Progastrin-releasing peptide (proGRP)

and its role in the differential diagnosis in lung cancer and management of small cell lung cancer patients

Key publication abstracts

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Lung cancer is one of the most common cancers in the world with 1.35 million new cases diagnosed every year and represents approximately 13 % of all new cancers. It is also one of the most common causes of death from cancer. Lung cancer is still the most common cancer worldwide in men (1.1 million cases, 16.5 % of the total). In females, incidence rates are generally lower, but worldwide, lung cancer is now the fourth most frequent cancer in women (516,000 cases, 8.5 % of all cancers). Almost half of the cases of lung cancer occur in developing countries, with men being affected more than women. The major risk factor to develop lung cancer is smoking.

There are two main histological types of the disease, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which is a neuroendocrine tumor. NSCLC is the most common form, accounting for approximately 80 % of all cases.

It is important to distinguish between these two subtypes as they have different treatments and prognoses. Whereas the early stages of NSCLC can be cured by surgery, SCLC is an aggressive neoplasm of rapid growth with high sensitivity to chemo- and radiotherapy. Often there is metastasis into regional lymph nodes and/or distant organs at the time of SCLC diagnosis.

Data from cancer epidemiology database: http://globocan.iarc.fr/, accessed on January 2013.

ProGRP is the precursor form of Gastrin-releasing peptide (GRP). GRP is an important regulatory molecule that has been implicated in a number of physiological and pathophysiological processes in humans. GRP is a gut hormone and the mammalian counterpart of amphibian bombesin, originally isolated from porcine stomach and widely distributed throughout the mammalian nervous system and gastrointestinal and pulmonary tract. Its 148 amino acid preproprotein, following cleavage of a signal peptide, is further processed to produce the 27 amino acid **GRP and the 68 amino acid peptide ProGRP.**

GRPs are thought also to be produced by cells of SCLC where they act in the metastatic process via their autocrine activity or through cell-to-cell interactions. Due to its short half-life of 2 min. it is difficult to determine GRP in blood. Therefore, ProGRP which has a longer half-life in blood can be measured by immunoassays.

ProGRP is a specific tumor marker in patients with SCLC

Kim, H.-R. et al. (2011). Plasma ProGRP concentration is sensitive and specific for discriminating small cell lung cancer from nonmalignant conditions or non-small cell lung cancer. Oncology &Hematology, 26, 625-630.

This study evaluated the agreement between ProGRP levels in fresh serum and plasma in patients with various lung diseases. Pairs of serum and EDTA plasma were collected from 49 healthy individuals. At the same time, EDTA plasma from 118 lung cancer patients and 23 patients with benign pulmonary diseases were prospectively collected. Plasma ProGRP was higher in malignancy than in benign conditions. SCLC patients showed higher levels of ProGRP compared to other types of lung cancer. Based on the ROC curve analyses at a specificity of 95 %, the diagnostic sensitivity of plasma ProGRP was estimated to be 83.8 % in distinguishing SCLC from all the other conditions, and 86.5 % for discriminating SCLC from the nonmalignant cases. Among the SCLC cases, limited stage disease had lower levels of plasma ProGRP than extensive disease.

ProGRP is a biomarker for the early detection of SCLC

When ProGRP was used by itself, sensitivity in the range of 47 – 86 % was found for patients with SCLC. The detection rate even for patients with limited disease was about 70 %.

Molina, R. et al. (2005). Pro-gastrin-releasing peptide (proGRP) in patients with benign and malignant diseases: comparison with CEA, SCC, CYFRA 21-1 and NSE in patients with lung cancer. Anticancer Res., 25, 1773-1778.

When ProGRP was used in combination with neuron-specific enolase (NSE) and squamous cell carcinoma antigen (SCC), sensitivity was 79.5 % and specificity was 99.6 %. The negative predictive value (NPV) was 92.9 % and positive predictive value (PPV) was 98.6 %.

Molina, R. et al. (2009). Usefulness of serum tumor markers, including progastrin-releasing peptide, in patients with lung cancer: correlation with histology. Tumour Biol., 30, 121-129.

In this meta-analysis 5146 subjects were included. The sensitivity and specificity (95 % confidence interval) of ProGRP was 0.716 (0.688 – 0.743) and 0.921 (0.909 – 0.932), respectively. The area under the receiver operating characteristic curve of ProGRP was 0.9236.
ProGRP has better sensitivity and high specificity as an auxiliary indicator for the diagnosis of small cell lung cancer.

Hui-jie ,Y. et al. (2011). Diagnostic value of pro-gastrin-releasing peptide for small cell lung cancer: a meta-analysis. Clin. Chem. Lab. Med., 49, 1039-1046.

ProGRP is the tumor marker of choice in SCLC and can be used for the differential diagnosis in lung cancer

Molina, R. et al. (2004). Progastrin-releasing peptide in patients with benign and malignant diseases. Tumor Biology, 25, 56.

In a study with 37 healthy subjects, 197 patients with benign diseases and 310 patients with malignant diseases of different origins, specificity and sensitivity of ProGRP was evaluated. None of the healthy subjects had abnormal ProGRP levels. Raised ProGRP values (<80 ng/mL) were found in 2.5 % (4/160) of patients with benign diseases and in 4.9 % of patients with active malignancies other than lung cancer or neuroendocrine tumors (<110 ng/mL). Abnormal ProGRP serum levels were found in 26.2 % of patients with non-small cell lung cancer (NSCLC) and in 76.8 % of patients with small cell lung cancer (SCLC). ProGRP serum levels >300 pg/mL were only found in SCLC patients (41.4 %). ProGRP results were related to tumor extension in SCLC (sensitivity in limited disease 58.3 %, in extensive disease 95.5 %) but not in NSCLC. The most frequent source of false-positive results with ProGRP was renal failure.

