Editorial

Personalized post-surgical care?—possible strategies for NSCLCs with *EGFR* mutation

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Introduction

Personalized treatment has become the standard of care for advanced stage non-small-cell lung cancer (NSCLC) patients (1). Mutational status of driver genes, such as epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and *ROS1*, as well as membranous protein expression of programmed death-ligand 1 (PD-L1) in tumor cells are used to select the appropriate systemic therapy for these patients. However, in earlier stage cases, NSCLCs are still being treated as one disease even though surgical resection provides large amounts of tumor tissue for molecular analyses.

The risk of post-surgical recurrence is still problematic even when locoregional control is thought to have been achieved by "complete" surgical resection; e.g., a recent Japanese registry study for surgically resected lung cancer patients (n=18,973) reported that the disease-free survival rate at 5 years was 67.8% (2). Currently, TNM staging is the sole established prognostic factor to stratify the risk of recurrence. The pathological stage is used to guide surgeons in deciding intervals of post-surgical surveillance and determining indications for adjuvant therapy. As a next step, how can we optimize the post-surgical treatment strategy to improve the outcomes of surgically resected NSCLC patients? I propose that, similar to the advanced-stage setting, personalization will be an important component for this strategy and that personalized post-surgical care will consist of the following three steps: evaluate the personal risks of recurrence, predict the possible metastatic organ(s), and select an appropriate adjuvant therapy for high-risk patients.

In a recent study, Jianjiao Ni and colleagues analyzed the implications of routine immunohistochemistry (IHC) markers as prognostic factors and as predictors of initial recurrence sites in a large cohort (n=531) of surgically resected NSCLC patients (3). A noteworthy point of this study is that the study only included NSCLC patients with activating *EGFR* mutation. The authors reported two IHC markers, Ki67 and CK20, as independent predictors of overall recurrence, as well as some risk factors of site-specific recurrence. In N2-positive *EGFR*-mutant NSCLC patients, the authors found that adjuvant radiotherapy improved disease-free survival (but not overall survival).

In this Editorial, I would like to discuss the possibility of personalized post-surgical care in NSCLC patients, referring to the contributions from the recent publication by Ni and colleagues (3).

Personalizing the risk of recurrence: is EGFR mutation status useful?

Ni and colleagues performed an analysis using a cohort of surgically resected NSCLC patients selected by the presence of *EGFR* mutation (3). The first question to consider is whether driver mutation data are useful to estimate the risk of post-surgical recurrence.

After the discovery of *EGFR* mutations in NSCLCs, numerous studies have evaluated the prognostic implications of *EGFR* mutation status in surgically resected NSCLC patients. However, the results are still controversial, even in recent analyses of large cohorts. For example, Kim and colleagues analyzed 689 patients with stage I–III lung adenocarcinoma patients and concluded that *EGFR* mutation was a better independent prognostic factor for overall survival, and a more favorable prognostic effect was seen in younger patients; the hazard ratio for *EGFR* mutation was 0.14 at 50 years, 0.26 at 60 years, and 0.50 at 70 years (4). In contrast, Ito and colleagues performed a multicenter database analysis (n=1,155, pN0–1M0 lung adenocarcinoma) and reported that *EGFR* mutation-positive cases showed worse recurrence-free survival among those with higher risk of recurrence (5). Furthermore, a recent meta-analysis of literature (n=4,872) concluded that disease-free survival of NSCLC patients with *EGFR* mutation was similar to that of wild-type patients in the overall population and in the stage I subgroup (6). These results indicate that while the data on whether *EGFR* mutation is a better or worse prognostic factor are controversial, *EGFR* mutation is, at the least, not a definitively strong prognostic factor, and therefore examination of *EGFR* mutation status will not help surgeons evaluate the personal risk of recurrence after pulmonary resections.

Prognostic biomarkers specific for NSCLCs with EGFR mutation

To date, numerous attempts have been made to identify prognostic molecular markers, e.g., expression status of a specific molecule or gene expression signatures, in surgically resected NSCLC patients. However, no marker or signature has been successfully adopted in clinical practice partially because of poor reproducibility. A recent comprehensive study that performed multi-region whole-exome and RNA sequencing, as a part of the TRACERx lung study, reported that the poor reproducibility could be explained by tumor sampling bias, which is caused by the intratumor heterogeneity of expression status of candidate genes (7). In addition to the influence of intratumor heterogeneity, inter-tumor heterogeneity, such as a difference in oncogenic driver mutation, may affect the significance of candidate "prognostic" markers; e.g., a poor prognostic factor "A" in NSCLCs with *EGFR* mutation may have no prognostic impact in NSCLCs with *ALK* fusion.

Currently, some retrospective data by our group and by others have supported this hypothesis. In 2014, we reported that high mRNA expression of aromatase, an intrinsic estrogen synthetase, was a poor prognostic factor in terms of recurrence-free and overall survival only in lung adenocarcinoma patients with *EGFR* mutation but not in patients without *EGFR* mutation (8). Poor prognostic implications, specific for NSCLCs with *EGFR* mutation, were also reported for estrogen receptor-alpha expression (9), *EGFR* gene amplification (10), and *TTF-1* gene amplification (10). However, none of these results have been confirmed in independent studies. Therefore, it is interesting to consider whether the identified prognostic IHC markers by Ni and colleagues (3), the combination of Ki67 and CK20 in addition to tumor size and N stage, is reproducible and specific for NSCLCs with *EGFR* mutation.

Can the presence of an EGFR mutation predict possible recurrence organ(s)?

