Gene expression assays as prognostic and predictive markers in early stage non-small cell lung cancer

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Lung cancer is the no.1 cancer killer in both men and women. Non-small lung cancer (NSCLC) comprises about 80% of all lung cancers and approximately one third of these patients are diagnosed at stage I-IIIA where treatment intention is curative (1). Due to a significant risk of relapse after surgery, adjuvant platinum-based chemotherapy is today recommended in NSCLC stage II-III (2-4). Prospective randomised data failed to show significant survival benefit from adjuvant chemotherapy in stage IB (except in an unplanned subset analysis of patients with tumour size >4 cm) and even a detrimental effect was observed in stage IA (2). The fact that 30-40% of stage I patients relapse after surgical resection alone, indicates, however, that some of these patients might benefit from adjuvant treatment.

Hitherto, tumour stage has been the best validated among well established predictors of NSCLC patient survival, but identification of new robust prognostic (long term outcome for untreated patients or those receiving standard treatment) and predictive (identify patients who are likely or unlikely to benefit from a specific treatment) markers is warranted to individualize and optimize NSCLC treatment.

Gene expression profiling in NSCLC, i.e., the systematic identification and characterization of those genes activated or expressed in a cell, may be studied by a wide range of analytical procedures at genome (DNA), transcriptome (mRNA) and proteome (protein) level as reviewed by Shao *et al.* (5). In addition, microRNAs role in NSCLC have been elucidated during recent years (6). A widely used approach is quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Quantitative RT-PCR is a relatively simple analysis, highly reproducible and practical in prognostic models based on gene expression of a limited number of genes.

Several gene expression studies have addressed the need for further prognostic subclassification within each stage of resected NSCLC patients, many based on a microarray platform and need of snap-frozen tissue samples. Many studies show promising results, but a robust validation is often missing, and in studies where validation is carried out the results fail to support the training set (7). Validation is especially important in this setting as the specific signatures identified in these studies show minimal overlap (8). But to be useful in the clinical setting, a prognostic signature should provide additional risk stratification beyond what stage or other established clinicopathological variables can contribute with.

In 133 stage IB-II NSCLC patients enrolled in the JBR.10 study, a 15 gene expression profiling (mRNA) was carried out to identify stage independent subgroups that might benefit from adjuvant chemotherapy (9). The gene signature demonstrated a potential to select stage IB to II patients most likely to benefit from adjuvant chemotherapy with cisplatin/vinorelbine. However, this signature has not been validated and the authors conclude that the predictive role of their signature should be tested in prospectively planned adjuvant chemotherapy trials.

In a recent comprehensive study in The Lancet, Kratz, He and co-workers used a 14-gene expression assay (quantitative PCR) on formalin-fixed paraffin-embedded non-squamous NSCLC tissue to identify early stage patients with high risk of mortality after surgical resection (10). A cohort (n=361) from the University of California, San Francisco, US, was used as a training set. The results were validated in a cohort (n=433) from Kaiser Permanente Northern California Hospitals, and in a substantial cohort (n=1,006) from several leading Chinese cancer centres that are part of the China Clinical Trials Consortium (CCTC). The training cohort included stage I-IV, the CCTC validation cohort stage I-III and the Kaiser validation cohort only stage I patients.

No potential conflict of interest.

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Many of the 14 genes in their prognostic algorithm are related to well-known pathways in NSCLC pathology as KRAS, BRAF, EGFR, HER2, ALK and p53. However, the selection of genes is based on a combination of genes identified by study investigators and literature review, hence a potential limitation in that novel cancer genes may have been excluded (11). The authors summarize the strengths of this assay/study as: (I) possibility to use formalin-fixed paraffin-embedded tissue; (II) independent of laboratory; (III) large sizes of the validation cohorts; (IV) large disparity between the genetic background of validation cohorts (US and China). They found the molecular assay to be a stronger predictor of 5 years lung cancer mortality than the clinopathological variables sex, age, smoking status, tumour size end even stage. The authors conclude that the assay outperformed the National Comprehensive Cancer Network's guidelines (12) used to identify high risk patients with stage I and could differentiated between low, intermediate and high-risk within all the clinical disease stages.

As indicated by the authors, a prospective confirmative study is needed to draw any firm conclusions. Though, they argue that the evidence provided from this study is comparable to the evidence used to justify some of the clinicopathological variables as predictive markers for stage IB and II NSCLC adjuvant chemotherapy treatment. In a Nature review, Subramanian and Simon asked the question "What should physicians look for in evaluating prognostic gene expression signatures?" (13). They stated that validation studies should be prospectively planned, but that archived specimens from multiple suitable clinical trials may provide a high level of evidence of clinical value. As this 14 genes assay has not been tested in clinical trials designed to study the impact of adjuvant chemotherapy, the assay has so far only proven to be a good prognosticator, and its predictive impact is still to be explored.

The study by Kratz, he and co-workers is comprehensive and robust, and seems promising with regard to clinical utility. The authors implicit question - what to do while waiting for the results from a prospective designed study to address the impact of this assay as a predictive marker? - is therefore highly relevant. Its clinical role as a predictive marker for adjuvant chemotherapy in early stage non-squamous NSCLC can not be settled until results from a prospective study is at hand to address this question.

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