

Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer



EGFR Testing in Lung Cancer is Ready for Prime Time

By Fred R. Hirsch, MD, PhD

The epidermal growth factor receptor (EGFR) protein is widely expressed in non-small cell lung cancers (NSCLC). The gene is sometimes amplified, but it is often increased in copy number and, less frequently, mutated with activating mutations. EGFR-directed therapies include the reversible specific tyrosine kinase inhibitors (TKIs) gefitinib (Iressa®) and erlotinib (Tarceva®) and the monoclonal antibody cetuximab (Erbix®). Also, more recently, irreversible pan-Her inhibitors were introduced into clinical trials.

In unselected patients treated with EGFR inhibitors, a minority will achieve an objective response, but many more will have symptomatic improvement with stable disease. Large, randomized studies failed to demonstrate any additional clinical benefit by adding an EGFR TKI to chemotherapy in first line treatment. However, major breakthroughs in patient selection were made by studying tumor specimens from patients in these trials. Many objective responders had EGFR mutations occurring specifically in exons 19 and 21 associated with never-smoker status, Asian ethnicity and adenocarcinoma histology¹. Single-arm studies selecting patients for these mutations showed response rates and progression free survival times superior to those seen with chemotherapy². These studies led to recently reported randomized phase II and III trials in chemo-naïve patients with advanced NSCLC. In one of the largest trials (IPASS), 1,217 NSCLC patients of Asian ethnicity, never or light smoking status, and adenocarcinoma histology received either gefitinib or multi-agent chemotherapy³. Patients with EGFR mutations treated with gefitinib had much higher response rates and longer progression free survival than patients treated with chemotherapy. In marked contrast, patients without EGFR mutations fared much better on chemotherapy than on gefitinib, and the response rate to gefitinib was only 1%. Thus, the molecular features (EGFR mutations) of the tumor trump the clinical features, and the therapy of choice for patients with EGFR mutations in this setting seems to be gefitinib.

Are these findings similar in Caucasians and with erlotinib? A randomized phase II trial in Caucasians randomized chemo-naïve NSCLC patients to erlotinib alone or chemotherapy plus erlotinib. In patients with EGFR mutations, the response rates and progression free

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survival favored erlotinib alone, whereas erlotinib alone was inferior in those without these mutations⁴. Thus, both gefitinib and erlotinib seem superior to chemotherapy in patients with EGFR mutations, and such testing is now ready for prime time! In most studies, direct sequencing is used to detect EGFR mutations. The sensitivity of these methods is about 10%, i.e. a mutation can be detected in specimens having 10% tumor cells. Newer techniques using amplification may be more sensitive in detecting mutations in specimens having less than 1% tumor cells. While the optimal test for mutation detection has yet to be determined, direct sequencing can be recommended in routine practice.

High EGFR gene copy number determined by fluorescence in situ hybridization (FISH) occurs in 30-50% of NSCLC patients and about 10% have gene amplification⁵. High EGFR gene copy number/amplification predicted superior outcome in NSCLC patients who previously received chemotherapy and were randomized to receive erlotinib versus placebo, or gefitinib versus placebo^{6,7}. However, EGFR FISH did not predict a superior outcome in patients randomized to gefitinib versus chemotherapy, in part because high gene copy number predicted a superior outcome in both groups. While EGFR mutations might not be expected to predict outcome with cetuximab, because the receptor is active even in the absence of the ligand, EGFR FISH predicted a superior outcome after cetuximab in the SWOG 0342 trial⁸. This randomized phase II study of chemotherapy with sequential or concurrent cetuximab was conducted to determine whether one schedule or the other was preferable for subsequent phase III testing against chemotherapy alone. Two hundred and twenty-nine patients with advanced NSCLC were enrolled. EGFR FISH was performed by using the Colorado criteria, and increased EGFR copy number by FISH was associated with a 100% prolongation in progression free survival and overall survival compared to the EGFR FISH negative patients. Objective responses were dramatically higher in FISH positive patients (45%) versus FISH negative patients (26%), while disease control rate was statistically superior (81% versus 55%) in the FISH positive group. Patients with FISH positive tumors had a median progression free survival of 6 months compared to 3 months for FISH negative patients ($p = 0.0008$). The median overall survival was 15 months for FISH positive patients versus 7 months for FISH negative patients ($p = 0.04$).

