



Editorial

Molecular Staging and Prognosis in Lung Cancer[☆]

Estadificación y pronóstico molecular del cáncer de pulmón

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The term “molecular staging” has been used to refer to the determination of tumor markers in the lymph tissue as an indicator of the presence of neoplastic cells. It is known that there are often minimal tumor cell foci or micrometastases (diameter less than 2 mm) which may be missed in the histopathological examination and that are usually only detectable by immunohistochemistry. Recently, newly developed techniques, such as those based on the polymerase chain reaction (*quantitative reverse-transcriptase-polymerase chain reaction* [qRT-PCR]), are able to detect tumor markers and certain mutations or epigenetic alterations (especially methylations) in the DNA of even minimal tumor pieces, which can have great prognostic value.^{1,2}

In addition, the remarkable advances made in genetic analysis (microarray techniques), which simultaneously analyze the degree of expression of a multitude of genes, have created great interest due to their diagnostic, prognostic, predictive and therapeutic usefulness in many tumors, among these lung cancer (LC).^{1–8} Numerous studies have found associations between certain profiles or “signatures” of gene expression on one hand, and the existence of micrometastasis in the bone marrow,⁹ early relapse after surgical resection^{1–4,7,8} and disease-free or overall survival^{6–8} on the other.

The potential practical utility of these markers is clear because, in addition to the prognostic value *per se*, they are expected to be especially helpful in therapeutic decision-making. Testing for certain unique mutations (EGFR, EML4-ALK, K-RAS, F-RAS) in patients in advanced stages, who would traditionally be candidates for chemotherapy and/or radiotherapy, is already a reality in clinical practice. Furthermore, its practical value is unquestionable as there are effective drugs aimed against these specific molecular alterations of some tumors, considered to be new therapeutic targets (gefitinib, erlotinib, crizotinib, afatinib, etc.).^{10–13}

The search for new molecules or targets, which are crucial in the development of some tumors and susceptible to being blocked with specific drugs, is an area of great interest. Presumably, this will contribute to slowly improving the survival of specific subgroups of patients with LC. However, these comments will be especially centered around another situation of great therapeutic importance

that still has not matured enough to be incorporated into clinical practice. I am referring to the indication, according to molecular profiling, of adjuvant chemotherapy (CTx) in patients with completely resected LC.

Adjuvant CTx is currently recommended in completely resected patients in stages II and III, but not in IA. Its use in stage IB is debatable.¹⁴ Nevertheless, it is clear that its indiscriminate indication (without considering the possible biological-molecular features of the tumor) leads to the application of CTx in patients who either could have been completely cured after surgery, or who are carriers of micrometastases that are insensitive to the CTx regime applied. On the other hand, tumors in stage IA that are completely resected, with high metastatic potential and high probability for relapse, could benefit from adjuvant CTx. Therefore, the search for markers that help us to more precisely identify the candidates for said CTx has been and continues to be an area of special interest in LC. In addition to several clinical (age, gender, smoking, comorbidities, capability of doing usual work activities either at work or home or “performance status”),¹⁵ anatomical (tumor size, invasion of the pleura, etc.)^{15,16} and histological (types, degree of differentiation)^{15,16} factors, a large variety of immunohistochemical markers have been studied^{16,17} with the intention of determining which tumors are more likely to relapse. Some of these markers have been associated with a favorable response to CTx.^{18,19} In recent years, groups of genes or “genomic signatures” have been examined with microarray techniques with this objective.^{1–8,20} In an interesting study based on a cohort of patients who had participated in an extensive randomized assay about adjuvant CTx with cisplatin and vinorelbine, the authors were able to analyze, using genomic signature, not only the prognostic value but also the predictive value of the response to the specific CTx regime. Their results confirm a high prognostic value in patients under observation as well as a good capacity for predicting the response in those who received CTx. There was an especially interesting finding that CTx had a favorable effect over placebo in the group at high risk for relapse (risk according to the genomic signature) and, contrarily, a negative effect on survival in the low-risk group.²⁰ This and other studies require confirmation by new studies done in cohorts of patients that are completely independent, and even geographically different.^{8,21}

Unfortunately, there is hardly any similarity or equivalence among the genes that the different authors analyze.⁹ Even so, it has been suggested that, although they are different, they may form

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part of similar metabolic routes or pathways.²⁰ In a recent critical analysis of many of these studies, Subramanian and Simon²² have found several methodological defects that make it difficult for these results to be reproduced by other authors. They conclude that said signatures are still not properly validated in order to be incorporated into clinical practice. These authors provide an extensive guide of recommendations to follow in these studies with the aim of establishing their possible practical use: in addition to the utmost transparency and detail in the presentation of the gene selection procedures and preparation of the model (which often requires the use of sophisticated statistical tests), the authors recommend verifying that said genomic signatures demonstrate a high prognostic value, independent from other standard prognostic factors, separately analyzing each of the TNM stages.²²

In spite of the apparent difficulties, a very similar objective has already been achieved in breast cancer with a group of 73 genes (*Mamma Print*),²³ whose laboratory examination was later simplified²⁴ and approved by the Food and Drug Administration (FDA). Another similar signature (Ecotype DX) has been recommended by the American Society of Clinical Oncology (ASCO) in a certain subgroup of patients with lung cancer in order to decide on the use of adjuvant treatment.²⁵

In a short period of time, the power of these new genome analysis techniques has accumulated an enormous quantity of information. Although still preliminary and fragmented, this new information is starting to transform into an understanding of the physiology of neoplastic cells. It is exceedingly dynamic and changing and depends on a complex network of interactions, which at the same time depends on the activation and/or suppression of certain cellular metabolic pathways or routes. These pathways are the foundation for certain biological functions or specific capabilities that neoplastic cells acquire in successive stages, known as the "hallmarks" of cancer²⁶: (a) limitless reproductive potential; (b) capability to induce angiogenesis; (c) capability to evade apoptosis or programmed cell death; (d) sustained proliferation signals; (e) capability to elude anti-growth signals; and (f) capability to activate tissue invasion and metastasis. Recently, Hanahan and Weinberg²⁶ have added another two new features: the reprogramming of cellular energy metabolism and the capability to evade destruction by the immune system.

In recent years, studies have been published examining the value of the genetic signatures in bronchial biopsies obtained with bronchoscopy or in samples of hilar-mediastinal lymph nodes using endobronchial ultrasound.²⁷ Said tumor signatures have even been examined in total blood samples.²⁸ Nevertheless, the majority of studies with large series have been based on the analysis of surgical pieces, both of the primary tumor as well as of the lymph nodes.^{1-9,20} In any case, the clinical translation of this new knowledge requires the availability of precise, reliable, fast, standardized and validated tests that are reasonably cost-efficient. In order to meet these objectives, it now seems essential for there to be multidisciplinary collaboration among pulmonologists, thoracic surgeons, oncologists, pathologists and other laboratory specialists who can work with sufficiently extensive multicenter databases and who shall avail not only properly processed and preserved tumor samples but also detailed information on staging and clinical features as well as a close follow-up of the patients included and their survivals.

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