Outcomes and efficacy of thoracic surgery biopsy for tumor molecular profiling in patients with advanced lung cancer

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Background: Molecular testing of patients with advanced non–small cell lung cancer for personalized therapy often is limited by insufficient specimen from nonsurgical biopsies. We measured the feasibility, patient safety, and clinical impact of thoracic surgical tumor biopsy in patients with stage IV non–small cell lung cancer.

Methods: This is a single institution retrospective analysis. Patients with stage IV non–small cell lung cancer undergoing elective surgical tissue biopsy for molecular analysis were evaluated from March 2011 to November 2012. Perioperative specific variables were measured.

Results: Twenty-five patients with known or suspected stage IV non–small cell lung cancer undergoing surgical biopsy were identified. All cases were discussed at a multidisciplinary thoracic oncology conference or a multidisciplinary thoracic oncology clinic. Preoperative histologies included adenocarcinoma in 20 patients (80.0%) and squamous cell carcinoma in 2 patients (8.0%). Surgical procedures consisted of video-assisted thoracic surgery wedge biopsy (16, 64%), video-assisted thoracic surgery pleural biopsy (4, 16.0%), mediastinoscopy (2, 8.0%), supraclavicular/cervical lymph node excisional biopsy (3, 12.0%), and rib/chest wall resection (2, 8.0%). There were no deaths and 5 postoperative complications (20.0%). Surgery identified potentially targetable molecular information in 19 of the total patients undergoing operation (76.0%) and changed the treatment strategy in 14 patients (56.0%); 10 of the total cohort (40.0%) were enrolled into therapeutic targeted clinical trials.

Conclusions: These data suggest that thoracic surgical biopsy can be safely performed in appropriately selected patients with stage IV non–small cell lung cancer and direct personalized therapy and enrollment into relevant clinical trials. Patients with advanced-stage non–small cell lung cancer should be discussed in a multidisciplinary setting to determine the need and strategy for thoracic surgical biopsy for molecular analysis. (J Thorac Cardiovasc Surg 2014;148:36-40)

Seventy percent of patients with non–small cell lung cancer (NSCLC) present with stage IV disease.[1] Molecular testing for targeted personalized therapy has led to progress in treating patients with NSCLC. Clinically validated targetable biomarkers include epidermal growth factor receptor (EGFR) sensitizing mutations, echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (EML4-ALK) fusion oncogene, and excision repair cross-complementing rodent repair deficiency, complementation group 1 expression.[2-4] The clinical success of targeted therapy based on a lung cancer's molecular and genomic profile has led to clinical guidelines advocating the routine testing for EGFR mutation and EML4-ALK fusion oncogene at the time of diagnosis for all patients presenting with stage IV disease or recurrence or progression in patients who may have originally presented with lower-stage disease but do not have genomic information.[5]

These and other biomarkers require significant tissue to achieve an accurate molecular profile, and for most genomic analysis, at least 200 to 400 malignant cells are needed to develop successful information.[6] Because the majority of patients with NSCLC present with advanced disease, diagnosis often is made with small fine-needle aspiration or core needle biopsies. In the initial presentation of stage IV NSCLC, tissue acquisition has the dual goal of histologic diagnosis and molecular tumor profiling, and computed tomography (CT)-guided percutaneous and

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Abbreviations and Acronyms

CI	= confidence interval
CT	= computed tomography
EGFR	= epidermal growth factor receptor
EML4-ALK	= echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase
NSCLC	= non–small cell lung cancer
PLOS	= prolonged length of stay
RRM1	= ribonucleoside-diphosphate reductase large subunit
TKI	= tyrosine kinase inhibitor

endobronchial strategies (eg, endobronchial ultrasound-transbronchial needle aspiration) offer excellent results, demonstrating success in providing adequate tumor specimen for molecular analysis in 80% to 90% of patients. However, endobronchial biopsy specimen results in a mean percentage area of tumor of 33%, with less than half of endobronchial biopsy specimen containing tumor, and CT-guided core specimen may be inadequate in 10% of specimen after 4 to 5 passes.[7,8]

As a result of the variability of success of percutaneous or natural orifice biopsy of NSCLC for molecular profiling, thoracic surgeons are frequently requested to perform minimally invasive surgical biopsies in patients with stage IV disease. Thoracic surgical procedures in patients with advanced-stage NSCLC, even if performed minimally invasively, might be high risk with an elevated complication rate.