The results of SWOG 0342 were quite compelling and led to the design of the SWOG 0819 study. SWOG 0819 is a randomized phase III trial which will prospectively validate EGFR FISH as a predictive biomarker in NSCLC patients treated with chemotherapy and bevacizumab (if eligible), with or without cetuximab. In immunohistochemistry based selected patients, cetuximab added to chemotherapy in the large, randomized FLEX study showed significant survival benefit with a Hazard Ratio (HR) = 0.87 ($p = 0.04$) and a difference in median survival of 10.1 months with chemotherapy alone compared to 11.3 months with added cetuximab⁹. In unselected patients, cetuximab is associated with minimal clinical benefit, as demonstrated in the BMS-099 study¹⁰. Additional trials evaluating EGFR gene status by FISH in patients considered for cetuximab is a high priority. Final biomarker analysis from the FLEX and BMS-099 studies with cetuximab is underway.

K-ras mutations occur in 15-20% of the tumors from NSCLC patients and are associated with low response rates to EGFR inhibitors. In lung cancer, K-ras mutations are rarely present together with EGFR mutations. However, despite the low response rates in patients with these mutations, the presence of K-ras mutations has not been able to predict significantly inferior survival outcomes in NSCLC patients treated with erlotinib or cetuximab. Thus, the clinical relevance of K-ras testing in NSCLC is still unclear.

A serum proteomic classifier can be used to select patients with a good or a poor outcome after EGFR inhibitor therapy¹¹. This classifier is today commercialized as the VeriStrat® (Biodesix, Broomfield, CO). Additional prospective studies evaluating this method are in progress.

Which material is suitable for EGFR testing? Mutation testing is DNA based. How can we obtain sufficient DNA for this testing and how can tumor DNA be separated from non-tumor DNA? Micro dissection of specimens is generally done, but it is labor intensive. Mutation assays for testing circulating tumor cells in blood have been developed¹². EGFR mutations are detected in both circulating DNA and circulating tumor cells from NSCLC patients whose tumors have EGFR mutations. However, the sensitivity of EGFR mutation detection in peripheral blood is only about 70%, while the specificity is near 100% when compared to tumor

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tissue detection. While EGFR testing in peripheral blood is promising, it is still the focus on ongoing research and is not yet ready for clinical practice.

Most cancer patients are diagnosed with advanced disease based on a small biopsy or a fine needle aspiration. The success rates for obtaining sufficient tissue for biomarker assessment range from 30-80%. Factors that may affect success are multiple: the requirement of tissue quality for the specific biomarker assay, investigational site capacity and infrastructure, the physician-patient dialogue, and the understanding of importance of sufficient tissue. A strong educational effort from investigators and a close dialogue between the investigators and patients are important to increase the yield of tissue acquisition. In biomarker-driven trials, a robust infrastructure to obtain sufficient tissue is crucial for tissue acquisition.

What does the success rate of tissue acquisition mean for interpretation of study results? The answer is not clear. The type of tissue required for a specific biomarker assessment might be important. For many assays we lack comparative studies of different types of specimens (tissue versus cytology versus blood, for example). Another question is whether the classification systems (positive/negative) based on one type of specimen (e.g. histology) or assay is immediately applicable to another type of specimen (e.g. cytology) or assay.

We are still lacking good studies comparing biomarker expression in primary tumors and metastases, which might explain the differences in published frequencies of certain biomarkers. Biomarker expression in primary tumors might differ from metastatic lesions due to clonal selection in the metastatic process. In the adjuvant RADIANT study (based on primary tumors)¹³, the EGFR marker expressions were very different from the same biomarker expressions in the BR-21 study, which was a study in advanced disease. Ethnic differences in biomarker expressions are well known, but eventual differences between countries within the same region have not been clarified. Preliminary data comparing EGFR expressions in Caucasians and African-Americans disclosed differences which may significantly influence sensitivity to the EGFR inhibitors¹⁴.

An important factor to take into account when biomarker associations with specific therapeutics are discussed is how these associations are achieved. For EGFR, we initially discovered

the association between the biomarker expression and the sensitivity to the EGFR TKIs based on a comparison of EGFR expression in pretreatment specimens compared to response and outcome of EGFR TKIs given as second or third line therapy. A true biological association to second line therapy requires that first line therapy does not affect the biomarker expression, which may not be true. The optimal situation would be to assess biomarkers in a specimen obtained just before the relevant therapy is given, but this could be difficult in clinical practice. Hopefully, that will be easier in the future when patients have a better understanding of the importance of biomarker determination before any given therapy.

