



# State of Practice: Unresectable Stage III NSCLC

VOLUME 2, ISSUE 4

*CHEST Clinical Perspectives™*

## Introduction

Lung cancer remains one of the leading causes of cancer-related deaths worldwide, and between 80% and 85% of lung cancer cases are non-small cell lung cancers (NSCLCs).<sup>1,2</sup> Patients with NSCLC present with symptoms late, thus, diagnoses usually occur at more advanced stages of the disease.<sup>1</sup> In these cases, timely and stage-appropriate treatment regimens are critical for disease management and prolonged patient survival.

Clinical staging of NSCLC helps to determine whether a patient is a candidate for resection and also plays a role in helping to determine the best treatment plan. PET-CT scans are useful for evaluating regional disease spread and provide an increased sensitivity than either of the two techniques individually.<sup>3</sup> Mediastinal staging is recommended by the American College of Chest Physicians (CHEST) for patients with enlarged mediastinal nodes or suspicion of mediastinal node involvement.<sup>4</sup> Mediastinal staging can be achieved using surgery or needle aspiration. However, image-guided biopsies, such as endobronchial ultrasound and transbronchial needle aspiration (EBUS-TBNA), are often preferred because they are highly sensitive (approaching 90%) and minimally invasive.<sup>4</sup>

The College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology (CAP/IASLC/AMP) recommends molecular profiling for stage IIIB and stage IV NSCLC, and the National Comprehensive Cancer Network (NCCN) recommends molecular profiling for stage IV NSCLC cases.<sup>5-7</sup> The histologic origin of the malignancy and the presence of biomarkers help to predict NSCLC prognosis and determine the optimal treatment. The majority of the biomarkers that can be targeted by therapeutic agents are present in adenocarcinomas. Biomarkers have been identified in squamous cell carcinomas, but no targeted therapies are currently available for this histologic subtype.<sup>8</sup>

Available treatment options for advanced NSCLC largely vary by stage. The standard therapy for unresectable stage III NSCLC is a combination of platinum-based chemotherapy and radiation. In addition to chemotherapy and radiation, targeted therapies may also be used for patients with stage IV NSCLC who have common biomarkers. For example, tyrosine kinase inhibitors, such as erlotinib and crizotinib, target two common NSCLC biomarkers—EGFR mutations and ALK translocations, respectively.<sup>5</sup> However, resistance to these drugs can emerge over time, and the majority of patients with NSCLC do not harbor these biomarkers.<sup>5</sup> In light of the drawbacks of targeted therapies, the need for new NSCLC treatment options is evident. Ongoing clinical trials are currently investigating the use of other adjuvant and concurrent immunotherapeutic agents for all stages of NSCLC.<sup>9</sup>

As the treatment landscape for NSCLC continues to evolve, survival rates are expected to rise. Better patient outcomes, however, will greatly depend on physicians' knowledge of and adherence to the current diagnostic and treatment guidelines and their knowledge of emerging treatments. Keeping up with changes in treatment options can be especially difficult for medical professionals who do not specialize in oncology, and referrals to oncologists help to overcome these barriers. For this study, we will focus on pulmonologists' perceptions regarding curative therapies for stage III NSCLC and the role these perceptions play in the likelihood of oncologist referrals.

## BACKGROUND AND PURPOSE

In this issue of *CHEST Clinical Perspectives*, CHEST is undertaking primary research with pulmonologists to assess perceptions regarding curative intent when it comes to treating patients diagnosed with stage III NSCLC. The objectives of this research are to:

- Understand the role of the pulmonologist in diagnostic process, including diagnosis, cell type, staging.
- Understand the process of referral for treatment of patients with stage III NSCLC diagnosed in pulmonary practices, including frequency of referral to oncology and barriers to referral.
- Understand knowledge levels about stage III NSCLC, including differences between patients with stage III and stage IV and how that impacts referral for treatment.
- Understand extent to which pulmonologists consider stage III patients to be in a curative state.

