High tumor metabolic activity is associated with circulating tumor DNA detection in early-stage lung cancer patients

Anine Larsen Ottestad[1]
Håkon Johansen[2], Tarje Onsøien Halvorsen[1], Hong Yan Dai[3], Sissel Gyrid Freim Wahl[3], Elisabeth Fritzke Emdal[3] and Bjørn Henning Grønberg[1]
[1] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU) & Department of Oncology, St. Olavs Hospital, Trondheim, Norway
[2] Department of Radiology and Nuclear Medicine, St. Olavs Hospital, Trondheim, Norway
[3] Department of Pathology, Clinic of Laboratory Medicine, St. Olavs Hospital, Trondheim, Norway

Background & objectives

The analysis of circulating tumor DNA (ctDNA) can be used to evaluate treatment response or detect minimal residual disease. Such approaches may require ctDNA detection before treatment, which is challenging in early-stage lung cancer since the ctDNA level is frequently below the limit of detection. Studies on metastatic lung cancer suggest that high a ctDNA level is correlated with high tumor metabolic activity, which can help identify those who may benefit from ctDNA analysis. This study aimed to explore this association in early-stage lung cancer patients.

Methods

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT) was used to assess the tumor metabolic activity by quantifying the tumor glucose uptake. Three parameters were derived: the maximum glucose uptake (SUVmax), the tumor volume of above-threshold glucose uptake (MTV), and the total glucose uptake within the tumor volume (TLG). Sensitive, tumor-informed approaches were used to analyze plasma ctDNA, which was quantified by the mutant allele frequency.

Results

The study included 63 patients with stage I-III non-small cell lung cancer, of which 90 % had adenocarcinoma. ctDNA was detected in 19 patients (30 %) who had higher SUVmax, MTV, and TLG than those without detectable ctDNA ($p<0.001$). For these patients, the ctDNA level correlated with the MTV (Spearman's $\rho=0.53$, $p=0.021$) and the TLG (Spearman's $\rho=0.56$, $p=0.013$), but not with the SUVmax

(Spearman's ρ=0.034, p=0.15). High MTV and TLG were associated with ctDNA detection independently of disease stage (OR 8.9, 95% CI: 2.1-66.5, p=0.0110 and OR 4.7, 95% CI: 1.6-20.9, p=0.0160, respectively), while SUVmax was not (OR: 7.65, 95% CI: 0.42-238.7, p=0.192). Notably, we observed patients with high tumor metabolic activity and undetectable ctDNA and vice versa.

Conclusion

This study indicated a positive association between tumor metabolism and ctDNA level, which has also been shown in a few previous studies on early-stage non-small cell lung cancer. However, the results suggest that ctDNA release cannot be explained by metabolic activity alone.