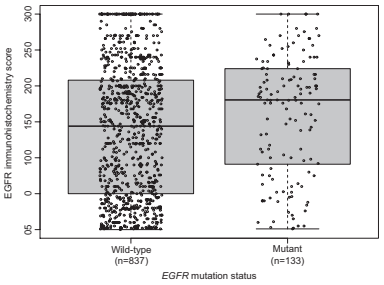
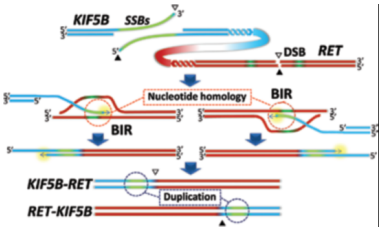
IN THIS ISSUE

- **Relationship between EGFR Expression, *EGFR* Mutation Status, and the Efficacy of Chemotherapy Plus Cetuximab in FLEX Study Patients with Advanced Non–Small-Cell Lung Cancer**



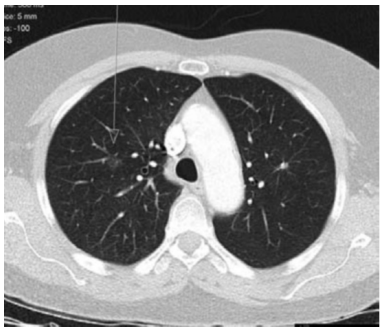
Survival benefits of combining cetuximab to chemotherapy were reported in the phase III FLEX trial in patients with advanced non–small-cell lung cancer expressing increased levels of EGFR (immunohistochemistry score of ≥200; scale 0–300). The current analysis was aimed to investigate the effect of tumor *EGFR* mutation status on the activity of cetuximab–chemotherapy combination observed in the FLEX study population. Efficacy end points such as overall survival time, progression-free survival (PFS) time, objective response, and time-to-treatment failure (TTF) were included. Of the 971 FLEX study patients screened for tumor mutations, *EGFR* mutations (exons, 18–21) were found in 14% of them. Tumors with *EGFR* mutations showed improved median survival and response rate versus *EGFR* wild-type tumors in both chemotherapy plus cetuximab (17.3 versus 9.6 months; 54.5% versus 32.9%) and chemotherapy alone (19.8 versus 9.6 months; 35.8% versus 27.0%). Findings from patients with *EGFR* wild-type tumors revealed that a survival benefit from the cetuximab–chemotherapy combination was observed in the high EGFR expression group (immunohistochemistry score of ≥200; hazard ratio [HR] 0.79) versus no benefit in the low EGFR expression group (HR, 0.98). PFS and TTF were similar across treatment and EGFR expression groups, whereas higher response rate was found in high expression group in these patients receiving cetuximab–chemotherapy combination versus chemotherapy alone (39.5% versus 27.4%). Findings from relatively small number of patients with *EGFR* mutations showed that a survival benefit may have derived from cetuximab–chemotherapy combination in the high EGFR expression group. Median survival of this group versus chemotherapy alone was 21.9 versus 19.5 months (HR, 0.74), whereas the same comparison for the low EGFR expression group was 12.3 versus 23.8 months (HR, 1.82). In patients with *EGFR* mutations, improved PFS, TTF, and response rates were observed across EGFR expression groups receiving cetuximab–chemotherapy combination versus chemotherapy alone. Taken together, *EGFR* mutation status did not affect the survival advantage of combining cetuximab in first-line chemotherapy for patients with advanced non–small-cell lung cancer expressing high levels of EGFR. High EGFR expression is a potential biomarker in predicting the clinical outcome of this combination treatment in the study population. (p. 717)

- **Molecular Mechanisms Underlying Oncogenic *RET* Fusion in Lung Adenocarcinoma**



