METABOLIC PHENOTYPE BY NMR SPECTROSCOPY: A BIOMARKER FOR LUNG CANCER

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INTRODUCTION

- Globally, lung cancer is the most common cancer in men and the 4th in women. Moreover, it is the leading cause of cancer death worldwide.
- Until today no effective methods allow the early detection of lung cancer. Consequently, it is often only diagnosed at a metastatic stage. To address this problem, early detection methods with an improved specificity and sensitivity are urgently needed.
- The entire metabolism of cancer cells is reprogrammed to increase anabolic reactions that induce cell growth and proliferation (**Figure 1**). Disturbances in biological pathways which occur during the development of cancer provoke changes in the metabolic phenotype.

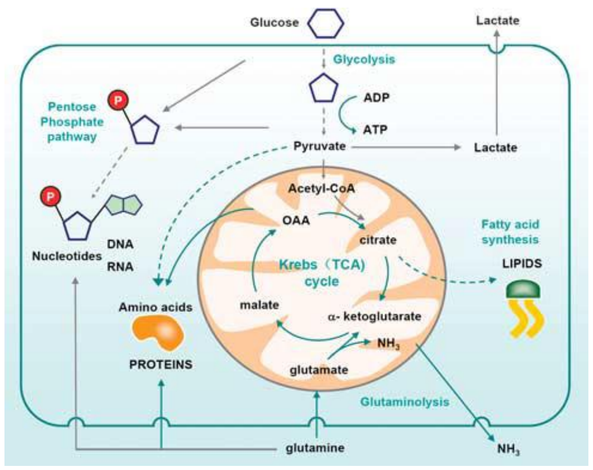


Figure 1. Reprogrammed metabolism of cancer cells

- Nuclear magnetic resonance (NMR) spectroscopy enables the identification and the quantitative analysis of complex mixtures of metabolites, as in plasma and serum, without an extended sample preparation. Recent studies have indicated the huge potential of this technique to detect different cancer types in an early stage. For several diseases, changes in the metabolic phenotype have been shown to correlate with the presence of a certain pathology. Identifying which changes in the metabolic phenotype correlate with the presence of lung cancer could allow us on the long-term to easily detect the presence of lung cancer in a simple blood sample.

HYPOTHESIS

Metabolic phenotype analyses by NMR spectroscopy permit the early detection of lung cancer

SUBJECTS AND METHODS

Study population

Patients with a new lesion in the lung detected by means of computed tomography (CT), were referred to a positron emission tomography (PET)/CT-scan in the *Limburg PET Center* (LPC) and included. These patients were referred by medical doctors from different hospitals in Limburg, namely Ziekenhuis Oost-Limburg (ZOL, Genk), Algemeen ziekenhuis Vesalius (AZV, Tongeren), Mariaziekenhuis Noord-Limburg (MZNL, Overpelt) and Ziekenhuis Maas en Kempen (ZMK, Maaseik). The diagnosis of lung cancer was confirmed by means of an anatomopathological research of a biopsy. Furthermore, a control group was included which consists of patients without oncology prehistory during the last 5 years and which did not undergo a CT- or a PET-scan. The study protocol was approved by the medical-ethical committees of ZOL and the University of Hasselt.

- Collection of fasting blood samples
- Analysis of the metabolic composition of blood plasma by means of a 400 MHz NMR spectrometer
- Calculation of metabolic differences between lung cancer patients and control subjects by Mann-Whitney tests and supervised orthogonal partial least squares-discriminant analyses (OPLS-DA)
- Identification and quantification of metabolites/targets and interpretation of involved biological pathways

