



# Computed tomography characteristics of non-small cell lung cancers with *EGFR* T790M mutation: role of imaging in the era of precision medicine

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Provenance: This is an invited Editorial commissioned by the Section Editor Jun Zhou (Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Comment on: Koo HJ, Kim MY, Park S, *et al.* Non-small cell lung cancer with resistance to EGFR-TKI therapy: CT characteristics of T790M mutation-positive cancer. *Radiology* 2018;289:227-37.

Submitted Sep 25, 2018. Accepted for publication Oct 04, 2018.

doi: 10.21037/jtd.2018.10.26

View this article at: <http://dx.doi.org/10.21037/jtd.2018.10.26>

Early clinical trials investigating the effectiveness of first generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) demonstrated significant prolongation of survival in patients with non-small-cell lung cancers (NSCLCs) harboring sensitizing mutations (1-3), leading to a major shift in the treatment landscape of NSCLCs. Indeed, EGFR-TKI is now the standard treatment option for lung cancer patients with activating *EGFR* mutations. Unfortunately, however, all patients receiving EGFR-TKIs will eventually develop resistance to therapy via acquired resistance mechanisms such as secondary T790M mutation in exon 20, *EGFR* amplification concurrent with T790M, bypass signaling activation (*MET* amplification, *Her-2* amplification, or *MAK* amplification), or phenotype transition to small cell lung cancers (4). Among them, secondary T790M mutation which comprises approximately 50–60% of the resistance has been shown to increase affinity for adenosine triphosphate (ATP) within the tyrosine kinase domain of *EGFR*, thereby leading to decreased binding of EGFR-TKIs (4).

Recently, Koo *et al.* (5) reported the computed tomography (CT) imaging characteristics of T790M mutation-positive NSCLCs in a retrospective analysis of 304 patients who underwent repeat biopsy using various methods for evaluation of disease progression after first-line EGFR-TKI therapy (gefitinib, erlotinib, or afatinib).

All patients had *EGFR*-sensitizing mutations and most of them were enrolled in clinical trials for osimertinib or olmutinib. According to their study results, CT findings including peripherally located tumors with vascular convergence [odds ratio (OR), 2.55], pleural tag (OR, 4.99), and air bronchogram (OR, 4.02) at repeat biopsy were demonstrated to be significantly associated with T790M mutation positivity. The discriminatory performance of the logistic regression model based on these findings showed a C-index of 0.753 and the addition of clinical information (time from TKI initiation to rebiopsy) achieved a C-index of 0.761. Interestingly, however, the authors described that only pleural tag was significantly associated with T790M mutation at multivariable analysis when using baseline CT characteristics. They hypothesized that air bronchogram, peripheral tumor location, and pleural tag observed in T790M mutation-positive tumors implied manifestations of the initial types of adenocarcinomas given that these are commonly found in bronchioloalveolar carcinomas.

The study by Koo *et al.* (5) brings timely contribution to the role of CT imaging in this era of precision medicine. CT imaging can non-invasively evaluate the entire tumor and has the potential to inform the clinical decision making via qualitative or quantitative imaging features that may allow a diagnostic or prognostic prediction as reported by Koo *et al.* (5). However, there is a caveat in that the

prediction of T790M mutational status based solely on CT imaging findings may not be practical, thereby lacking clinical applicability; in fact, the prediction model proposed in their study still warrants external validation. Then, what would be the real world, clinical value of radiogenomic findings? In patients with negative repeat biopsy results, as an example, it may be possible to recommend third repeat biopsy based on these CT findings. Furthermore, the diagnostic yield of repeat biopsy can be augmented by targeting peripherally located tumors with vascular convergence and air bronchogram, if feasible. Indeed, such a targeting strategy may lead to a breakthrough in overcoming inter-tumoral heterogeneity by specifically targeting T790M mutation-positive subsets. Therefore, prospective validation studies demonstrating the potential clinical benefit of radiogenomic association are warranted. In addition, the prognostic implication of these CT findings, which remind us of bronchioloalveolar carcinomas, is another interesting subject. In fact, peripheral tumor location with air bronchogram is a common finding in adenocarcinomas. Thus, the prognostic significance of these findings in adenocarcinomas in general or in patients with adenocarcinomas receiving targeted therapy may pique the readers' attention.