In conclusion, recent results support the use of EGFR mutations as a selection criterion for EGFR TKIs as first line therapy for NSCLC patients with advanced disease. However, EGFR mutations occur in about 50% of NSCLC patients in Asia and only in about 10% in Western countries. How do we select the 90% of Western NSCLC patients without EGFR mutations for EGFR TKI therapy, when more than 50% of them will have clinical benefit? EGFR gene copy number, EGFR protein expression and K-ras mutations, as well as the serum proteomic classifiers, should be included in clinical trials, as the role of these markers in patient selection is not yet clear. Future studies may one day define a selection paradigm combining multiple, rather than single, biomarkers which have both prognostic and predictive value in patient care.

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Selections from the Peer-Reviewed Literature

By York E. Miller, MD, Deputy Editor, Lung Cancer Frontiers



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1. Evidence for Common Clonal Origin of Multifocal Lung Cancers

Wang X, Wang M, MacLennan GT, Abdul-Karim FW, Eble JN, Jones TD, Olobatuyi F, Eisenberg R, Cummings OW, Zhang S, Lopez-Beltran A, Montironi R, Zheng S, Lin H, Davidson DD, Cheng L, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN. *J Natl Cancer Inst* 2009; 101:560-570

BACKGROUND: Lung cancer is the most common cause of cancer death in the United States. Multiple anatomically separate but histologically similar lung tumors are often found in the same patient. The clonal origin of multiple lung tumors is uncertain.

METHODS: We analyzed 70 lung tumors from 30 patients (23 females and seven males) who underwent surgical resection for lung epithelial tumors, of whom 26 had non-small cell carcinomas and four had carcinoid/atypical carcinoid tumors. All patients had multiple tumors (two to five) involving one or both lungs. Genomic DNA was extracted from paraffin-embedded tissue sections using laser capture microdissection and analyzed for loss of heterozygosity, TP53 mutations, and X-chromosome inactivation status. The percentage (95% confidence interval [CI]) of patients in whom there were concordant patterns of genetic alteration was calculated.

RESULTS: All 30 case subjects showed loss of heterozygosity (LOH) in at least one and at most four of the six polymorphic microsatellite markers. Completely concordant LOH patterns

between synchronous and metachronous cancers in individual patients were seen in 26 (87%) of 30 informative patients (95% CI = 75% to 99%). Identical point mutations were present in eight of 10 patients who exhibited TP53 mutation by sequencing. Tumors in 18 (78%) of 23 female patients (95% CI = 67% to 98%) showed identical X-chromosome inactivation patterns. Combining the results of LOH studies, TP53 mutation screening analyses, and X-chromosome inactivation data, we demonstrated that the multiple separate tumors in 23 (77%) of 30 patients (95% CI = 62% to 92%) had identical genetic changes, consistent with monoclonal origin of the separate tumors.

CONCLUSIONS: Our data indicate that the great majority of multifocal lung cancers have a common clonal origin and that multifocality in lung cancer represents local and regional intrapulmonary metastasis.

EDITORIAL COMMENT: The yearly incidence of lung cancer in high risk groups approaches 2%. Thus, it is not uncommon to find patients with two simultaneous lung cancers. The critical clinical issue is whether these patients are surgical candidates or not. The literature in this area is not comprehensive, but at least some surgical series report results that are encouraging. In the past, differing histology has been the most reliable evidence for two independent primary lung cancers. Genetic profiling may provide additional means to make this discrimination. Other groups have applied these techniques to patients with multiple lung tumors and concluded that these are most commonly independent primaries. Wang and colleagues applied a more extensive analysis than previously reported to a group of 30 patients with 70 lung tumors. They report that 77% of patients had tumors with similar mutational profiles, suggesting that multiple tumors most commonly represent metastases. This is in contradiction to some previous manuscripts.

One shortcoming of the manuscript is that we do not know if these patients had otherwise discernable metastatic disease. In addition, it appears that 23% of the subjects did have multiple independent primaries, which would optimally be treated by resection. Finally, the manuscript does not provide followup data to determine if identical mutational profiles define a group with a poor surgical outcome. As followup data become available, this will be an interesting topic for an additional publication.