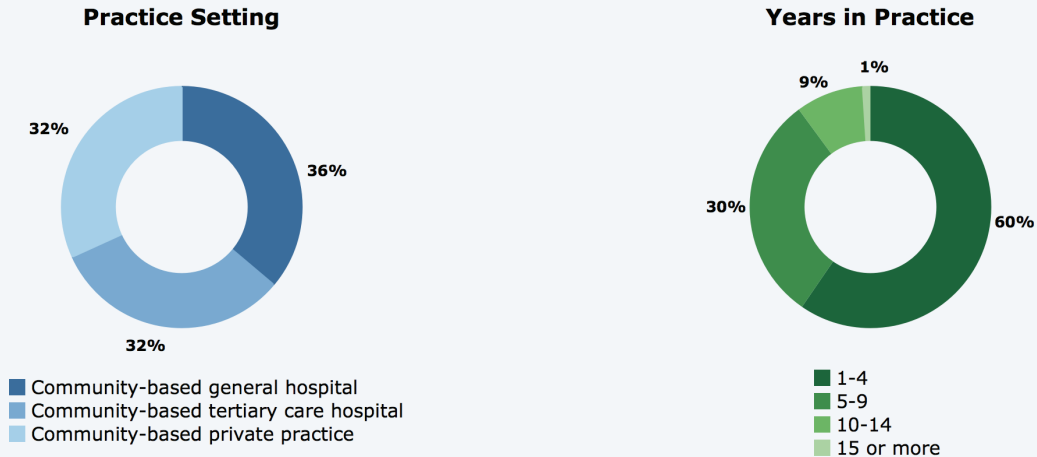
## METHODOLOGY

CHEST conducted an online survey with a sample of n=99 pulmonologists randomly selected from the CHEST member database. Respondents needed to diagnose at least one new case of NSCLC each month to qualify for survey participation. In order to understand perspectives of community-based clinicians who do not subspecialize in oncologic pulmonology, respondents practicing exclusively in academic medical center environments were screened out from participation. Further, soft quotas were established in order to ensure the ability to view and compare results between lower case volume respondents (diagnose one to four cases per month) and higher case volume respondents (diagnose five or more cases per month). Respondents were sent a link to the survey from CHEST, and data were collected from July 24-August 5, 2019.

Descriptive statistics were used to assess distributions of the data across new diagnostic case volumes. Inferential statistics were used to assess differences in descriptive and behavioral measures, which were cross-tabulated with patient volume and practice setting data. Depending on data type, a two-tailed independent samples t-test and a chi-square test were used to test for statistical significance ( $P < .1$  considered statistically significant).

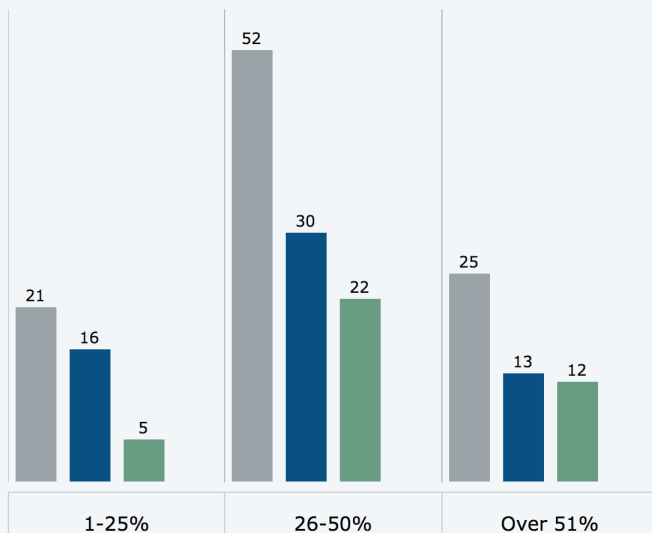
**PRACTICE PROFILE**

Respondents are relatively evenly distributed across community-based practice settings. Nearly two-thirds (60%) say they diagnose fewer than five new cases of NSCLC in a typical month.



Nearly three-fourths of respondents (73%) say that half or fewer of their patients with NSCLC are diagnosed as stage III. A third of respondents (37%) are unable to estimate the distribution of their stage III patients with NSCLC across the categories of IIIA, IIIB, and IIIC. Among those who are able to estimate the distribution, most (75%) report their stage III patients as IIIA or IIIB.

**Count Of Cancer Patients Discovered To Have Stage III NSCLC**

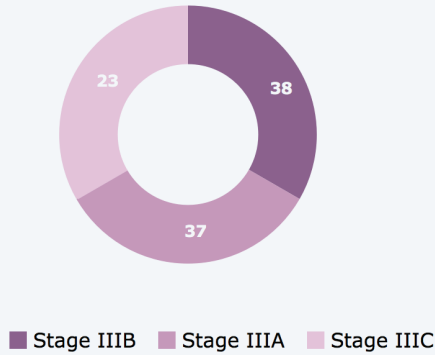


**Patients With Stage III NSCLC**



Respondents indicate that their stage III NSCLC skews IIIA and IIIB. Two-thirds of these cases (65%) are estimated to have been deemed unresectable by a thoracic surgeon.