The aims of our study were to (1) measure the feasibility and patient safety of thoracic surgical tumor biopsy in patients with metastatic (stage IV) NSCLC for molecular testing and (2) determine the impact of thoracic surgical biopsy for molecular testing on subsequent therapeutic decision-making.

PATIENTS AND METHODS

This is a single institution descriptive, retrospective analysis. Patients with suspected stage IV NSCLC undergoing elective surgical tissue biopsy for molecular analysis were evaluated from March 2011 to November 2012. All thoracic surgical biopsies were performed in the operating room using general anesthetic. The cases were prospectively discussed at a multidisciplinary thoracic oncology conference or a multidisciplinary thoracic oncology clinic. Discussions achieved consensus agreement on the likelihood of success of new or additional percutaneous or endobronchial biopsy, the appropriateness and best targets for surgical biopsy, the timing of operation in the day to best coordinate optimal tissue transport, and what analytic tests will be performed. Patient, tumor, and postoperative outcome specific variables were measured. The institutional review board of the University of California, Davis Medical Center, approved the study of these patient cohorts.

Patient and Hospital Demographics and Perioperative Outcomes

Patient demographics studied included age, sex, race, performance status as defined by Zubrod performance status score (score 1-5), and American Society of Anesthesiologists physical status classification system class (class 1-6). Tumor-specific variables included histology, preoperative (if any) and postoperative molecular profile, and reason for surgical biopsy (ie, disease progression, better define histology, second opinion for a clinical trial). Perioperative outcomes measured included type of thoracic surgical procedure, postoperative complications, length of hospital stay in days, occurrence of prolonged length of stay (PLOS) as defined by hospital stay more than 14 days, discharge disposition (routine to home, institutional care facility, or death at the time of discharge), same-stay reoperations, 30-day hospital readmissions, and 30-day revisits defined by emergency department visits, unplanned clinic visits, or telephone encounters requiring clinical intervention, all not resulting in a hospital readmission.

Molecular Tumor Analysis

The molecular profile of tumor surgical samples from patients with confirmed NSCLC were analyzed by Response Genetics Inc (Los Angeles, Calif). Molecular information included EGFR activating mutations (exon-19 deletion, L858R and L861Q) and resistance mutations (T790M), EML4-ALK fusion, V-Ko-ras2 Kirsten rat sarcoma viral oncogene homolog mutations (Gly12Arg mutation), EGFR overexpression, excision repair cross-complementing rodent repair deficiency, complementation group 1 expression, ribonucleoside-diphosphate reductase large subunit expression, and Met proto-oncogene expression. Patient encounters were reviewed for change in medical oncology management or enrollment in a therapeutic targeted clinical trial on the basis of the thoracic surgical biopsy results.

Statistical Analysis

All analyses and descriptive and binomial confidence limits as proportions (95% confidence interval [CI]) were performed using Microsoft Excel Version 14.1.0 (Microsoft Corp, Redmond, Wash).

RESULTS

Patient Demographics

Twenty-five patients with known or suspected stage IV NSCLC undergoing surgical biopsy were identified (Table 1). Mean age was 55.8 years (range, 36-79 years), and mean Zubrod performance status was 1.2. Zubrod performance status was 0 in 2 patients, 1 in 16 patients, 2 in 5 patients, and 3 in 1 patient. Fourteen (56%) of the patients were female, and the majority of patients were of white race.

Tumor Characteristics

Preoperative histologies (Table 1) were adenocarcinoma (20, 80.0%), squamous cell carcinoma (2, 8.0%), neuroendocrine (1, 4.0%), and unknown (2, 8.0%). The 2 unknown histologies were suspected to be stage IV NSCLC tumors, but proved to be mesothelioma and angiosarcoma after thoracic surgical biopsy. Eight patients had undergone nonsurgical biopsy for molecular testing but had insufficient tissue (7 image guided and 1 endobronchial ultrasound guided). Eleven patients had preoperative molecular data. Four of the 7 patients with known tumors with preoperative EGFR-sensitizing mutations were found to have new EGFR resistance mutations after thoracic surgical biopsy. Two of the 3 patients who had a negative molecular target analysis of their tumors preoperatively were found to have molecular targets after thoracic surgical biopsy. The majority of patients underwent thoracic surgical biopsy for molecular