Factors associated with guideline-concordant biomarker testing in patients with stage IB-IIIA non-small cell lung cancer

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Abstract

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Background: Even with recent advances in identifying oncogenic genomic alterations and developing targeted therapies for non-small cell lung cancer (NSCLC), the uptake of molecular testing remains suboptimal among patients with advanced NSCLC, and comparable estimates for molecular testing in earlier stage NSCLC have not previously been published. This study describes and identifies factors associated with the receipt of 2021 guideline-concordant biomarker testing among patients with newly diagnosed stage IB-IIIA NSCLC within a community-based healthcare network.

Methods: This was a retrospective cohort study of adult patients with histopathologically confirmed stage IB-IIIA NSCLC diagnosed within the Providence-Swedish Health Alliance between March 1, 2021, and June 3, 2022. The study outcome was defined as receipt of

biomarker testing for somatic epidermal growth factor receptor (EGFR) mutations, concordant with 2021 National Comprehensive Cancer Network guidelines. Logistic regression analyses were performed to identify factors associated with receipt of guideline-concordant testing.

Results: Of 322 patients, 70 (22%) received guideline-concordant EGFR mutation testing. Overall, the likelihood of receipt of guideline-concordant testing was similar across age, sex, health insurance, and stage categories. While none of the patients of minority races, Hispanic or Latino ethnicity, and/or who had a preferred language that was not English received guideline-concordant testing, small numbers limit conclusions. Of the 134 (42%) patients who underwent surgical resection of their NSCLC, 31 (23%) had guideline-concordant EGFR mutation testing versus 39 of 188 patients (21%) who had not undergone surgery. Among 22 patients whose resected tumor had been tested for one or more biomarkers, 9 (41%) received guideline-concordant EGFR mutation testing. The proportion of patients who underwent guideline-concordant testing was similar across Commission on Cancer-accredited cancer programs and facilities in metropolitan counties. However, none of the patients undergoing management at facilities in non-metropolitan counties received guideline-concordant testing. The proportion of patients who received guideline-concordant testing was higher at facilities with a reflex testing program (37%) compared to the proportion at facilities without a reflex testing program (15%). After multivariable adjustment, patients managed at facilities with a reflex testing program were 3.23 (95% confidence interval: 1.85-5.83) times as likely to undergo guideline-concordant EGFR mutation testing as compared to patients managed at facilities without a reflex testing program.

Conclusions: This study highlights the suboptimal uptake of guideline-concordant EGFR testing in patients with early-stage NSCLC, notes potential disparities in testing, and underscores the

importance of a reflex testing program in facilitating appropriate biomarker testing. These findings emphasize the urgency for interventions aimed at increasing awareness, addressing disparities, and improving access to guideline-concordant testing to optimize treatment decision-making.

Introduction

Lung cancer is the third most commonly diagnosed cancer and the leading cause of cancer-related death in the United States, accounting for up to 25% of all cancer deaths.[1,2] The American Cancer Society estimated 236,740 new cases of lung cancer and 130,180 deaths from lung cancer in 2022.[1] While the age-adjusted mortality rate for lung cancer has been declining an average of 3% annually since 2008, 5-year survival among those with lung cancer remains low, ranging from 60% when diagnosed at a localized stage, to 33% and 7% when diagnosed at regional and distant stages, respectively.[3]

Recent advances in identifying oncogenic genomic alterations and developing targeted therapies for non-small cell lung cancer (NSCLC) have the potential to improve disease prognosis significantly.[4–15] For example, the randomized phase III ADAURA trial observed that adjuvant osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), improved disease-free survival and reduced the risk of recurrence in patients with stage IB-IIIA, EGFR-positive NSCLC.[16,17] In response to such advances, the National Comprehensive Cancer Network (NCCN) guidelines were updated in March 2021 to include biomarker testing for EGFR mutations in patients with resectable stage IB-IIIA NSCLC to determine whether adjuvant osimertinib may be considered for these patients.[18–20]

Data is beginning to emerge demonstrating improved clinical outcomes among patients who receive guideline-concordant biomarker testing and first-line therapy.[21,22] Nonetheless, even with established recommendations and emerging data, the uptake of molecular testing remains suboptimal among patients with advanced NSCLC, ranging between 7% and 86% depending on the histologic subtype and the actionable target.[23–27] However, comparable estimates for the uptake of molecular testing in earlier stage NSCLC have not previously been published.

This study describes and identifies factors associated with the receipt of 2021 guideline-concordant biomarker testing among patients with newly diagnosed stage IB-IIIA NSCLC within a community-based healthcare network.

