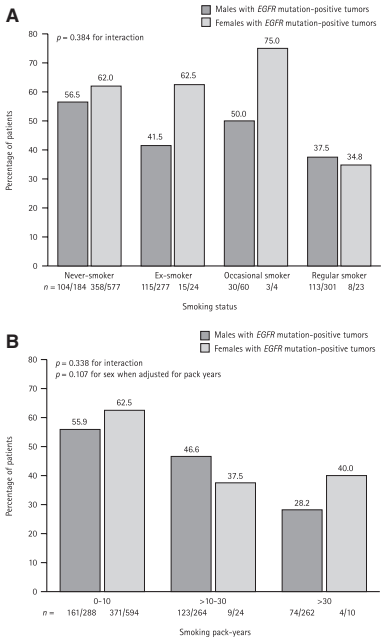
IN THIS ISSUE

- **A Prospective, Molecular Epidemiology Study of *EGFR* Mutations in Asian Patients with Advanced Non–Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER)**

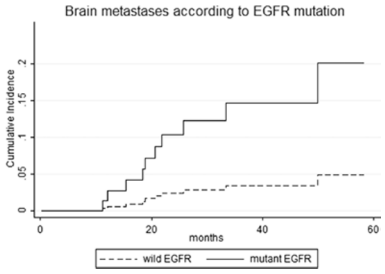


The PIONEER trial was conducted to evaluate epidermal growth factor receptor (*EGFR*) mutations in Asian patients with advanced lung adenocarcinoma. Patients were 20 years of age or more and had stage IIIB/IV adenocarcinoma with no prior treatment. The primary endpoint was *EGFR* mutation status in tumor samples. The frequency of the mutation was compared between demographic/clinical subgroups. Of the 1482 patients, 43.4% were female, 52.6% never-smoker, and 97.8% had tumors with evaluable *EGFR* mutations. Of these, 51.4% were *EGFR* positive and 48.6% *EGFR* negative. It is the first prospective study that confirmed such a high *EGFR* mutation incidence in Asian patients with lung adenocarcinoma. A statistically significant association was determined between mutation frequency and sex (female 61.1% versus male 44.0%), country (India 22% versus others 47.2%–64.2%), smoking status (never-smokers 60.7%), pack-years (higher as pack-years decreased), ethnicity, disease stage, and histology. The correlation with ethnicity and pack-years smoked were also significant in multivariate analysis whereas sex was not, after adjusting for smoking status. The authors concluded that the findings of high mutation frequency in demographic/clinical subgroups warrant mutation assessment for all Asian patients with stage IIIB/IV adenocarcinoma, including males and smokers. (p. 154)

- **The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) Response to the USPSTF Recommendations**

In response to the draft recommendations from the United States Preventive Services Task Force on low-dose computed tomography (CT) screening for lung cancer, The International Association for the Study of Lung Cancer Strategic Screening Advisory Committee recommended a few current issues to be considered for the implementation of lung cancer screening. First, the cost effectiveness of screening is important for the success of screening programs and could be further improved by including smoking cessation counseling. Data on cost effectiveness will be available from the NLST and NELSON trial. Volume measurement guidelines in CT imaging analysis of suspicious lung nodules to differentiate between benign and malignant lesions will potentially improve the management of the screening. In addition to the NLST selection criteria (age 55–74 years, ≥30 pack-years), the application of risk-prediction models, such as the one developed from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial data, could improve the sensitivity and positive predictive value of low-dose CT without compromising its specificity and mortality reduction. The committee discredited upper age limit (e.g., 80 years by the United States Preventive Services Task Force) as an accurate criterion for comorbidity in patient selection and suggested revisions as a better definition becomes available. Fitness evaluation was, however, recommended before and during the screening program to ensure the individual is well enough go through follow-up tests and treatment as a result of the screening, and not interfering with the treatment outcome. Harms from overdiagnosis, nodule discovery, and workup should be minimized and could be achieved through careful fitness evaluation, less-invasive procedures of workup of nodules, and adherence to low-dose protocols. (p. 141)

- ***EGFR* Mutation and Brain Metastasis in Pulmonary Adenocarcinomas**

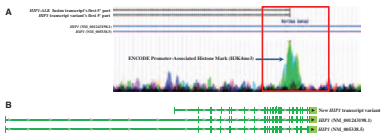


This study explored the relationship between epidermal growth factor receptor (*EGFR*) mutation status and brain metastases at diagnosis, as well as the prognostic significance of *EGFR* mutations in the development of brain metastasis in patients with surgically resected lung adenocarcinomas. In 138 patients with *EGFR* mutations of 314 analyzed, mutations occurred with statistically higher frequency in patients with brain metastases (64.7% brain metastases; 39.8% no metastases; 40.2% extracranial metastases; $p = 0.005$). *EGFR* mutation status was associated strongly with brain metastasis (adjusted odds ratio = 3.83, $p = 0.001$) whereas no association was observed between *EGFR* mutation and extracranial metastases (adjusted odds ratio = 1.73, $p = 0.079$). Further analysis in patients with brain metastases (n=51) demonstrated that *EGFR* mutation was significantly linked to extended tumor spread, that is, higher number of brain metastases ($p = 0.029$), but not the size of brain metastases.

A subgroup analysis in 133 surgically resected patients was performed to assess prognostic significance of *EGFR* mutation for the risk of brain metastasis. The findings showed that *EGFR*-mutated tumor posed a significant higher risk of recurrence of brain metastasis (hazard ratio = 4.49, $p = 0.026$) after adjustment by pathologic N stage. To conclude, this is the first study to suggest a significant association between *EGFR* mutation and a higher possibility of brain metastases in patients with pulmonary adenocarcinomas at initial diagnosis and after surgery. *EGFR* mutations could be useful for early detection of brain metastases, but its predictive value should be evaluated in further studies. (p. 195)

BRIEF REPORT

- **HIP1-ALK, A Novel Fusion Protein Identified in Lung Adenocarcinoma**



In addition to the five fusion proteins anaplastic lymphoma kinase (ALK)-EML4, -TFG, -KIF5B, -KCL1, and -PTPN3 reported to be involved in ALK overexpression and activation in non–small-cell lung cancer, a novel fusion gene, huntingtin interacting protein 1 (*HIP1*)–*ALK*, was discovered by Hong and colleagues. Reverse transcriptase polymerase chain reaction and immunohistochemistry were used in the detection of this fusion gene and protein expression, respectively. It was localized to the cytoplasm, mainly in the submembrane area. HIP1 is essential for clathrin trafficking and cell survival in relation to its epsin N-terminal homology domain. The coiled-coil domain of HIP1 and the juxtamembrane of ALK on the fusion protein demonstrated potential constitutive dimerization and aberrant activation of the ALK tyrosine kinase activity, which could indicate strong transforming potential. This case report presented *HIP1–ALK* as a novel diagnostic and therapeutic candidate for lung adenocarcinoma, which warrants further studies.

RESEARCH WATCH

- **Integrative and Comparative Genomic Analysis of Lung Squamous Cell Carcinomas in East Asian Patients**

The authors set out to investigate somatic genome abnormalities in lung squamous cell carcinomas (SCC) in Korean patients to determine therapeutically actionable targets and conduct comparative analyses in lung SCC. DNA from 104 SCC samples and paired normal tissues from Korean patients were subject to whole-exome sequencing and analyses of copy number and transcriptome (subset of samples). Clinical significance of the genetic