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While this publication brings into question the commonly held assumption that multiple lung tumors most often represent independent primaries that would optimally be treated by resection, it is not definitive. We need larger series with more extensive genetic profiling, coupled with more clinical information regarding the results of traditional staging as well as outcome after resection. In addition, these results need to be stratified by histology, as it is conjectured that adenocarcinoma with bronchioloalveolar features often spreads by endobronchial metastasis. The authors are to be congratulated on advancing an area that is clinically important for a subset of patients and of considerable theoretical interest in regard to the concept of field cancerization

2. The Pittsburgh Lung Screening Study (PLuSS): Outcomes within 3 Years of a First Computed Tomography Scan

Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, Luketich JD, Siegfried JM, Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA. *Am J Respir Crit Care Med* 2008; 178:956-961

RATIONALE: The role of computed tomography (CT) screening for lung cancer is controversial, currently under study, and not yet fully elucidated.

OBJECTIVES: To report findings from initial and 1-year repeat screening low-radiation-dose CT of the chest and 3-year outcomes for 50- to 79-year-old current and ex-smokers in the Pittsburgh Lung Screening Study (PLuSS).

METHODS: Notified of findings on screening CT, subjects received diagnostic advice from both study and personal physicians. Tracking subjects for up to three years since initial screening, we obtained medical records to document diagnostic procedures, lung cancer diagnoses, and deaths.

MEASUREMENTS AND MAIN RESULTS: 3,642 and 3,423 subjects had initial and repeat screening. A total of 1,477 (40.6% of 3,624) were told about noncalcified lung nodules on the initial screening and, before repeat screening, 821 (55.6% of 1,477, 22.5% of 3,642) obtained one or more subsequent diagnostic imaging studies (CT, positron emission tomography [PET], or PET-CT). Tracking identified 80 subjects with lung cancer, including 53 subjects with tumor

seen at initial screening. In all, 36 subjects (1.0% of the 3,642 screened), referred for abnormalities on either the initial or repeat screening, had a major thoracic surgical procedure (thoracotomy, video-assisted thoracoscopic surgery [VATS], median sternotomy, or mediastinoscopy) leading to a noncancer final diagnosis. Out of 82 subjects with thoracotomy or VATS to exclude malignancy in a lung nodule, 28 (34.1%) received a noncancer final diagnosis. Forty of 69 (58%) subjects with non-small cell lung cancer had stage I disease at diagnosis.

CONCLUSIONS: Though leading to the discovery of early stage lung cancer, CT screening also led to many diagnostic follow-up procedures, including major thoracic surgical procedures with noncancer outcomes.

EDITORIAL COMMENT: The authors report a prospective single arm screening trial carried out in the context of an NCI sponsored Specialized Program of Research Excellence in Lung Cancer. While a number of single arm screening trials have now been published, this contains interesting information on outcomes. Approximately 40% of 3642 subjects had non calcified nodules on initial screen; 69 non small cell lung cancers were identified, 58% of whom had stage I disease. These findings are similar to other single arm trials, although the fraction with stage I disease is somewhat lower than some.

The novel findings are related to what happened after nodules were discovered. The investigators were assiduous in advising patients and physicians regarding guidelines for indeterminate lung nodules, such as those provided by the Fleischner Society and I-ELCAP. However, the investigator advice was not always followed and 36 subjects (1%) underwent a major surgical procedure for benign disease. Of major surgeries, one third were for benign disease, much higher than reported in other single arm trials. No doubt, patient and physician anxiety lead to surgery on nodules that might have been better managed by serial CT evaluation or “watchful waiting”. The PLuSS results may represent a real world situation in which CT screening is applied outside of institutions with a high level of expertise in lung nodule workup. We desperately need additional biomarker based tests to inform clinical decision making in the setting of indeterminate pulmonary nodules, not only to decrease unnecessary invasive testing, but also to allay patient anxiety as nodules are followed for stability.

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3. Do Evolving Practices Improve Survival In Operated Lung Cancer Patients? A Biobank May Answer

Vlastos F, Lacomme S, Wild P, Poulain S, Siat J, Grosdidier G, du Manoir S, Monga B, Hillas G, Varsovie R, Claudot F, Marie B, Vignaud JM, Szymanski N, Centre of Biological Resources/U 724 INSERM, Central Hospital, Cour d'Anatomie, Nancy, France. *J Thorac Oncol* 2009; 4:505-511

INTRODUCTION: Biobanks may play a pivotal role in lung cancer patients' management, research, and health policy. The Nancy "Centre of Biologic Resources" analyzed the evolving profiles of operated lung cancer patients and their management over 20 years.

METHODS: A total of 1259 consecutive patients operated upon from 1988 till 2007 were included. Survival rates were statistically compared before and after 1997. The parameters associated with a significant improvement of survival were determined.

