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Title: Frequency of T790M substitution in exon 20 of EGFR gene in brain metastases in chemotherapy-naive non-small cell lung cancer patients (NSCLC)

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Body: Reversible tyrosine kinase inhibitors (TKI) of EGFR (erlotinib, gefitinib) have shown limited efficacy in patients with activating mutations of EGFR gene. The resistance to reversible TKI and the sensitivity to irreversible pan-HER inhibitors (afatinib, neratinib) are related to secondary mutations in EGFR gene, especially T790M mutation (50% of resistance). However, data concerning the frequency of primary T790M substitution in NSCLC metastases is scarce. Our study was aimed to develop a new method for T790M EGFR gene mutation analysis and to estimate the frequency of this mutation in chemotherapy-naïve patients with NSCLC brain metastases. DNA was isolated from 150 paraffin-embedded tissue samples using Qiamp DNA FFPE tissue kit. We used ASP-PCR (allele-specific PCR) technique and fluorescence CY5 labelled primers, which are specific for mutated or wild-type EGFR gene exon 20. The analysis was performed on ALF Fragment Analyzer. Method proved sufficient and sensitive enough to estimate the presence of T790M mutation in all examined samples. 3 patients (2%) with T790M substitution were detected, one suffering from non-differentiated NSCLC (non-smoker) and two with squamous cell carcinoma (10- and 20-pack-years smokers). Coexistence of T790M and activated EGFR gene mutations was not detected. The primary T790M substitution of EGFR gene is detectable in chemotherapy- and TKI EGFR-naïve patients. It is recommended to perform complete EGFR gene mutation analysis, including exon 20, before treatment.