NMR spectroscopy

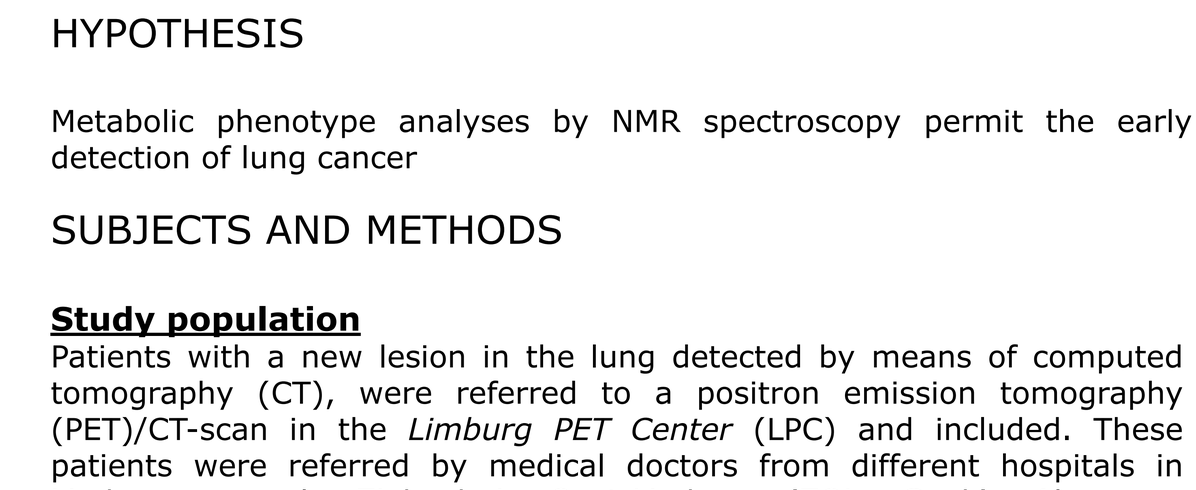


Figure 2. Determination of the metabolic phenotype of a blood sample by means of NMR spectroscopy

RESULTS

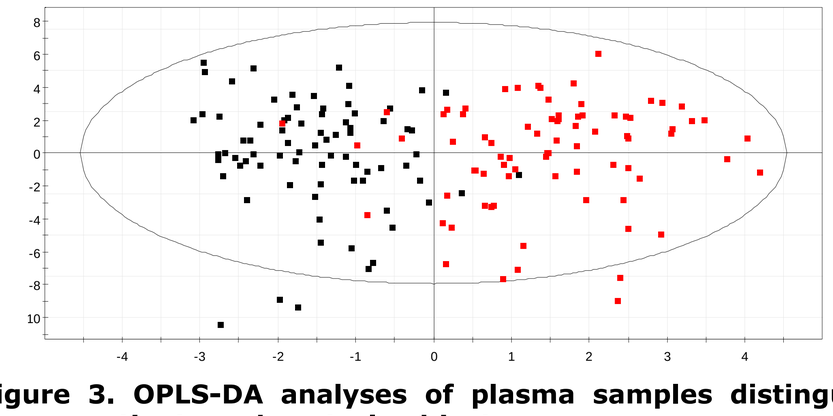
Subject characteristics

	Lung cancer patients	Control subjects
Number of patients	79	78
Gender	Male: 53 (67%) Female: 26 (33%)	Male: 45 (58%) Female: 33 (42%)
Average age	68 ± 1	64 ± 1
Average BMI	25,6 ± 0,5	26,7 ± 0,6
Smoking habits	Active: 51 Stopped > 6m: 25 Never: 3	Active: 19 Stopped > 6m: 27 Never: 32
Average number of pack years (1 pack year: smoking of 1 pack of cigarettes a day during one year)	37 ± 4	17 ± 3

Table 1. Subject characteristics

Discrimination between lung cancer patients and control subjects based on their metabolic phenotype

- The metabolic phenotype of 79 lung cancer patients (■) and 78 control subjects (■) was analyzed by means of NMR spectroscopy
- By means of OPLS-DA analyses on a well-defined and selected panel of metabolites present, a high degree of discrimination between control subjects and lung cancer patients was achieved with a specificity of 96% and a sensitivity of 94%



- Specificity: 96%
- Sensitivity: 94%

Figure 3. OPLS-DA analyses of plasma samples distinguish between lung cancer patients and control subjects

FUTURE RESEARCH

- Find out which targets/biological pathways contribute to the development of lung cancer
- Evaluate the statistical classifier (the model which contains the main metabolites contributing to the discrimination between lung cancer patients and control subjects) in a new and bigger patient population (250 lung cancer patients and 250 control subjects)
- Investigate whether metabolic changes in the blood correlate with metabolic perturbations in the tumor, visible on a PET-scan
- Examine whether patients who respond to a specific therapy can be discriminated from patients who do not respond based on metabolic changes in the blood

ACKNOWLEDGEMENT

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