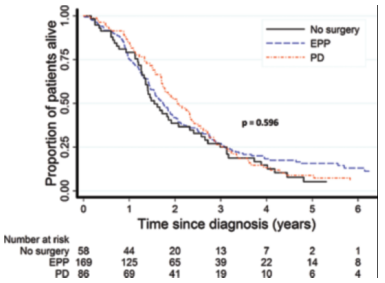
IN THIS ISSUE

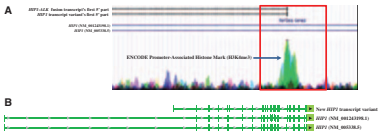
- **Does Surgery Improve Survival of Patients with Malignant Pleural Mesothelioma? A Multicenter Retrospective Analysis of 1365 Consecutive Patients**



To assess the effect of surgical treatment with pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP) on the outcome of patients with malignant pleural mesothelioma (MPM), a multicenter retrospective study of 1365 consecutive patients with MPM was conducted. Patients were given chemotherapy alone (n = 172) or palliative care (n = 690) or surgery (P/D, n = 202 or EPP, n = 301) with or without chemotherapy. Among 16.8% of patients who were alive after a median follow-up of 6.7 years, median survival was 11.7 months for those who received palliative care, 20.5 months for chemotherapy alone, and 18.8 months for P/D and EPP. The 30-day mortality after P/D and EPP was 2.6% and 4.1%, respectively (p = 0.401). Epithelial histology and chemotherapy were independent favorable prognostic factors. Among 131 patients with all the favorable prognostic factors, the findings showed that median survival was similar between those receiving chemotherapy only (18.6 months), P/D (24.6 months), and EPP (20.9 months) (p = 0.596). The authors concluded that, though no significant improvement in patient survival was observed with surgery, further evaluation of the modest benefit after surgery versus chemotherapy is warranted. In addition, investigating MPM patients with good prognostic factors, who receive P/D after induction chemotherapy versus chemotherapy alone, in a large multicenter randomized trial is required. (p. 383)

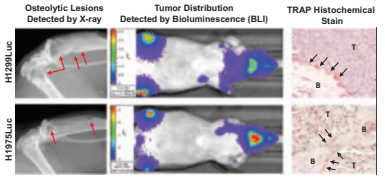
BRIEF REPORT

- **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, Hong and colleagues discovered a novel fusion gene, huntingtin interacting protein 1 (*HIP1*)–*ALK*. 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. (p. 412)

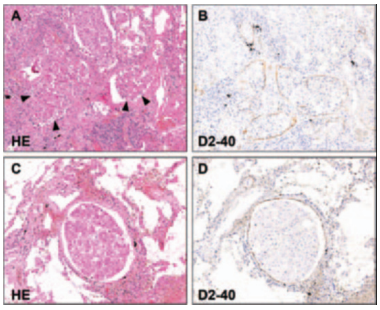
- **RANKL Inhibition Blocks Osteolytic Lesions and Reduces Skeletal Tumor Burden in Models of Non–Small-Cell Lung Cancer Bone Metastases**



RANK ligand (RANKL), crucial for osteoclasts and skeletal destruction because of bone metastasis, is believed to be involved in tumor cell–mediated osteolysis, which is yet to be confirmed in the case of non–small-cell lung cancer (NSCLC). The authors evaluated the effects of RANKL inhibition by using human osteoprotegerin-Fc (OPG-Fc), either alone or in combination with docetaxel, on osteolysis, skeletal tumor burden, and survival in two novel mouse models of NSCLC bone metastasis. Mice bearing skeletal NSCLC tumors were treated with OPG-Fc and tumor progression was monitored using radiography, longitudinal bioluminescent imaging, and histology. The results from both NSCLC bone metastasis models showed that RANKL inhibition reduced osteolytic lesions and skeletal tumor progression. This observation was associated with reduced tumor-associated osteoclasts. These findings indicated that RANKL is needed for tumor-mediated osteolytic bone destruction in NSCLC cells in vivo. The effect of RANKL inhibition on skeletal tumor progression could be a result of indirect suppression of tumor-mediated osteoclastogenesis hence blocking the release of growth

factors and calcium from the bone microenvironment. In addition, significantly enhanced inhibition of skeletal tumor growth was observed in OPG-Fc plus docetaxel compared with either agent alone. To conclude, this in vivo study provided solid evidence supporting the antitumor effect and a survival advantage of RANKL inhibition in NSCLC. It also indicated the therapeutic potential of targeting bone environment to achieve better outcomes in patient, which warrants further clinical studies. (p. 345)

- **Impact of Extratumoral Lymphatic Permeation on Postoperative Survival of Non–Small-Cell Lung Cancer Patients**



Lymphatic permeation has been a prognostic factor for patients with resected non–small-cell lung cancer and the authors set out to evaluate its survival impact in these patients based on its location, which is in this study, in extratumoral area. From the long-term follow-up data (2001–2006), 1069 consecutive patients with resected NSCLC were analyzed and categorized by absence of (ly0), intratumoral (ly1), and extratumoral (ly2) lymphatic permeation. Majority of the patients (79%) showed no lymphatic permeation; 12% were ly1 whereas 9% were ly2. Ly2 has a higher incidence in patients with advanced disease and intrapulmonary metastases, and significantly worse 5-year overall survival rate (34%) versus ly0 (75%, $p<0.01$) and ly1 (63%, $p<0.01$). The findings also demonstrated ly2 as an independent poor prognostic factor (hazard ratio, 1.73; $p < 0.01$). There was no significant difference in overall survival and recurrence-free survival between the different pT status of tumor where ly2 was present: T1 and T2 ($p = 0.43$ and $p = 0.94$, respectively) and T3 ($p = 0.77$ and $p = 0.94$, respectively). This study demonstrated a marked difference in the adverse prognostic impact of lymphatic permeation based on its intra-/extratumoral locations. It therefore underscores the importance of assessing locations of lymphatic permeation in resected NSCLC patients. (p. 337)

RESEARCH WATCH

- **Structural, Biochemical, and Clinical Characterization of Epidermal Growth Factor Receptor (EGFR) Exon 20 Insertion Mutations in Lung Cancer**

Although epidermal growth factor receptor (*EGFR*) mutations (G719X, exon 19 deletions/insertions, L858R, and L861Q) are associated with sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs) in advanced non–small cell lung cancer (NSCLC), *EGFR* exon 20 insertion mutations are associated with insensitivity to TKIs. This study evaluated the mechanism of this primary resistance by investigating a range of exon 20 insertion mutations in vitro for TKI sensitivity and comparing it with patients' responses to gefitinib and erlotinib. The findings showed that most of these exon 20 mutations were resistant to EGFR TKIs. Analysis of the crystal structure demonstrated that the TKI-insensitive mutant (D770_N771insNPG) adopts a structure of adenosine triphosphate–binding pocket and the helix, which helps the active kinase conformation, and activates EGFR by not enhancing its affinity for EGFR TKIs. Interestingly, a novel mutation EGFR-A763_Y764insFQEA uncovered in this study was shown to be highly sensitive to EGFR TKIs in vitro. Its presence in NSCLC patients was associated with response to erlotinib. Further evaluation of this mutant revealed an altered structure in area affected by the TKI-sensitive EGFR-L858R. The results of this study demonstrated complex and detailed interplay between EGFR mutations and their response to EGFR TKIs. It also guides the treatment of NSCLC harboring *EGFR* exon 20 insertion mutations.

Yasuda H, Park E, Yun C-H, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sc Translat Med* 2013;5:216ra177.