RESULTS: After 1997, lung cancer was diagnosed at an earlier stage. For Squamous Cell Lung Cancer (SQCLC), stages IA increased from 5.4 to 19.5% and for Adenocarcinoma (ADC), stage IA increased from 9.9 to 24.7%. More women with stage I ADC were operated upon after 1997 ($p = 0.01$). More patients with Large Cell Lung Cancer were diagnosed recently. Recent patients received more adjuvant or neo-adjuvant chemotherapy ($p < 0.001$) and less radiotherapy (stage I SQCLC: $p = 0.019$, stage I ADC: $p < 0.001$). A longer overall patients' survival was observed after 1997 (chi test for SQLC and ADC independently $p < 0.002$). Among SQCLC long survivors, those at stage I-II, below 50 years, were more numerous. A longer survival was associated with early stage in ADC patients. Stage was the single constant factor for overall outcome.

CONCLUSION: Overall and stage-adjusted survival of operated lung cancer patients has been improved in the last decade due mainly to earlier diagnosis. The generalized use of computed tomography scan, chemotherapy, and a collegial management improved patients' survival.

EDITORIAL COMMENT: This group of French investigators report the outcomes of surgically treated lung cancer from 1988 to 2007. Positive trends with time include earlier stage disease and improved survival time. In addition, the authors report that the establishment of a research Biobank improved

collegiality and collaboration between providers. These improvements are to be expected with earlier diagnosis based on CT scan, improved staging, and improvements in surgical techniques. Participation in research trials such as this is also highly associated with improvements in patient care and outcomes. Presumably, patient selection for surgery has also improved based on these factors. It is reassuring to see that the outcomes in this study showed improvement over time, even if causation was multifactorial. While these results are encouraging, we should not be overly pleased, as the overall 5 year survival for lung cancer remains approximately 15%, well under that for the other major cancers.

4. Survival And Treatment Pattern Of Non-Small Cell Lung Cancer Over 20 Years

Pitz MW, Musto G, Demers AA, Kliewer EV, Navaratnam S, Department of Hematology and Medical Oncology, CancerCare Manitoba, Winnipeg, Canada. *J Thorac Oncol* 2009;4:492-498

INTRODUCTION: The multidisciplinary treatment of non-small cell lung cancer (NSCLC) has evolved, however, the impact on population outcomes remains unclear. We examined the treatment and survival pattern of patients with NSCLC over 20 years in Manitoba, Canada.

METHODS: All diagnoses of NSCLC from January 1, 1985, to December 31, 2004, were extracted from the Manitoba Cancer Registry. Treatment and survival data from the registry were combined with administrative medical claims data. Patients were grouped by treatment: surgery, chemotherapy, radiotherapy, or no antineoplastic treatment. Adjuvant therapies were also examined.

RESULTS: A total of 10,908 diagnoses of NSCLC were identified. The proportion treated with surgery and radiotherapy declined over time (annual percent change (APC) -0.28, $p = 0.009$; APC -0.74, $p < 0.0001$, respectively), while more received chemotherapy or no antineoplastic treatment (APC 0.57, $p < 0.0001$ and 0.45, $p = 0.0002$, respectively). Postoperative radiotherapy use declined over time (APC -0.87, $p < 0.0001$). Median survival time improved for the entire cohort after 1997 (0.46 months per annum (MPA), $p = 0.04$), and for those treated with primary surgery (post-1994: 2.85 MPA, $p = 0.05$), chemotherapy (0.49 MPA, $p < 0.0001$), and concurrent chemoradiotherapy (0.30 MPA, $p = 0.03$).

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CONCLUSIONS: The survival of patients with NSCLC has improved over time, driven by improvements in those treated initially with surgery or chemotherapy. This occurred in the setting of fewer surgical resections and increased chemotherapy use suggesting improved patient selection. Coincident with these changes, multidisciplinary case conferences, clinical practice guidelines, and consolidation of service may have contributed to these phenomena.

EDITORIAL COMMENT: This manuscript is an interesting companion to the previous one. The data is from the Manitoba Cancer Registry, 1985-2004. Over this time period, the

numbers of patients treated with surgery and radiotherapy declined modestly, with an increase in chemotherapy cases. Overall survival improved, as well as survival for surgical, chemotherapy and chemoradiotherapy groups. Improved staging, early diagnosis and surgical case selection were likely the major drivers of improvements in surgical survival. As noted above, while survival for NSCLC is improving modestly, it is still very poor compared to other common cancers.

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