Methods

Study Design and Setting

This was a retrospective cohort study of adult patients with histopathologically confirmed stage IB-IIIA NSCLC diagnosed within the Providence-Swedish Health Alliance between March 1, 2021, and June 3, 2022. During the study period, this health alliance included 24 diagnostic facilities spanning Alaska, California, Montana, Oregon, and Washington.

The authors obtained ethical and regulatory approval for the study from the Providence St Joseph Health Institutional Review Board. The Strengthening the Reporting of Observational studies in Epidemiology reporting guidelines were followed.[28]

Patient Identification and Eligibility

Adult patients diagnosed with stage IB-IIIA NSCLC between March 1, 2021, and June 3, 2022, were identified through a targeted data pull from the health alliance's electronic medical record, cancer registry, and enterprise clinical data warehouse. Diagnostic facilities were labeled as having a Commission on Cancer (CoC)-accredited cancer program if listed on the American College of Surgeons CoC website.[29] There is strict oversight and regulatory review of CoC-accredited programs to ensure compliance with standards. Data on self-reported race and ethnicity were collected to describe the cohort characteristics. In addition, the county in which the diagnostic facility was located was designated as metropolitan, non-metropolitan, or rural

using the United States Department of Agriculture Rural-Urban Continuum Codes.[30] Information on cigarette smoking status was not available for 90% of cohort members; as a result, cigarette smoking was not considered further in the analysis. All data were aggregated and de-identified. Initially, 333 patients were identified. After excluding 11 patients with missing clinical data, 322 patients were included in the final analysis.

Outcomes

The study outcome was defined as receipt of biomarker testing for somatic EGFR mutations, concordant with 2021 NCCN guidelines.[18–20] Only the first testing information following the date of diagnosis was included.

A reflex testing program was defined as a program where biomarker testing was initiated at the time of histopathological confirmation of NSCLC. A facility was defined as having a reflex testing program if located in a state where the healthcare system had implemented a reflex testing program and the program was being routinely utilized.

Statistical Analysis

The proportion of patients receiving guideline-concordant testing was estimated overall and according to patient, clinical, and facility characteristics. Logistic regression analyses were performed to identify factors associated with receipt of guideline-concordant EGFR mutation testing. Factors exhibiting little variation within and between categories (sex, race, ethnicity, preferred language, and county classification), and therefore not appropriate for regression models, were excluded. Since the outcome was not rare, odds ratios and confidence intervals

obtained from logistic regression models were converted to risk ratios and their associated confidence intervals.[31] All analyses were performed using Rstudio, version 2023.03.0 (R Project for Statistical Computing).

Results

Of the 322 patients, 70 (22%) received guideline-concordant EGFR mutation testing [Table 1]. In the total cohort of patients, 50% were 73 years and older. The cohort was predominantly male (58%), white (88%), non-Hispanic/Latino (95%), and preferred English as their primary language (96%). Patients also predominantly utilized commercial or Medicare health insurance (51%) and had stage IB-IIB NSCLC (66%). The likelihood of receipt of guideline-concordant versus non-guideline-concordant testing was similar across age, sex, health insurance, and stage categories. However, none of the patients of minority races, Hispanic or Latino ethnicity, and/or who had a preferred language that was not English received guideline-concordant testing, though the number of such patients were small.

Of the 134 (42%) patients who underwent surgical resection of their NSCLC, 22 (16%) had biomarker testing of their surgical specimen. Of these 22 patients, 9 (41%) had guideline-concordant EGFR mutation testing. In an unadjusted regression analysis, patients whose surgical specimens were sent for testing were 2.44 (95% confidence interval: 1.02-5.15) times as likely to undergo guideline-concordant EGFR mutation testing as patients with only diagnostic biopsies [Table 2]. Of the remaining 112 patients who underwent surgical resection and did not undergo initial biomarker testing of their surgical specimen, 22 (20%) had guideline-concordant testing at some other point in their management. This proportion is similar to the proportion of patients who had guideline-concordant testing on biopsy specimens (21%).

The proportion of patients who underwent guideline-concordant testing was similar in facilities that had versus did not have CoC-accredited cancer programs. A similar proportion for guideline-concordant testing was observed in facilities in metropolitan counties. None of the patients undergoing management at facilities in non-metropolitan counties received guideline-concordant testing. The proportion of patients who received guideline-concordant testing was higher at facilities with (37%) versus without a reflex testing program (15%). In an unadjusted regression analysis, patients managed at facilities with a reflex testing program were 3.29 (95% confidence interval: 1.91-5.73) times as likely to undergo guideline-concordant testing as patients managed at facilities without a reflex testing program. After multivariable adjustment, patients managed at facilities with a reflex testing program were 3.23 (95% confidence interval: 1.85-5.83) times as likely to undergo guideline-concordant EGFR mutation testing than patients managed at facilities without a reflex testing program.