Radiogenomics is an evolving field that may go hand in hand with advancements in targeted therapy and the need for personalized medicine. Previously, Hasegawa *et al.* (6) revealed that *EGFR* mutation was significantly associated with the convergence of structures (vessels or bronchi around the primary tumor), ground-glass opacity, and the notch sign at CT. In a detailed study for *EGFR* mutational subtypes performed by Lee *et al.* (7), they demonstrated that ground-glass opacity volume percentage in adenocarcinomas with exon 21 missense mutation was significantly higher than that in tumors with other mutations (7). In addition, Choi *et al.* (8) analyzed the CT characteristics of lung adenocarcinomas with two distinct driver mutations, reporting that tumors with anaplastic lymphoma kinase rearrangement were more likely to be solid masses with lobulation than those with *EGFR* mutations. As for the association between T790M mutational status and imaging findings, Yoshida *et al.* (9) observed that patients with the T790M mutation showed lower levels of <sup>18</sup>F-2-fluoro-2-deoxyglucose uptake on positron emission tomography compared to those without the T790M mutation. More recently, Kim *et al.* (10) suggested that smaller lung nodule size and selection of metastatic lung lesions as biopsy targets were associated with the detection of the T790M mutation at repeat biopsy.

In addition to these imaging features, the clinical characteristics associated with the T790M mutation need to be mentioned. Kawamura *et al.* (11) reported that post-surgery recurrence and longer duration of EGFR-TKI were associated with T790M detection, while Oya *et al.* (12) found that gender (male), initial EGFR-TKI response (complete or partial response), duration of progression-free survival (>6 months), and progression pattern (solitary lesion progression) were independent predictors for the T790M mutation.

At present, osimertinib is the recommended standard of care for patients with acquired T790M mutation (13). This third generation EGFR-TKI irreversibly binds to the cysteine-797 residue in the ATP-binding site via covalent bond formation (13). Recent clinical trials have shown promising results for the usage of osimertinib as a first-line treatment option for *EGFR*-mutant advanced NSCLCs (14,15). However, current practice is still based on the confirmation of acquired resistance to EGFR-TKIs and the presence of T790M mutation. Thus, specimen acquisition and mutational testing remain relevant and repeat biopsy is required at the time of disease progression. Several case series have already shown the clinical feasibility of repeat biopsy in terms of diagnostic yield and complication rates (10,16-19).

An alternative method to tissue sampling is the analysis of cell-free circulating tumor DNA (ctDNA), also referred to as "liquid biopsy". Liquid biopsy is convenient, less-invasive, and can be performed on a serial basis for the evaluation of disease status at multiple time-points. Furthermore, it can deliver information of the entire tumor burden contrary to conventional biopsy which is intrinsically limited by tumor heterogeneity. Therefore, liquid biopsy without tissue biopsy has the potential to inform the treatment plan in patients receiving targeted therapy (20), albeit with some remaining issues in pre-analytical and analytical validity (21). It is also worth noting that a subset of patients have exhibited discordant results between tissue and ctDNA genotyping, i.e., mutational status was negative in the tissue sample but positive at ctDNA, and vice versa (21,22). Thus, it has been suggested that tissue biopsy and blood-based analyses may have complementary roles in assessing the genetic profile of these patients (22). In this circumstance, imaging studies may aid in identifying individuals with DNA-shedding or non-shedding tumors in addition to those with the possibility of false negative liquid biopsy results or discordant mutational profiling. Nevertheless, investigations into these issues have remained paltry, and

thus further studies are strongly warranted.

In recent years, CT imaging findings associated with oncogenic driver mutations in NSCLC have been described (7,23,24). This radiogenomic analysis can be conducted using semantic features and/or radiomics features as well as the deep learning technique which may be a novel promising tool for capturing and modeling imaging characteristics (25). The next challenges that remain to be solved would be standardization of methodology, validation of these radiogenomic relationships in a large prospective cohort, and development of a reproducible multi-class classification model which would enable the discrimination of various targetable driver mutations (e.g., *EGFR*, *KRAS*, *ALK*, *BRAF*, or *ROS1* rearrangement).

### Acknowledgements

We would like to thank Chris Woo, BA, for this editorial assistance.

*Funding:* This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A1B04032467).

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Kim H, Lee HJ. Computed tomography characteristics of non-small cell lung cancers with EGFR T790M mutation: role of imaging in the era of precision medicine. *J Thorac Dis* 2018;10(Suppl 33):S4126-S4129. doi: 10.21037/jtd.2018.10.26