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

TABLE 1. Patient and tumor characteristics

Characteristic	Result
Age	Mean 55.8 y, median 56 (range, 36-79) y
Zubrod score	Mean 1.2, median 1.0 (range, 0-3)
ASA physical status classification system	Mean 2.8, median 3 (range, 1-4)
Characteristic	**N (%)**
Sex	
Male	14 (56.0)
Female	11 (44.0)
Race	
White	19 (76.0)
Black	1 (4.0)
Asian/Pacific Islander	4 (16.0)
Hispanic/Latino	1 (4.0)
Preoperative histology	
Adenocarcinoma	20 (80)
Squamous cell	2 (8.0)
Neuroendocrine	1 (4.0)
Unknown	2 (8.0)
Preoperative molecular target data (yes)	11 (44.0)
EGFR-sensitizing mutations	7 (28.0)
EGFR resistance mutations	0
EML4-ALK fusion	1 (4.0)
No molecular target identified	3 (12.0)
Clinical impetus for procedure	
Disease progression after frontline therapy	21 (84.0)
Define histology	2 (8.0)
Second opinion for clinical trial	2 (8.0)

ASA, American Society of Anesthesiologists; *EGFR*, epidermal growth factor receptor; *EML4-ALK*, echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase.

TABLE 2. Perioperative characteristics

Characteristic	N (%)
Surgical procedure	
VATS lung biopsy	16 (64.0)
VATS pleural biopsy	4 (16.0)
Mediastinoscopy	2 (8.0)
Chest wall biopsy/rib resection	2 (8.0)
Supraclavicular/cervical lymph node biopsy	3 (12.0)
Discharge	
Home	25 (100)
ICF	0
Death	0
Complications (minor)	3 (12.0)
Wound infections	2 (8.0)
Urinary tract infections	1 (4.0)
Complications (major)	2 (8.0)
Hemothorax	1 (4.0)
ICU admission	1 (4.0)
Length of stay, in days	Median 1 (range, 0-4)
PLOS	0
Same-stay reoperations	1 (4.0)
30-d readmissions	1 (4.0)
30-d revisits	3 (12.0)

ICF, Institutional care facility; *ICU*, intensive care unit; *PLOS*, prolonged length of stay (>14 days); *VATS*, video-assisted thoracic surgery.

analysis because of disease progression after first-line therapy (21, 84%).

Perioperative Results

Surgical procedures (Table 2) 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%). Review of postoperative outcomes demonstrated no deaths (0%; 95% CI, 0-13.7), and all patients were discharged to home. There were 3 minor postoperative complications (12.0%), consisting of 2 wound infections and 1 urinary tract infection. There were 2 major complications (8%) consisting of 1 hemothorax requiring the only same-stay reoperation and 1 unplanned intensive care unit admission. A total of 5 patients had complications (20%; 95% CI, 6.8-40.7). The median length of stay was 1 day (range, 0-4 days), with no incidence of PLOS. There was one 30-day readmission for a partial small-bowel obstruction unrelated to the thoracic surgical biopsy. There were three 30-day revisits; 2 telephone encounters requiring clinical intervention (1 surgical wound infection and 1 unrelated port-a-catheter site infection) and 1 emergency department visit for a chronic obstructive pulmonary disease exacerbation.

Surgical biopsy led to the identification of potentially targetable molecular information in 19 of the total patients undergoing operation (76.0%; Table 3). Surgical biopsy was diagnostic in all but 1 patient (96.0%). Surgical data changed the treatment strategy for 14 patients (56.0%), and 10 of those patients (71.4%; 40.0% of total cohort) were enrolled into therapeutic targeted clinical trials on the basis of surgical pathology results. Of the 11 patients who had preoperative molecular data, surgical biopsy changed the treatment strategy in 5 patients (45.5%), although this resulted in only 2 of those patients to be enrolled into targeted therapeutic clinical trials (18.2%).

DISCUSSION

This study demonstrated that elective thoracic surgical biopsy in patients with stage IV NSCLC for the specific purpose of molecular testing is feasible and safe, offering a low morbidity and mortality. In addition, thoracic surgical biopsy changed the subsequent treatment strategy in the majority of patients and allowed 40% of patients to be enrolled into targeted therapeutic clinical trials.