Discussion

This study investigated the prevalence of EGFR mutation testing concordant with 2021 NCCN guidelines and factors associated with the receipt of guideline-concordant testing among patients with stage IB-IIIA NSCLC within a community-based healthcare network. Only 22% of patients included in the study received guideline-concordant EGFR mutation testing. None of the small number of patients of minority races, Hispanic or Latino ethnicity, and/or with a preferred language other than English received guideline-concordant testing. In addition, none of the patients managed at facilities in non-metropolitan counties received guideline-concordant testing. Factors including age, sex, health insurance, stage, and CoC-accredited cancer program participation were not associated with the receipt of guideline-concordant testing. However,

patients who underwent surgical resection and had their surgical specimens sent for biomarker testing were more likely to undergo guideline-concordant EGFR mutation testing; and when adjusting for covariates, patients who were managed at facilities with a reflex testing program were more likely to undergo guideline-concordant EGFR mutation testing.

Although lung cancer incidence and mortality are declining in the US, the profile of detected disease is changing.[3] Progress in smoking cessation and the widespread implementation of lung cancer screening following the detection of a mortality benefit in the National Lung Screening Trial has resulted in lung cancer stage migration from advanced to earlier stages.[32–35] Comparing the results of this study to published literature, the findings are consistent with the suboptimal uptake of molecular testing observed among patients with advanced NSCLC; however, this study adds to the existing literature by focusing on early-stage disease.[23–27] Barriers contributing to the suboptimal uptake of testing in patients with advanced disease include lack of access to resources, poor patient prognosis, and inadequate tumor tissue procurement and processing.[23,24,27,36,37] In addition to these barriers, a challenge for early-stage testing may be the short time lag between the demonstration of a survival benefit in patients receiving adjuvant osimertinib in the ADAURA trial, subsequent recommendations for EGFR testing, and the study period; that is, there has been limited time for the distribution of guidelines, the spread of awareness among healthcare providers, and adoption in clinical practice.[16–19,37]

The present study observed a more than double the proportion of patients who received guideline-concordant testing when managed at facilities with a reflex testing program compared to facilities without a reflex testing program, and an association between the receipt of guideline-concordant testing and receiving management at a facility with a reflex testing program after

multivariable adjustment. These findings underscore the importance of a reflex testing program in facilitating appropriate biomarker testing. The benefits of implementation of reflex testing programs for molecular biomarker testing in patients with lung cancer have been previously reported, with a decrease in turnaround time and a higher variant detection proportion compared to standard molecular biomarker ordering practices.[38,39] However, challenges exist in the adoption of reflex testing programs in practice, and in our experience these include billing issues, existing partnerships with external pathology practices, and logistical regulations for ordering testing for hospitalized Medicare patients.

The observation that patients whose surgical specimens were sent for biomarker testing were over two times as likely to undergo guideline-concordant EGFR testing as compared to those with only diagnostic biopsies suggests that surgical resection may play a role in appropriate biomarker testing. Testing should be performed as early as possible in the management pathway to ensure results are available prior to starting any therapy, and while biopsies are performed at the beginning of the diagnostic process, the sample is often inadequate or insufficient for molecular testing.[37,40] This suggests that optimizing the utilization of surgical specimens for testing purposes may improve the frequency of guideline-concordant testing and subsequently enhance the accuracy of treatment decisions.

A strength of the study is its focus on a community-based healthcare network, which provides insights into real-world clinical practice across multiple facilities outside of academic medical centers. However, the study also has limitations. The retrospective nature of the study design and the use of data from electronic medical records may introduce biases and limitations in data collection, completeness, and accuracy. The study's sample size is relatively small, and it was conducted within a specific healthcare network, which may limit the generalizability of the

findings to other settings, specifically relating to access to biomarker testing laboratories. Additionally, the study did not include information on smoking status. Differing tumor characteristics have been identified in never-smokers versus smokers, including a higher prevalence of EGFR mutations and a higher prevalence of biomarker testing.[22,24,41–43]

Further investigation of the barriers and facilitators of guideline-concordant biomarker testing in early lung cancer is crucial. Qualitative studies exploring patient perspectives, healthcare provider attitudes and practices, and organizational factors can provide valuable insights into the underlying reasons for the observed suboptimal uptake of testing. Additionally, prospective studies evaluating the impact of interventions aimed at increasing testing prevalence and reducing disparities would be valuable in guiding evidence-based strategies for improving clinical practice.

