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Lung cancer (LC)

Benefits of serum and molecular markers in diagnosis and therapy

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The serum markers currently used
NSE – CYFRA 21 – CEA – SCC

(Neuron Specific Enolase – Cytokeratin Fragment – Carcinoembryonic Antigen – Squamous Cell Carcinoma)

« Correct use of serum markers »

- They are neither 'cancer specific' nor 'organ specific', and are under no circumstances used for 'cancer screening'.
- The sensitivity and specificity represent a compromise for a threshold value and are thus inadequate for a diagnostic value.
- Their kinetics are however helpful for diagnosis, therapeutic monitoring and detecting recurrence. Their initial values and repeated assays during treatment can also have a prognostic value.

Reminder:

1. **NSE:** a marker for small-cell lung cancer (SCLC), and more generally for neuroendocrine tumours, can be associated with Chromogranin A.
2. **CYFRA 21:** a marker for non-small-cell lung cancer (NSCLC) – alone (squamous cell cancer) or combined with CEA (adenocarcinoma).
3. **SCC:** a marker for NSCLC (SCC > 2 ng/mL), and more generally for squamous cell carcinomas, can be combined with CEA.

NSE and CYFRA 21 are helpful for differential diagnosis of SCLC and NSCLC.

They are not specific for LC. High concentrations can be found in benign pulmonary disorders (embolisms) or other pathologies (cirrhosis, pancreatitis, etc.), and in other tumour pathologies (urological, gynaecological, gastrointestinal).

Kidney failure increases the level of all these markers.

NEW ProGRP - Pro Gastrin Releasing Peptide

GRP is a neuropeptide identified in 1983 in SCLC. Due to its extremely short half-life (two minutes), **ProGRP**, which comes from the same pre-protein but is more stable, is measured instead.

Primary diagnosis of SCLC

Its sensitivity at a threshold of 50 pg/mL (76.6%) is greater than NSE sensitivity at a threshold of 25 ng/mL (65.1%).
Its correlation with the histological type (area under the ROC curve AUC = 0.85) is greater than the NSE correlation (AUC = 0.82).
However, according to studies, the sensitivity of ProGRP can be increased (between 14% and 23%) in combination with NSE.
Its concentration correlates with tumour size.
The probability of having SCLC is 93% for a serum concentration of ProGRP over 150 pg/mL.

Differentiation of LCs and benign (non renal) disorders

Concentrations of ProGRP are less than 100 pg/mL in all cases, and even less than 50 pg/mL in 88.6% of lung diseases and in 83.3% of other benign pathologies (liver, metabolic, autoimmune, inflammatory, etc.).

Differentiation of LC from other cancer pathologies

Concentrations of ProGRP are:

- Under 100 pg/mL in 96.4% of NSCLCs and 90% of other neuroendocrine cancers.
- Over 200 pg/mL in 60% of SCLCs and 80% of medullary thyroid cancers.

Therapeutic monitoring

The kinetics of the expressed markers are monitored.

Standard values (ECLIA Roche technique)

At the 95th percentile, the ProGRP concentrations are below **68.3** pg/mL for a serum sample (< **59.5** pg/mL in EDTA).

In case of kidney failure: between 50 and 300 pg/mL.

The combination of serum markers
ProGRP – NSE – CYFRA 21 – SCC – CEA

The combinations with the highest sensitivity (Molina 2005)

For SCLC ▶ ProGRP and NSE
Sensitivity of 88% at the thresholds of 50 pg/mL and 20 ng/mL, respectively.