**Patients With Stage III NSCLC**

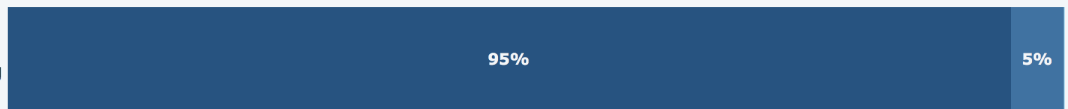


**Attitude and Practice Related to Determining Cell Type and Staging NSCLC**

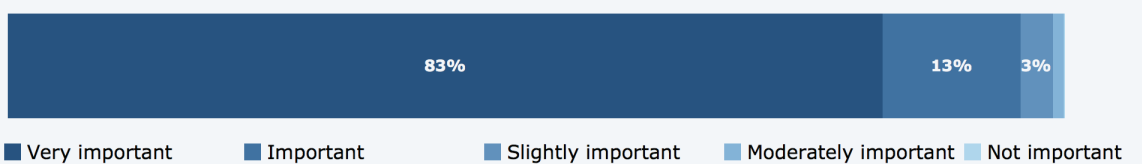
Most respondents—even among those who diagnose comparatively low volumes of patients with NSCLC in a typical month—agree that it is very important to both determine cell type and stage of cancer when evaluating a patient for NSCLC.

**Importance Of Determining Cell Type And Stage When Evaluating A Patient For NSCLC**

Determine stage of cancer when you are evaluating a patient for non-small cell lung cancer.

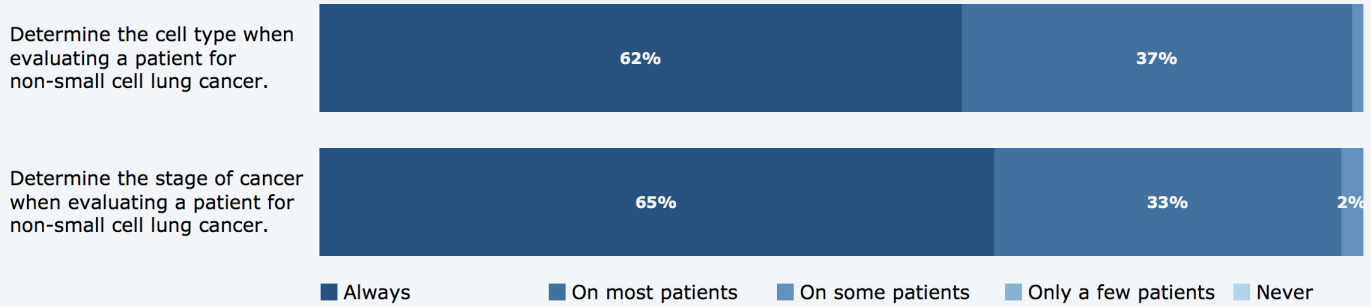


Determine the type of cancer cell (adenocarcinoma vs squamous carcinoma) when you are evaluating a patient for lung cancer.



However, despite the importance assigned to these clinical actions, performance is not universal. Only 62% say they determine cell type on all patients being evaluated for NSCLC, and only 65% determine stage. In both cases, low volume diagnosticians report they are less likely to universally take these actions.

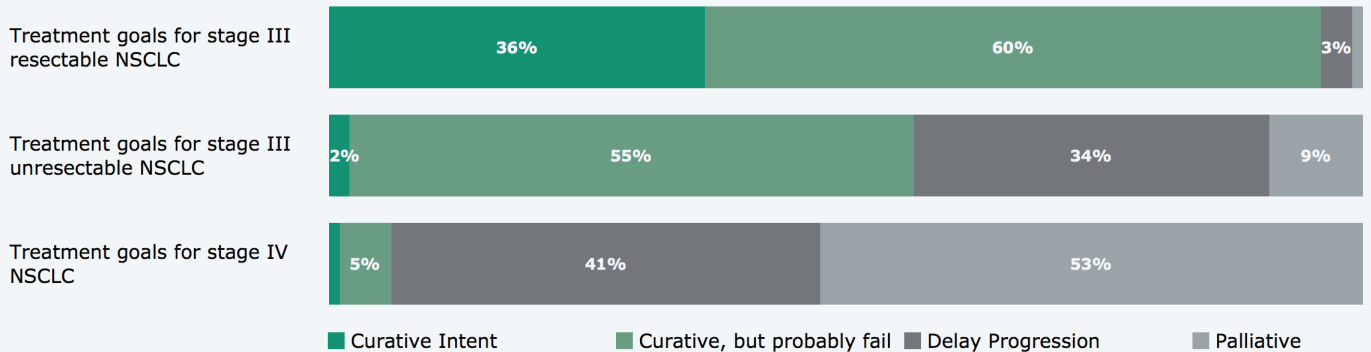
**Frequency Of Determining Cell Type and Stage When Evaluating A Patient For NSCLC**



