EGFR mutation testing in advanced stage adenocarcinoma of the lung

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Non-Small Cell Lung Cancer (NSCLC) comprises 80-85% of all lung cancer and the majority of patients present with advanced disease. Over 220,000 patients will be diagnosed and 158,000 will die in 2015 in the US alone. Despite recent therapeutic advances long term prognosis remains poor, with an estimated overall 5 year survival rate of less than 5% for patients with metastatic disease. Within the past decade, genotype-directed therapies have led to significant improvements in response rates and progression free survival compared to patients treated with traditional cytotoxic chemotherapies. This is particularly true in the case of epidermal growth factor receptor (EGFR) directed tyrosine kinase inhibitors (TKIs).

EGFR is a protein expressed on the surface of epithelial cells that is often overexpressed in many human malignancies. EGFR can also be mutated in malignancy and the presence of certain "activating" mutations such as exon 19 deletions, exon 21 L858R, exon 18 G719X or G719, and exon 20 S768I are predictive of responsiveness to EGFR directed TKIs, though exon 20 mutations are noted to be more resistant. The prevalence of sensitizing mutations is 10% in Caucasian patients and up to 50% in Asian patients. These mutations are also more prevalent in women, in non-smokers, and in adenocarcinomas.

EGFR TKIs such as erlotinib, gefitinib, and afatinib have now been established as effective first line therapies in NSCLC with activating mutations. Response rates range from 70-80% and their median progression free survival is 12 months. This is compared to more traditional cytotoxic chemotherapies where the response rates are between 30-50% with progression free survival of only 5-6 months. Most importantly, these patients also experience an improved quality of their lives while on TKI therapy. The success of these agents has launched a new era of personalized medicine in advanced NSCLC in which treatments are determined by the molecular characteristics of an individual's tumor.

Pathologic evaluation of non-small cell lung cancer has traditionally focused on classification of histologic subtype and staging studies. The NCCN now specifically advocates that for patients with metastatic disease with adenocarcinoma, large cell neuroendocrine carcinoma, and NSCLC not otherwise specified (NOS) that DNA mutational testing be performed. Various assays can be used to determine the mutation status including multiplexed PCR and next generation sequencing. It is strongly recommended that this molecular testing takes place within the context of broader molecular profiling. The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology also released a 2013 molecular testing guideline which also recommended testing for EGFR in all patients with advanced stage adenocarcinoma regardless of sex, race, smoking history, or other clinical risk factors.

At Thomas Jefferson University Hospital the Department of Pathology's Molecular and Genomic Pathology Laboratory has created a 42 gene panel to analyze the genotype of both solid and hematologic malignancies. This panel specifically includes EGFR exons 18, 19, 20, and 21 and can be run on small volumes of tissue including fine needle aspirates.

We examined the number of patients in 2014 whose pathology was assessed at TJUH. There were a total of 75 cases of metastatic (AJCC 7th edition stage IV) adenocarcinoma of lung origin seen here. Of these cases 34 had molecular testing for EGFR performed. 8 were positive and 26 were negative. An additional 44 cases were also seen at TJUH in 2014 that represented other non-small cell non-squamous histologies including large cell neuroendocrine, and NSCLC NOS. Of those 44 cases 10 had molecular testing performed.

Histology	Total Patients	EGFR Tested	EGFR Positive
Adenocarcinoma	75	34	8
Large Cell Neuroendocrine	9	3	0
Not Otherwise Specified / Poorly Differentiated Non-Small Cell Lung Cancer	35	7	1
TOTAL	119	44 (37%)	9 (7.6%)

At the 2015 European Lung Cancer Conference in Geneva a survey of 562 oncologists world-wide revealed that only 75% of patients with NSCLC have genetic testing performed. The most common reason was a lack of diagnostic material. Lung cancer specimens are often difficult to access and/or small in size and there is insufficient cellular material from which DNA can be extracted. Patients may also experience a precipitous decline in their functional status or decline therapy, making the additional testing unnecessary.

The Department of Medical Oncology and the Department of Pathology, Anatomy, and Cell Biology have taken steps in 2015 to reflexively test both for EGFR and a lung-cancer specific panel of molecular abnormalities not only in metastatic disease but in locally advanced cases as well to prepare for further advances in the field of molecular lung cancer. These plans include an addendum to make providers aware when there is insufficient cellular material present for genetic testing and not simply "a lack of the test being ordered."

With regards to treatment, for the total of 9 patients who found to be EGFR positive, all 9 (100%) received erlotinib, and EGFR directed TKI, as their first line of therapy.