Who to Test for an EGFR Mutation or ALK Rearrangement: Filtering Based on TTF-1 Status

Thyroid transcription factor-1 (TTF-1) is a protein seen on the surface of thyroid cells, but also on about 70-75% lung adenocarcinomas and only a small minority (~10%) of squamous cell NSCLC tumors. In fact, the presence of TTF-1 on a NSCLC tumor provides a good hint for the pathologist that this is an adenocarcinoma. It’s an immunohistochemical (IHC) test that is done on the vast majority of lung cancers, and there’s some new information that suggests it may also be useful for predicting which patients are especially unlikely to have an EGFR mutation or ALK rearrangement. This is especially important as we are now faced with a question of whose tissue to send for these particular tests, especially if this decision involves obtaining another biopsy.

A few months ago, a group from Seoul, Korea published their results on the correlation between ALK positivity in a series of 221 patients with lung adenocarcinoma and other clinical and pathologic features. In this somewhat selected group of Asian patients with an adenocarcinoma, 45 (20%) had an ALK rearrangement, and this population skewed toward being younger than other patients (49 vs. 61), but didn’t differ in smoking status (about half were never-smokers in both groups for this population) or gender distribution, but they did have two striking features. ALK rearrangements were mutually exclusive with an EGFR mutation (they were never seen in the same patient), and there were no patients with an ALK rearrangement who tested negative for TTF-1 expression.

It remains to be seen whether this negative predictive value will be confirmed in other patient populations, but it’s interesting that in an ASCO presentation this year by Drs. Neeta Somajiah and my friend George Simon, both previously at Fox Chase Cancer Center and now at Medical University of South Carolina (MUSC) in Charleston, they found only 2 of 224 patients with a lung adenocarcinoma had an EGFR mutation if they tested negative for TTF-1, so there was a 99% chance that this would be a negative test if TTF-1 was known to be negative. The Korean paper on the association of ALK and TTF-1 noted that an EGFR mutation was present in 6% of patients who were TTF-1 negative. And prior work from a group in France has also shown that patients with bronchioloalveolar carcinoma (BAC) who received the EGFR inhibitor Iressa (gefitinib) were far more likely to respond if their cancer was positive for a TTF-1, which I suspect is because this is closely correlated with the presence of an EGFR mutation (or, probably more accurately, the absence of TTF-1 is closely related to not having an EGFR mutation.

It will be helpful to see these results corroborated or perhaps refuted by other groups as testing for these mutations becomes more widespread, particularly in broader audiences. Given that these results are all from patient groups limited to those with an adenocarcinoma, what I’d most like to see is whether the small minority of people with squamous cell or large cell NSCLC are also TTF-1 positive. If so, this may help demonstrate which patients who don’t fit the usual clinical profile for an ALK rearrangement or EGFR mutation should definitely be tested, while allowing us to have confidence about NOT testing some patients. And with these tests running into the thousands of dollars per patient, with some risk if patients need another
biopsy to get tissue, it would be helpful to be better able to identify a subset of patients who really don’t need to be tested for these markers.