**Treatment Goals and Referral Behavior for Patients With Unresectable Stage III NSCLC**

**Perspectives regarding treatment goals for unresectable stage III NSCLC.** While nearly all respondents (96%) say that curative intent is a treatment goal for their patients with stage III resectable disease, the majority believe that most patients will not be cured (60%). Alternatively, only 58% say that curative intent is a goal for their patients with stage III unresectable disease, with a majority (56%) believing that treatment will not succeed. Most say that treatment goals for their patients with stage IV disease are either to delay progression (41%) or palliative care (53%).

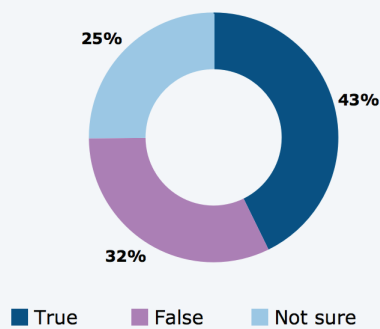
**Variation in Treatment Goals by NSCLC Patient Classification**



**Attitude toward potential for unresectable stage III NSCLC to be cured.**

Respondents are clearly divided in their overall beliefs regarding the potential for curing unresectable stage III NSCLC. Less than half (42%) agree that it is curable, while a third (32%) disagree. A fourth (25%) are uncertain. This may help to explain why many respondents are fairly reluctant to discuss with patients that unresectable stage III NSCLC is potentially curable (only a third—35% mention that possibility with at least some patients).

**True/False: Unresectable Stage III NSCLC Is Potentially Curable**

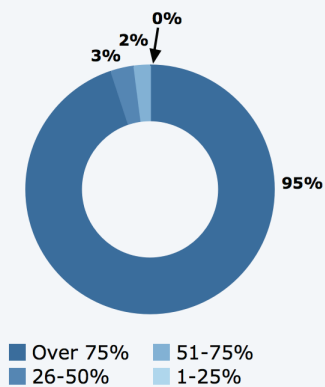


**Reported Frequency Of Telling Patient That Unresectable Stage III NSCLC Is Potentially Curable**

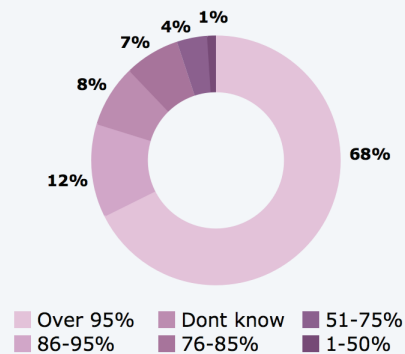
|                     | Total Cases | 1-4 Cases | 5+ Cases |
|---------------------|-------------|-----------|----------|
| Never               | 38%         | 51%       | 20%      |
| Only a few patients | 26%         | 22%       | 33%      |
| On some patients    | 24%         | 19%       | 33%      |
| Most/Always         | 11%         | 8%        | 15%      |

**Referral practice.** The vast majority of respondents—regardless of new diagnostic case volume—indicate that more than 75% of their patients with unresectable stage III disease are referred to an oncologist for consultation regarding treatment. The majority indicate that discussion of treatment options is included in that consult for virtually all patients.

**Share of Unresectable Stage III NSCLC Patients Referred For Oncology Consult**



**Share of Referred Patients Who Discuss Treatment Options During Consult**



Among patients with unresectable stage III NSCLC who are not referred for an oncology consult, patient refusal of additional treatment (74%) is most frequently cited as the reason for nonreferral. This is particularly prevalent among lower case volume diagnosticians. Disability/limitations (eg, ECOG >3) or advanced age are next most frequently mentioned (55%). However, a significant minority (35%) say that poor prognosis leads to a nonreferral. Only 3% say lack of knowledge regarding therapy options is a barrier to referral. However, this knowledge is critical to mitigating other barriers to referral, especially patient refusal of additional treatment.