The success of targeted therapy based on the molecular tumor profile in advanced NSCLC has increased the demand for abundant representative tissue. Especially in the setting when diagnostic percutaneous or natural orifice

TABLE 3. Molecular targets identified

Description	N	Patient tumors confirmed tested for this target	%
Principle lung cancer molecular targets			
EGFR-sensitizing mutations	10	22	45.5
EGFR resistance mutations	5	21	23.8
EML4-ALK fusion	2	21	9.5
KRAS mutations	2	21	9.5
Secondary lung cancer molecular targets			
EGFR overexpression	7	21	33.3
ERCC1 low expression	9	21	42.9
RRM1 low expression	2	20	10.0
c-MET overexpression	7	19	36.8

c-MET, Met proto-oncogene; *EGFR*, epidermal growth factor receptor; *EML4-ALK*, echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase; *ERCC1*, excision repair cross-complementing rodent repair deficiency, complementation group 1; *KRAS*, V-Ko-ras2 Kirsten rat sarcoma viral oncogene homolog; *RRM1*, ribonucleoside-diphosphate reductase large subunit.

biopsy does not provide enough tissue for molecular testing or the original tissue for patients who present with disease progression or recurrence is unavailable, thoracic surgeons are increasingly asked to perform minimally invasive surgical procedures to acquire tissue for molecular analysis. Conventional wisdom would suggest that patients with stage IV NSCLC would pose an at-risk population who could make thoracic surgical biopsy for molecular profiling relatively prohibitive. However, a review of our results demonstrates a postoperative complication rate similar to and a postoperative mortality rate superior to elective surgical lung biopsy for interstitial lung disease.[9,10]

In the current environment of patient-centered quality, the determinants of a successful surgical diagnostic and treatment strategy go beyond the simple measurement of postoperative complications and mortality. Discharge to institutional care facilities, PLOS, 30-day readmissions, and same-stay reoperations are all important metrics that measure the effects of a procedure on the quality of life of patients and potential strain on the healthcare system.[11,12] In our study, thoracic surgical biopsy, for molecular testing, was complicated only by an isolated 30-day readmission and same-stay reoperation, and no discharges to institutional care facility or incidence of PLOS. In addition, we sought to identify increased healthcare resource use that would not be captured by measuring hospital readmissions, defining the "30-day revisit," or unplanned postdischarge encounters requiring clinical intervention but not resulting in a readmission. The 30-day revisit rate in our study group was 12%. Although this result seems low, the 30-day revisit rate is a new, not yet validated metric, and therefore it is unclear whether a 12% rate is a satisfactory result.

In the examined cohort, thoracic surgical biopsy influenced the patient management. 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. Identification of patients with EGFR resistance mutations can change the treatment strategy from first-generation EGFR tyrosine kinase inhibitors (TKIs) to second- or third-generation novel EGFR TKIs.[13] Specifically, surgical data changed the treatment strategy in 56% of the patients, with 40% of the total cohort being enrolled into therapeutic targeted clinical trials on the basis of surgical pathology results. This result is important for the support of clinical trials for the advancement of knowledge of the optimal treatment of lung cancer, but there is evidence from the California Cancer Registry, queried by Chow and colleagues,[14] that patients with lung cancer who participate in clinical cancer trials have a survival benefit. In addition, patients with advanced NSCLC with EGFR mutant and ALK+ tumors have longer survival compared with those who do not have these genetic abnormalities. These patients respond well to both EGFR TKIs and the ALK targeting drug crizotinib and chemotherapy. Improvement in overall survival has been difficult to demonstrate because survival is confounded by cohort crossover and the availability of many other active lines of therapy, because these patients receive not only targeted therapy but also multiple lines of chemotherapy. First-line trials of targeted agents do not have survival benefit over chemotherapy (except for tumor response rate and progression-free survival), but second-line and beyond trials have exhibited survival benefit.[3,15,16]

Study Limitations

Limitations of this study include the small cohort size and the retrospective nature. The limitation of the small sample size is reflective in the wide 95% CIs for mortality and complication rates. All patients were discussed in a multidisciplinary stetting. The patients selected for thoracic surgical biopsies were reviewed for the extent of their disease, current availability of analyzable tissue, appropriateness for percutaneous or endobronchial biopsy, and potential available clinical trial. In addition, the patients selected for biopsy exhibited relatively preserved performance status (mean Zubrod and American Society of Anesthesiologists scores of 1.2 and 2.8, respectively), which would suggest favorable clinical postoperative outcomes. One of the patients in the study had a Zubrod score of 3. The reason to biopsy patients with NSCLC with a Zubrod score of 3 is to determine whether the cancer is oncogene-driven (EGFR or ALK). Although chemotherapy is not recommended for patients with a Zubrod performance status of 3 or greater, treatment with TKIs is recommended.[17]

CONCLUSIONS

Although CT-guided percutaneous or endobronchial biopsy should be considered the frontline approach for tissue acquisition for molecular profiling in patients with stage IV

NSCLC, this study suggests that thoracic surgical biopsy for molecular tumor analysis can be feasibly, safely, and successfully performed in appropriately selected patients and should be in the resource armamentarium for the multidisciplinary care of these challenging patients. Surgical biopsy provides valuable pathologic and molecular information that can direct appropriate personalized therapy and serves to foster enrollment into relevant clinical trials. Patients with advanced-stage NSCLC should be discussed in a multidisciplinary setting to determine the need and strategy for thoracic surgical biopsy for molecular analysis.

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