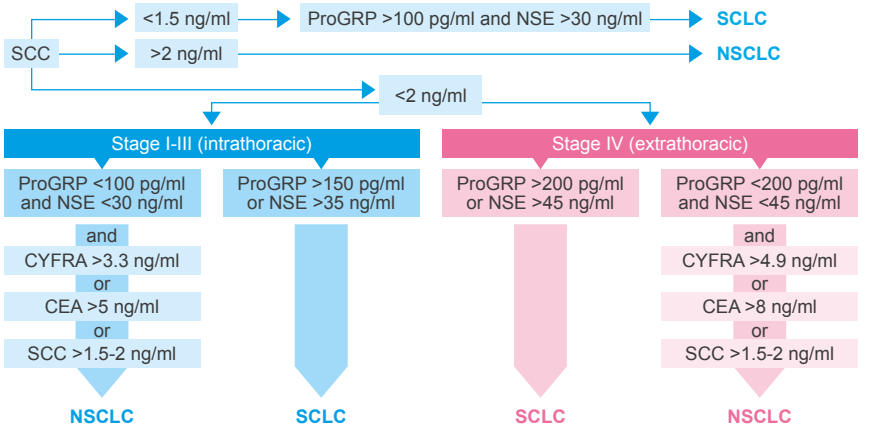
For NSCLC ▶ CEA and CYFRA 21
Sensitivity of 82% at the thresholds of 5 ng/mL and 3.3 ng/mL, respectively.

Recommendations for use of markers according to histologies of lung cancer and application forms, NACB 2006

Histology	Before therapy	Post-therapy follow-up
Unknown	CYFRA 21-1, CEA, NSE, ProGRP	After surgery : following histology In advanced disease : using the leading marker
Adenocarcinoma	CYFRA 21-1 and CEA	CYFRA 21-1 and/or CEA
Squamous cell carcinoma	CYFRA 21-1 and CEA (and SCCA)	CYFRA 21-1 and/or CEA (and/or SCCA)
Large cell carcinoma	CYFRA 21-1 and CEA	CYFRA 21-1 and/or CEA
Small cell carcinoma	NSE and ProGRP	NSE and/or ProGRP

CEA, carcino embryonic antigen, CYFRA 21-1, cytokeratin 19 fragments, NSE, neuron specific enolase, ProGRP, Pro Gastrin Releasing Peptide, SCCA, squamous cell carcinoma antigen

Algorithm to suggest the specific histological diagnosis using serum tumour markers



Molina et al. 2009 Tumor Biol 2009, 30 :121-129 Fig 2

Prognostic and therapeutic use of gene mutations and rearrangements

In addition to serum markers, the molecular characterisation of tumours has first enabled the creation of a molecular classification, used for diagnosis and/or prognosis and furthermore for treatment stratification (concept of targeted therapy with companion test).

The main gene mutations and rearrangements currently described are EGFR (15%), ALK (10%), ROS (2%), KRAS (21%), BRAF (2%) and MET (<5%).

In advanced-stage NSCLC, the recommendations for prescribing a targeted therapy are analysis of the mutational status of EGFR and the research of a rearrangement of ALK, then ROS. These analyses are used to decide whether to begin TKI treatment (tyrosine-kinase inhibitor) or not and, for certain EGFR mutations, to identify mutations creating resistance to TKI.

The presence of these molecular anomalies is tested with different techniques:

- IHC (immunohistochemistry) for ALK.
- FISH (fluorescence in situ hybridisation) for ALK, ROS or MET.
- Or with molecular biology techniques for EGFR, KRAS and BRAF.

The analysis of the tumour DNA from peripheral blood (liquid biopsy) can be used to improve the treatment of patients in whom a molecular analysis of tumour tissue cannot be performed.