Cho, W.C. (2007). Potentially useful biomarkers for the diagnosis, treatment and prognosis of lung cancer. Biomed Pharmacother., 61, 515-519.

ProGRP concentrations of >200 pg/L are highly suspicious for lung cancer and >300 pg/L for SCLC if renal function is not impaired.

In a retrospective study with a total of 1,747 patients, ProGRP had a 57 % diagnostic efficacy (true positive results) in SCLC patients at 99 % specificity. In combination with cytokeratin fragment 19 (CYFRA 21-1), carcinoembryonic antigen (CEA), and NSE, ProGRP could identify 78 % true positives for SCLC at > 99 % specificity.

Gruber, C. et al. (2008). CEA, CYFRA 21-1, NSE, and ProGRP in the diagnosis of lung cancer: a multivariate approach. J Lab Med, 32, 361–371.

ProGRP is elevated in 68 – 86 % of patients with SCLC, 4 – 30 % of NSCLC patients, 0 – 7 % of patients with benign lung disease, and 0 % of healthy controls.

Gastrin-releasing peptide: different forms, different functions. Biofactors 2009, 35, 69-75.

In a study with 66 SCLC and 175 NSCLC patients, SCC <2 ng/mL always identified NSCLC patients whereas ProGRP >100 ng/L and NSE >35 ng/mL always identified SCLC patients.

Molina, R. et al. (2009). Usefulness of serum tumor markers, including progastrin-releasing peptide, in patients with lung cancer: correlation with histology. Tumour Biol., 30, 121-129.

ProGRP alone or in combination with NSE is helpful to monitor therapy response in SCLC patients

Schneider, J. et al. (2003). Pro-gastrin-releasing peptide (ProGRP) and Neuron specific enolase (NSE) in therapy control of patients with small-cell lung cancer. Clin. Lab., 49, 35-42.

In this prospective study ProGRP was compared to the established marker NSE. 34 consecutive SCLC patients were included and the changes of the blood levels of ProGRP and NSE were compared to the clinical evaluation. 19 patients had remission, 8 with stable disease and 7 with tumor progression while under therapy. NSE and ProGRP were measured in sera before and after treatment with polychemotherapy. After tumor remission, NSE and ProGRP levels decreased significantly under treatment. As suspected, pre- and post-treatment marker concentrations did not differ significantly in patients with stable disease. In progressive SCLC patients, an increase of ProGRP and NSE were detected. Overall, a decrease of NSE was seen in 95 % of all responders, while an increase during progression could be detected in 86 % of the patients. A long-term follow-up indicated that ProGRP can be used to monitor disease either with tumor regression under therapy as well as detection of subsequent progression. ProGRP is well suited to complete the present diagnostic panel for lung cancer.

For 128 SCLC patients receiving first-line chemotherapy, baseline values of ProGRP before the second treatment cycle were able to differentiate patients with disease progression vs. those with stable disease or remission (AUC = 71.3%).

Holdenrieder, S. et al. (2008). Nucleosomes, ProGRP, NSE, CYFRA 21-1, and CEA in monitoring first-line chemo-therapy of small cell lung cancer. Clin Cancer Res., 14, 7813-21.

ProGRP levels dropped progressively in SCLC patients receiving consecutive cycles of chemotherapy. Significant differences in ProGRP levels were found between patients with progression and remission.

Wójcik, E. et al. (2008). ProGRP and NSE in therapy monitoring in patients with small cell lung cancer. Anticancer Res., 28, 3027-33.

Conclusions from publications

ProGRP is the tumor marker of choice in SCLC

- ProGRP is highly stable in blood and easy to measure via a simple immunoassay.
- ProGRP is specifically elevated in SCLC patients.
- In non-SCLC patients and patients with non-tumorous lung diseases, ProGRP serum level is rarely elevated.
- ProGRP has a high sensitivity in SCLC patients even at a relatively early stage of this disease.
- Changes in the serum ProGRP level showed an excellent correlation with the therapeutic responses in SCLC patients.
- ProGRP is superior to NSE as an accepted tumor marker of SCLC patients.
- ProGRP and NSE complement each other as sensitivity can be enhanced by using them in combination.

Elecsys® ProGRP and Elecsys® NSE

ProGRP, a fully automated assay used for the quantitative determination of ProGRP in human serum and plasma to aid in the differential diagnosis in lung cancer.

- Data from this multicenter evaluation of the Elecsys® ProGRP assay demonstrate that ProGRP is a specific tumor marker for SCLC, which supports differential diagnosis in lung cancer.
- Increased stability of the Elecsys® ProGRP assay in serum and plasma offers clear benefits over existing assays.
- This first evaluation of a ProGRP assay in China demonstrated comparable differentiation potential among different ethnicities.

Korse, C.M. et al. (2015). Multicenter evaluation of a new progastrin-releasing peptide (ProGRP) immunoassay across Europe and China. Clin. Chim. Acta, 438, 388-395.

Technical assay features of ProGRP and NSE

	ProGRP	NSE
Total duration	18 min.	
Assay principle	Immunoassay based on ECLIA	
Sample volume	30 µL	20 µL
Sample material	Serum and plasma	Serum; Do not use plasma. Centrifuge blood within 1 hour. NSE in erythrocytes and platelets leads to tele-vated results in hemolyzed or incorrectly centrifuged samples
Measuring range	3 – 5,000 pg/mL	0.050 – 370 ng/mL
Traceability	Abbott Architect ProGRP	Enzymun-Test NSE method. An international standard for NSE does not exist
Kit size	100 determinations	

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