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Urine Metabolomics Reveals Response-Specific Biomarkers in Non-small Cell Lung Cancer Patients Undergoing Carbon Ion Radiotherapy

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Objectives

Carbon ion radiotherapy (CIRT) offers promising outcomes for non-small cell lung cancer (NSCLC) patients, yet treatment response varies significantly. This study aimed to identify urinary metabolic signatures predictive of CIRT outcomes and develop a non-invasive prognostic tool to guide treatment decisions.

Methods

We collected paired pre- and post-treatment urine samples from 153 stage III NSCLC patients undergoing curative-intent CIRT (70-80 Gy(RBE) in 20-22 fractions). Patients were classified as responders (complete/partial response or stable disease; 58.2%) or non-responders (progressive disease; 41.8%). Urinary metabolomics analysis was performed using Ultra-High Performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometer (UHPLC-QTOF-MS) with both reversed-phase and Hydrophilic Interaction Liquid Chromatography (HILIC) separation modes. Data processing was conducted using our self-developed MetaboQuality v1.0 software (2023SR0256527). Predictive modeling employed our proprietary MetaboClinCore v1.0 R-based platform, implementing feature selection, class imbalance handling, and model validation.

Results

A 23-metabolite urinary signature achieved excellent predictive performance in an independent test cohort. Glutamine emerged as the strongest positive predictor of non-responder (coefficient +0.758), while 1-(3,4-dimethoxyphenyl) ethane-1,2-diol showed the strongest negative correlation (coefficient -0.431). The signature encompassed diverse metabolic pathways including amino acid metabolism (glutamine, phenylalanine), gamma-glutamyl cycle (gamma-glutamyl-glycylglycine, gamma-glutamylvaline), energy metabolism (cis-4-decenoylcarnitine, 3-methylglutarylcarnitine), and xenobiotic metabolism. Feature importance analysis revealed that treatment non-response was associated with elevated glutamine, aromatic sulfates, and specific plant-derived compounds, while responder correlated with altered phenylalanine metabolism, modified nucleosides, and carbohydrate dysregulation.

Conclusions

We established the first comprehensive urinary metabolic signature for predicting CIRT response in NSCLC patients. This non-invasive biomarker panel enables early identification of potential non-responders before or during treatment. The distinctive metabolic patterns provide insights into the biological determinants of carbon ion radiation sensitivity and suggest potential targets for enhancing treatment efficacy.The predictive model based on urinary metabolites offers a completely non-invasive approach for monitoring and predicting CIRT outcomes, facilitating personalized treatment decisions and potentially improving clinical outcomes for locally advanced NSCLC patients.