This study analyzed the mechanism of oncogenic *RET* fusion, which was recognized as a driver mutation for the development of lung adenocarcinoma (LADC). Genomic polymerase chain reaction and a next-generation sequencer were used to analyze genomic segments with breakpoint junctions for *RET* fusions and to determine the mechanisms for DNA strand breaks and illegitimate joining of DNA ends. Eighteen *RET* breakpoints were evaluated, of which, 16 were discovered from the 671 LADC cases screened. The finding of the location of 17 of the 18 *RET* breakpoints in a 2.0-kb region between exon 11 and intron 11 with no breakpoint within four base pair of each other implied that *RET* fusion could be induced by the generation of DNA strand breaks at nonspecific sites in this region. Simple reciprocal inversion and DNA repair mechanisms (nonhomologous end joining and break-induced replication) that involves illegitimate joining of DNA ends were found to have contributed to 10 of 18 *RET* fusions in LADC. The results demonstrated multiple mechanisms driving oncogenic *RET* fusions in LADC, which involves illegitimate repair of DNA strand breaks via different mechanisms to those in papillary thyroid carcinoma. (p. 622)

- **Outcomes of Unresected Ground-Glass Nodules with Cytology Suspicious for Adenocarcinoma**



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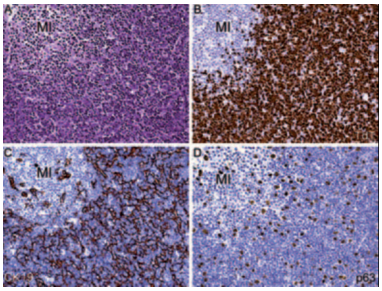
Gulati et al. conducted a study to compare the clinical outcomes of patients who were resected immediately after abnormal cytology results suspicious for early lung adenocarcinoma and those who selected watchful waiting. Sixty-three patients without prior history of lung adenocarcinoma, who had computer tomography–guided fine-needle aspiration of ground-glass lesions suspicious for early adenocarcinoma, were identified for the study. Of the 16 patients opted to observe their ground-glass lesions with suspicious cytology results, 37.5% eventually had growth or increase in solid component of the ground-glass lesion. Of these, five patients underwent surgical resection or radiation therapy. No distant metastasis or lung cancer–associated deaths were found in the observed group. In 47 patients opted for immediate resection after abnormal cytology results, metastasis (n = 2), new cancers in remaining lung (n = 5), and existing ground-glass lesion progression (n = 3) were observed. This study indicates that watchful waiting after ground-glass lesion biopsy did not show higher metastatic rates or cancer-related deaths and suggests that delayed resection does not deteriorate the outcomes. (p. 685)

- **ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria and Reporting**



The World Health Organization (WHO) classification (2004) assigns thymic epithelial tumors into A, AB, B1, B2, and B3 and (rare other) thymomas and thymic carcinomas (TC) based on fundamental morphological differences. Nevertheless, poor interobserver reproducibility or inconsistencies in some studies prompted the organization of an interdisciplinary panel by the International Thymic Malignancy Interest Group to refine histological criteria while maintaining the WHO classification for better management of morphological overlap between some thymoma subtypes and TC. A team of 18 pathologists, two surgeons, and an oncologist reviewed 72 hematoxylin and eosin–stained and immunohistochemically processed sections of prototypic and difficult-to-classify thymic epithelial tumors ("borderland" and "combined" thymomas and TC) at an international consensus slide workshop. Consensus was achieved on refined criteria for A/AB "borderland," distinguishing B1, B2, and B3 thymomas, and separation of B3 thymomas from TCs. A new type A thymoma variant, namely "atypical type A thymoma," has emerged tentatively. New reporting strategies for tumors with more than one histological pattern are recommended. Although the proposed new criteria and guidelines need to be tested and validated in further studies, they set the stage for reproducibility and improvement of the prognostic and predictive values of the WHO classification. (p. 596)

RESEARCH WATCH

- **The Potential Effects of Tobacco Control in China: Projections from the China SimSmoke Simulation Model**

The authors sought to project the potential impact of complete implementation of tobacco control in China as recommended by the World Health Organization Framework Convention on Tobacco Control via computer simulation model. In a study population of men and women aged 15 to 74 years, current and former smoking prevalence, initiation and cessation rates, and past policy levels were included to predict past smoking rates and project future status quo rates. The model projected future