“Reflex Testing” in Lung Cancer: Who to Test and When?

It’s probably the biggest debate in lung cancer right now, and the answers are evolving every few months:

1) Which patients should be tested for molecular markers like EGFR, KRAS, ALK, etc.?

2) What tests should be sent?

3) When should these studies be sent? Right at the time of diagnosis (“reflex testing”), or after an oncologist has assessed how important these tests are really going to be, and decide which studies to send accordingly?

This morning, I and my colleagues debated some of these issues in our multidisciplinary thoracic oncology tumor board session, which brings together medical oncologists, our thoracic surgeons, radiation oncologists, pathologists, radiologists (including our interventional radiology colleagues who get many of the biopsies), and pulmonologists. We wanted to develop a set of guidelines for our institution about whether we should be sending off these markers from the pathology lab even before these patients find their way to an oncologist or not, since most patients may go at least a few days and sometimes a week or two between the diagnosis of lung cancer being established and them seeing an oncologist to shape the plan.

There are a few background points to clarify. First, having more tissue is always better, and this is a shift from the way things have always been in lung cancer, when just getting a few cells from a fine needle aspirate was enough to make a diagnosis of NSCLC vs. SCLC, and that was all you needed. These days, NSCLC subtype in terms of histology — adenocarcinoma, squamous, large cell neuroendocrine, etc. — are now routinely used in shaping our recommendations about one treatment or another. And now the potential to dramatically alter the course of someone’s treatment by identifying a mutation associated with a high probability of a prolonged response to a targeted therapy raises the stakes.

Meanwhile, we can also make some clear statements about the significance of some of the markers. The high probability of a great benefit from EGFR tyrosine kinase inhibitors in someone with an EGFR mutation or from crizotinib in someone with an ALK rearrangement leads us to want to give these agents to the person with the relevant target as soon as possible. Though crizotinib has yet to be approved by the FDA, that’s expected soon; in the meantime, multiple trials have shown that patients with an EGFR mutation do significantly better in terms of progression-free survival and response rate, with a trend toward better survival, by receiving first line EGFR tyrosine kinase inhibitor (TKI) therapy. In contrast, those without an EGFR mutation are poorly served by starting with an EGFR TKI therapy and do clearly better with chemo. While we know that EGFR mutations are more common in women than men, Asian than Caucasian patients, those with an adenocarcinoma vs. other histology, and in never-smokers compared with current or former smokers, these are all just probabilities — in the IPASS trial, 40% of Asian never smokers with an adenocarcinoma didn’t have an EGFR mutation, while a very recently published article from Memorial Sloan-Kettering Cancer
Center showed that among more than 2000 patients with a lung adenocarcinoma, plenty of patients with an EGFR mutation were former smokers, as well as some current smokers, and about a third were men.

So we know that clinical selection (presumption of mutation results based on factors like patient sex, smoking status, race, etc.) is not sufficient and that guessing wrong (either way) can harm a patient. These results led the National Comprehensive Cancer Network (NCCN) to update their guidelines in the initial evaluation of metastatic NSCLC to recommend immediate clarification of the tumor histology and then, for all patients with non-squamous NSCLC, to seek EGFR mutation status results immediately:

While the association of EGFR mutations (and ALK rearrangements, for that matter) with adenocarcinoma histology is well established, it’s less clear that the prevalence of EGFR mutations in other non-squamous histologies ranging from large cell NSCLC to “poorly differentiated, NSCLC not otherwise specified” is very high, but the NCCN group felt that the evidence was most sufficient to say that the probability of having an EGFR mutation in squamous NSCLC was low enough to not include them for immediate testing.

And by the way, why is it important to consider reflex testing vs. just waiting for an oncologist to order these tests? Because there can be a lag time of a few weeks between the first time a tissue diagnosis of NSCLC is established and the time an oncologist sees a patient and makes recommendations. If someone’s tissue is sent for testing right at diagnosis, then sees an oncologist two weeks later, the time required for the test (typically in the range of 1-2 weeks, and sometimes longer) doesn’t need to be added after the patient sees the oncologist. This means that fewer patients need to wait for a few weeks to get the best recommendation of what treatment to start.

Even though everyone in our group agreed on several of the principles, here were a few of the questions that were discussed, and some without a clear answer yet:

1) Do we definitely test all patients with non-squamous NSCLC, even if patients with a large...
cell or very poorly differentiated NSCLC probably have a very low probability of having a mutation?

2) In patients who don’t have enough tissue, in which patients will we feel strongly enough about getting tissue testing that we’d push for an extra biopsy, with the added time, expense, and (minimal, but some) risk that this would entail?

3) Do we test patients with earlier stages of NSCLC, either in consideration of immediate management or to just have the information quickly if their cancer progresses?

4) Do we just test for EGFR, which is the only one specified in the guidelines, or do we also include KRAS and ALK testing? Others that are less established?

5) Will insurers pay for these tests? If not, will patients accept the costs, which can exceed $1000 for just a few tests?

I’ll continue with the actual back and forth discussion of these questions in my next post.

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