INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide. It is often diagnosed owing to symptoms of advanced disease. This underscores the importance of a screening tool which allows to detect early stage lung cancer.

A promising tool for lung cancer screening is low-dose computed tomography, which has recently been shown to reduce lung cancer mortality by 20% compared with screening using chest radiography. However, it has several limitations, such as a low positive predictive value and high costs.

These limitations encourage the search for complementary, non-invasive tools which enable to detect early stage lung cancer.

Accumulating evidence has shown that the metabolism of cancer cells differs from that of normal cells. More specifically, the entire metabolism of cancer cells is reorganized to favor anabolic reactions which induce cell growth and survival. Disturbances in biochemical pathways which occur during the development of cancer provoke changes in the metabolic phenotype.

Nuclear magnetic resonance (NMR) spectroscopy enables a fast, non-invasive identification and quantification of complex mixtures of metabolites, as in blood plasma, in a single run and without extended sample preparation.

OBJECTIVES

1) Investigate whether the metabolic phenotype of blood plasma determined by 1H-NMR spectroscopy can be used to distinguish lung cancer patients and 226 controls (training cohort)
2) Examine the predictive accuracy of the metabolic phenotype by external validation in an independent validation cohort of 98 lung cancer patients and 89 controls
3) Explain the disturbed biochemical pathways in lung cancer

SUBJECTS AND METHODS

Study population

The lung cancer patients from both cohorts were included in the Limburg Positron Emission Tomography center (Hasselt, Belgium) and at the Department of Respiratory Medicine of University Hospitals Leuven (Leuven, Belgium). The diagnosis of lung cancer was confirmed by means of a pathological biopsy or by a medical doctor with expertise in radiological or clinical data. The control groups of both cohorts consist of patients with non-cancer diseases who were referred to the department of Nuclear Medicine in Ziekenhuis Oost-Limburg (Genk, Belgium) for a stress myocardial perfusion scintigraphy for the detection of coronary artery disease. The study was approved by the ethical committees of Ziekenhuis Oost-Limburg (Genk, Belgium), Hasselt University (Hasselt, Belgium) and University Hospitals Leuven (Leuven, Belgium).

1H-NMR spectroscopy

Figure 1. Determination of the metabolic phenotype by 1H-NMR-based metabolomics.

• Collection of fasting venous blood samples from lung cancer patients and controls.
• Analysis of the metabolic composition of blood plasma by means of a 400 MHz NMR spectrometer.
• The 1H-NMR spectra were segmented into 112 variable-sized spectral regions based on spiking experiments with known metabolites. After excluding water and TSP, the remaining 110 regions were integrated and normalized relatively to the total integrated area of all regions, resulting in 110 normalized integration values, being the variables for multivariate statistics.

Multivariate statistics

• Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to construct a statistical classifier (model) to discriminate between lung cancer patients and controls.
• The predictability of the model was assessed by means of external validation in an independent cohort. Furthermore, model robustness was evaluated by means of a receiver operating characteristic (ROC) curve.

RESULTS

Table 1. Subject characteristics of the training and validation cohort.

Table 2. Pathological diagnosis and stage of the lung tumors.

CONCLUSION

• Metabolic phenotyping of blood plasma by means of 1H-NMR spectroscopy can become an important tool to stratify high-risk individuals before subsequent screening with low-dose computed tomography.

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