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Epidermal Growth Factor Receptor Mutation in Newly Diagnosed Lung Adenocarcinoma

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Abstract

Introduction: Studies of EGFR mutation frequency in patients with non-small cell lung cancer (NSCLC) or lung adenocarcinoma were limited to clinical trials, convenient sample, retrospective studies of archived samples or studies involving advanced lung cancer only.

Methods: A cross sectional, single center, prospective study of EGFR mutation status among patients with newly diagnosed lung adenocarcinoma attending University Malaya Medical Center over a 4-year-period.

Results: Of 394 patients with adenocarcinoma, 166 (42.1%) were tested EGFR mutation-positive while the remaining 228 (57.9%) had EGFR wild-type tumour. Exon 19 deletion mutation was the most common EGFR mutation subtype (96 (24.4%)), followed by exon 21 L858R point mutation (64 (16.2%)). On univariate analysis, gender, smoking status and smoking pack-years ($p<0.001$) were significantly associated with EGFR mutation status. Multivariate logistic regression analysis identified smoking status and smoking pack-year ($p<0.001$) as independent predictive factors for EGFR mutation positivity. EGFR mutation frequency was significantly higher in never smokers (OR, 7.12; 95% CI, 3.79 – 13.38; $p<0.001$) and previous smokers (OR, 2.45; 95% CI, 1.18 – 5.09; $p=0.016$). Compared to current or previous smokers of more than 50 pack-years, those who smoked less than 10 pack-years (OR, 7.70; 95% CI, 2.06 – 28.74; $p=0.002$) and 10-20 pack-years (OR, 3.42; 95% CI, 1.02 – 11.50; $p=0.047$) had significant higher frequency of EGFR mutation.

Conclusion: EGFR mutation is common in Malaysian patients with lung adenocarcinoma. A never smoking status is a robust independent predictor of EGFR mutation positivity. EGFR mutation rate was inversely related to the amount of smoking, and is significantly lower in patients who smoked >20 pack-years.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1], with 85% of lung cancer being of non-small cell lung cancer (NSCLC) variety [2]. In recent years, adenocarcinoma has replaced squamous cell carcinoma as the commonest histological subtype of lung cancer in many parts of the world, including in Malaysia [3].

Presence of activating mutation in the epidermal growth factor receptor (EGFR) of NSCLC predicts clinical response to gefitinib, an oral first-generation reversible EGFR-tyrosine kinase inhibitor (EGFR-TKI) [4,5]. EGFR is a transmembrane glycoprotein that is coded by a gene located at the short arm of chromosome 7. Mutation in EGFR causes continuous tyrosine kinase activities that can lead to uncontrolled cellular proliferation, differentiation, migration and survival, which ultimately leads to lung cancer development [6]. The frequency of EGFR mutation has been found to be high among East Asian, women, non-smoker and adenocarcinoma subtype of NSCLC [7-9].

Several phase 3 clinical trials have demonstrated the superiority of EGFR-TKI over cytotoxic chemotherapy as first-line treatment in patients with EGFR mutant advanced NSCLC or adenocarcinoma in terms of response and progression-free survival [10-16]. Clinical guidelines recommend EGFR-TKI as first-line treatment in patients with EGFR-mutant advanced NSCLC [17,18]. As EGFR mutation testing is costly, understanding independent predictive factor of EGFR mutation become very important in prioritizing patients for this investigation. This is particularly true at the area with limited laboratory support and financial resources.