Determining *EGFR* mutation status after surgical resection would be important if the presence of *EGFR* mutation is predictive of future organ sites of recurrence. Currently, however, the frequency and target (such as intrathoracic organs, abdominal organs, bones, or brain) of image examination to detect post-surgical recurrences are not based on the mutational status of driver genes, and NSCLC patients are usually indicated to receive thoracic computed tomography scan, with/without contrast, every 3–6 months during the first 2–3 years and then every 6 months or annually for at least 5 years. No recommendations have been made concerning follow-up for brain, bone, or abdominal metastases.

Metastasis is regarded as a highly inefficient process, in that less than 0.01% of circulating tumor cells eventually succeed in forming secondary tumor growths (11). Although the metastatic organ(s) can be determined by the anatomy of vascular or lymphatic drainage from the site of primary tumors, some tumor cells are thought to preferentially grow in the microenvironment of selected organs (the "seed and soil" hypothesis) (12). Therefore, the mutational status of the driver gene, an important characteristic of tumor cells (the "seed"), may likely have something to do with the preferred metastatic organs (the "soil"). Some retrospective studies have been performed; however, the results are not consistent. Mizuno and colleagues reported a higher risk of pleural recurrence and lower risk of adrenal recurrence in *EGFR*-mutated NSCLCs and a higher risk

of locoregional recurrence in *ALK*-positive tumors (13). Renaud and colleagues reported a higher risk of liver and brain metastases in NSCLC patients with *EGFR* mutation, and patients with *KRAS* G12C and G12V developed significantly more bone and pleuro-pericardial metastases, respectively (14). Despite some discordances between reports, multiple studies have suggested a higher risk of brain recurrence in NSCLCs with *EGFR* mutation after pulmonary resection (14,15), which is also supported by the higher incidence of brain metastases in clinical stage IV NSCLCs with *EGFR* mutation (16).

Biomarkers to predict a possible recurrence site(s) in NSCLCs with EGFR mutation

The next question is whether there is any molecular biomarker for the organ-specific metastasis. There are several studies on metastatic organotropism, mainly the analyses of breast cancers, that report the roles of CXCR4 and CCR7 expression, which partner with chemokine ligands expressed in lymph nodes (CXCL12) and lung (CCL21) (17,18), or tumor exosome integrins, $\alpha_6\beta_4$ and $\alpha_6\beta_1$ for lung metastasis and $\alpha_v\beta_5$ for liver metastasis (19). Currently, there is no available evidence in NSCLCs with *EGFR* mutation. Therefore, significant risk factors reported in the study by Ni and colleagues (3), positive CK20 and synaptophysin for brain recurrence (HR 4.271, P=0.017 and HR 4.378, P=0.015, respectively), may have clinical implications if the results are confirmed by independent studies. Regarding the metastatic organotropism of NSCLCs with *EGFR* mutation, one recent paper reported that the presence of micropapillary pattern was associated with the development of brain metastases after pulmonary resection in lung adenocarcinomas with *EGFR* mutation (20).

Personalized adjuvant therapy for NSCLCs with EGFR mutation

Currently, platinum-based doublet chemotherapy is usually administered as an adjuvant therapy for surgically resected NSCLC patients with pathological stage II–III disease (and for some stage IB patients with extra risk factors). However, the clinical benefit is small, increasing the 5-year survival rate by only 5.4%. In addition, a recent propensity-score matching analysis of pathological stage II/III lung adenocarcinoma reported that platinum-doublet adjuvant chemotherapy was associated with favorable prognosis among patients with wild-type *EGFR*, but not among patients with *EGFR* mutation (21).

Because EGFR tyrosine kinase inhibitors (TKIs) are the most effective drugs for NSCLC patients with *EGFR* mutation in advanced-disease setting, it is reasonable to consider the use of EGFR-TKIs as adjuvant therapy instead of platinum-doublet chemotherapy or after platinum-doublet chemotherapy. To date, several groups have performed clinical trials of adjuvant EGFR-TKI monotherapy in NSCLC patients selected by the presence of activating *EGFR* mutations; these groups reported a prolonged recurrence free survival in EGFR-TKI groups, while overall survival data remain unclear or controversial (22). I consider that adjuvant EGFR-TKI has clinical benefit in patients with extremely high-risk for recurrence, even if the overall survival benefit is minimal, because survival without recurrence will be more meaningful than survival with recurrence for patients. The study by Ni and colleagues (3) also suggested the usefulness of adjuvant radiotherapy for *EGFR*-mutant NSCLC patients with N2-positive disease in terms of disease-free survival (3). Although this result should be confirmed in a larger cohort, future studies should investigate the best adjuvant treatment strategy for *EGFR*-mutant NSCLC patients with N2-positive disease, which should be one of the following: adjuvant radiotherapy, adjuvant EGFR-TKI monotherapy, or adjuvant radiotherapy followed by EGFR-TKI monotherapy.

Future perspectives and conclusion

In addition to the personalized post-surgical care, there are other potential approaches to improve the outcomes of surgically resected NSCLC patients. Such approaches include circulating tumor DNA detection (liquid biopsy to detect tumor recurrence earlier than computed tomography scans) and application of adjuvant/neoadjuvant immunotherapies. Combining some of these approaches may be a good strategy.

Personalized therapies have dramatically changed clinical practice and treatment outcomes of advanced-stage NSCLC patients. As described in this editorial, more and more data are needed to discuss the possibilities of personalized post-surgical care in earlier-stage NSCLC patients.

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