Benefits of serum and molecular markers in LC diagnosis and therapeutics

1. Contributes to early diagnosis
2. Differentiates between SCLC and NSCLC*
3. Identifies the stage of the disease
4. Facilitates rapid and multidisciplinary treatment
5. Adapts treatment (dosage, drug molecule(s))

** Should not however be a substitute for anatomical pathology diagnosis when possible.*

In practice

ProGRP

A patient must always be monitored using the same type of sample and the same technique

- **Technique:** ECLIA Roche
- **Sample:** 1 mL of serum in tube with phase separator
- **Storage and transport:** Frozen
- **Turnaround:** 2 working days
- **Frequency carried out:** Once per week

All the information about ProGRP (test code: **PRGRP**) and other serum markers can be found on **www.biomnis.com > Test Guide.**

Gene mutations and rearrangements

- **Sample type:** Tumour sample embedded in paraffin (returned after analysis)
- The histological report **must be attached**
- **Storage and transport:** Room temperature
- **Turnaround:** Contact us
- **Fluid biopsy (panels of key genes):** Contact us

Find out more: Read our document on '**Cytogenetic & genetic studies in patients with solid tumours'** on **www.biomnis.com > Resources > Focus on**

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General information about lung cancer
Key facts and figures

Epidemiology around the world

Incidence and mortality – Estimate for 2012*

(Estimate every five years – only data usable for trend over time)

	All	Men	Women
Incidence	1.8 million new cases (or 12.9% of all cancers)	1.2 million new cases (most frequent)	580,000 new cases (third most frequent)
Mortality	1.6 million deaths	1.1 million deaths (most frequent)	491,000 deaths (second most frequent)

5-year projection period* (Updated every two years)

	All	Men	Women
Prevalence	1.8 million cases	1.2 million cases	626,000 cases

**Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012*

Men:

- Incidence stabilising
- Mortality decreasing.

Women:

- Incidence and mortality rising.

Lung cancer (LC) is often diagnosed at a late stage (six out of ten cases are diagnosed at stage IV) involving a poor prognosis: the survival rate is of among the lowest for solid tumours (12% at five years).

Lung cancer is defined as a proliferation of malignant cells within the bronchial tree or surrounding lung tissue. As such, it is a set of tumours, heterogeneous in terms of histological characteristics and location / development, which is classified into stages according to the TNM classification (tumour, nodes, metastases).

We divide them into two histological types:

- approximately 20% of LCs are small-cell (SCLC)
- and approximately 80% are 'non-small cell' (NSCLC).

This differentiation is essential when deciding on treatment, with SCLC generally being fast-growing, tending to form metastases, with no surgical treatment, while NSCLC includes other heterogeneous forms, such as adenocarcinoma (50%), squamous cell carcinoma and large-cell carcinomas (30%).

Risk factors

Active smoking is the main risk factor for LC (quantity smoked and for how long).

The IARC (International Agency for Research on Cancer) has classified other factors as carcinogenic, such as asbestos, X- and gamma-rays, radon and air pollution. Occupational environmental factors also exist.

The risk of LC increases with age.

Objectives

1. Contribute to early diagnosis
2. Differentiate between SCLC and NSCLC
3. Identify the stage of the disease
4. Facilitate rapid and multidisciplinary treatment
5. Adapt the therapy (dosage, drug(s))

Diagnostic and therapeutic approach

Case history

Identifying history and risk factors.

Clinical examination

The symptoms are primarily respiratory (cough, shortness of breath, haemoptysis, respiratory infections, etc.) directly linked to the tumour or extra-pulmonary linked to regional spread or metastases.

Additional tests

Imagery: Radiography, scanner, fiberscopy, MRI, bone scintigraphy, PET scan.

Anatomical pathology makes the diagnosis with a histological and immuno-histochemistry (IHC) study of a biopsy or tumour mass (excised tissue).

Testing the tissues for genetic mutations (EGFR) or genetic rearrangements (ALK, ROS) provides the basis for the prescription of targeted therapeutics.

Treatment

According to standard procedures, the following regimens are very routinely applied:

- **SCLC:** Chemotherapy is the standard treatment, possibly combined with radiotherapy
- **NSCLC:** Surgery is the standard treatment for the early stages. Chemotherapy and/or radiotherapy are considered in combination, with or without surgery, according to the stage and wether the resection of the tumor is possible or not.

Selective therapeutics are proposed for advanced-stage NSCLC according to the molecular anomalies identified.

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