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Table 1. Description of patient and facility factors for the total cohort, as well as stratified by guideline-concordant testing status.

	Total cohort (N=322)	Guideline-concordant testing	
		Yes (n=70)	No (n=252)
Patient factors			
Age (years), number (%)			
<73	162 (50%)	34 (21%)	128 (79%)
≥73	160 (50%)	36 (22%)	124 (78%)
Sex, number (%)			
Female	134 (42%)	33 (25%)	101 (75%)
Male	188 (58%)	37 (20%)	151 (80%)
Race, number (%)			
American Indian or Alaska Native	2 (1%)	0 (0%)	2 (100%)
Asian	16 (5%)	0 (0%)	16 (100%)
Black or African American	4 (1%)	0 (0%)	4 (100%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	0 (0%)	1 (100%)
Other	15 (5%)	2 (13%)	13 (87%)
White	284 (88%)	68 (24%)	216 (76%)
Ethnicity, number (%)			
Hispanic or Latino	17 (5%)	0 (0%)	17 (100%)
Not Hispanic or Latino	305 (95%)	70 (23%)	235 (77%)
Preferred language, number (%)			
English	308 (96%)	70 (23%)	238 (77%)
Non-English	14 (4%)	0 (0%)	14 (100%)
Health insurance, number (%)			
Commercial	47 (15%)	12 (26%)	35 (74%)
Medicare	117 (36%)	26 (22%)	91 (78%)
Other	158 (49%)	32 (20%)	126 (80%)
Stage, number (%)			
IB	89 (27%)	21 (24%)	68 (76%)
IIA	34 (11%)	7 (21%)	27 (79%)
IIB	90 (28%)	16 (18%)	74 (82%)
IIIA	109 (34%)	26 (24%)	83 (76%)
Surgical specimen, number (%)			
No surgical resection	188 (58%)	39 (21%)	149 (79%)
Surgical specimen not tested	112 (35%)	22 (20%)	90 (80%)
Surgical specimen tested	22 (7%)	9 (41%)	13 (59%)
Facility factors			
Commission on Cancer facility, number (%)			
No	163 (51%)	33 (20%)	130 (80%)
Yes	159 (49%)	37 (23%)	122 (77%)
County classification, number (%)			
Metropolitan	319 (99%)	70 (22%)	249 (78%)
Non-metropolitan	3 (1%)	0 (0%)	3 (100%)

Reflex testing program, number (%)			
No	221 (69%)	33 (15%)	188 (85%)
Yes	101 (31%)	37 (37%)	64 (63%)

Table 2. Unadjusted and adjusted regression analyses for associations with receipt of guideline-concordant testing.

	Unadjusted analysis		Adjusted analysis*	
	Risk ratio	**95% CI**	**Risk ratio**	**95% CI**
Age (years)				
<73	1.00 (reference)		1.00 (reference)	
≥73	1.09	0.65-1.78	1.21	0.68-2.13
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	0.76	0.45-1.26	0.77	0.44-1.32
Health insurance				
Commercial	1.00 (reference)		1.00 (reference)	
Medicare	0.84	0.39-1.80	0.84	0.35-1.99
Other	0.75	0.36-1.58	0.67	0.29-1.54
Stage				
IB	1.00 (reference)		1.00 (reference)	
IIA	0.85	0.31-2.02	0.79	0.28-1.97
IIB	0.71	0.34-1.42	0.87	0.40-1.77
IIIA	1.01	0.54-1.88	1.34	0.66-2.64
Surgical specimen				
No surgical resection	1.00 (reference)		1.00 (reference)	
Surgical specimen not tested	0.93	0.52-1.61	1.33	0.70-2.43
Surgical specimen tested	2.44	1.02 -5.15	2.31	0.88-5.30
Commission on Cancer facility				
No	1.00 (reference)		1.00 (reference)	
Yes	1.18	0.71-1.94	0.77	0.42-1.35
Reflex testing program				
No	1.00 (reference)		1.00 (reference)	
Yes	3.29	1.91-5.73	3.23	1.85-5.38

CI, confidence interval.

*Adjusted for age, sex, health insurance, stage, surgical specimen, and Commission on Cancer facility.