidity between the ERCC1-positive and ERCC1-negative groups. In another study, their results showed that *ERCC1* expression had a statistically significant relationship with the degree of FDG uptake in thymic epithelial tumors (especially thymoma).[4] Further larger studies may be needed to confirm whether the FDG avidity of NSCLC or other tumors can be used as an indicator of *ERCC1* expression. RRM1 can predict and monitor the response of NSCLC patients to gemcitabine.[5] A feature of our study was first analyzing the correlation between *RRM1* expression and the degree of FDG avidity of NSCLC. Our results displayed that *RRM1* expression is negatively correlated with tumor SUV_{max}, MTV, and TLG in patients with NSCLC. The optimal cutoff value of SUV_{max} was approximately 10.1. However, the results have only 73.1% sensitivity and 68.3% specificity and have not been correlated with clinical outcome. According to our findings, ^{18}F-FDG PET/CT might serve as a simple and practical noninvasive method for predicting *RRM1* expression in NSCLCs, allowing the tailoring of chemotherapy to exclude gemcitabine if expression is elevated. Larger sample bench studies and clinical trials need to assess these findings' clinical applicability.

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Conflicts of interest

There are no conflicts of interest.

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