#### Reasons Identified For NOT Referring An Unresectable Stage III NSCLC Patient For Oncology Consult

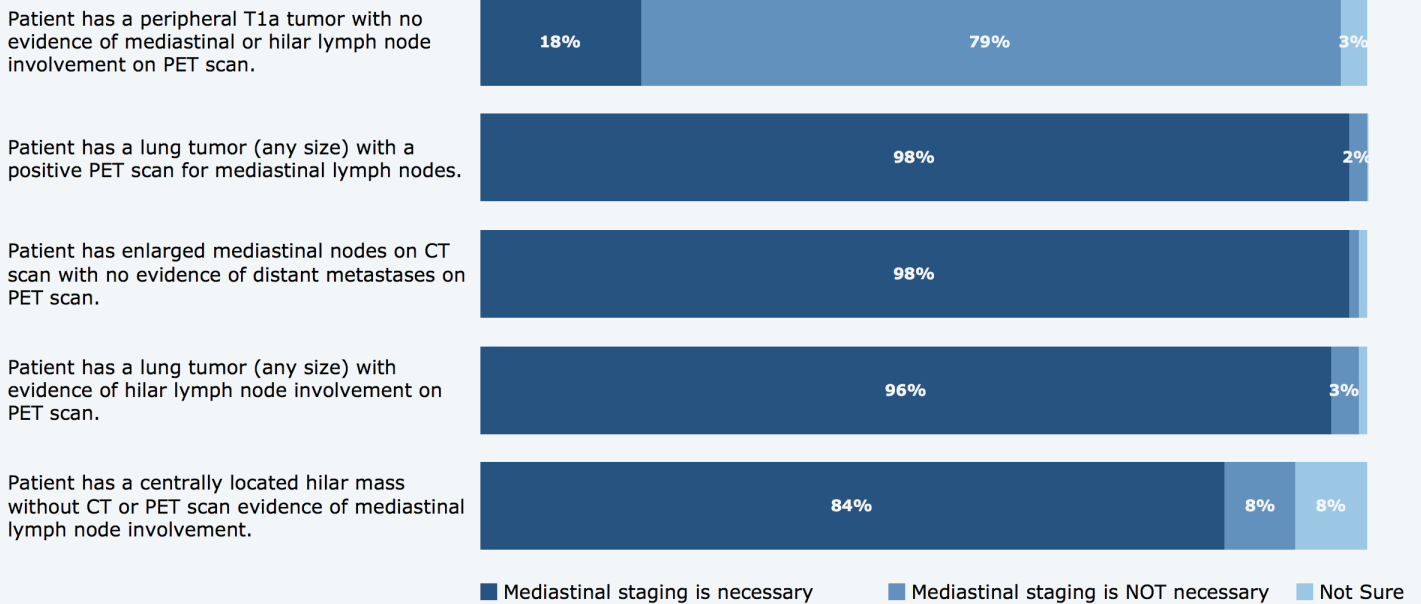
|   | Total Cases | 1-4 Cases | 5+ Cases |
|---|-------------|-----------|----------|
| Patient refuses to see an oncologist or pursue further treatment.   | 74%         | 85%       | 58%      |
| Patient is disabled/capable of only limited self-care and confined to chair or bed most or all of the day (eg ECOG>3) . | 55%         | 47%       | 65%      |
| Prognosis is poor   | 35%         | 27%       | 48%      |
| Patient not appropriate for further care based on advanced age.   | 29%         | 27%       | 33%      |
| Other   | 5%          | 5%        | 5%       |
| Therapy options are limited for patients with stage III NSCLC with unresectable cancer.                                 | 3%          | 3%        | 3%       |

#### Approach to Diagnostic Workup and Awareness of Curative Therapy for Unresectable Stage III NSCLC

**Diagnostic workup.** Nearly all respondents are able to identify the necessity of mediastinal staging in situations where the patient shows evidence of hilar lymph node involvement on PET scan; when the patient has enlarged mediastinal nodules on CT scan with no evidence of distant metastases on PET scan; and when the patient has a positive PET scan for mediastinal lymph nodes. Judgment regarding necessities is more mixed in other situations.

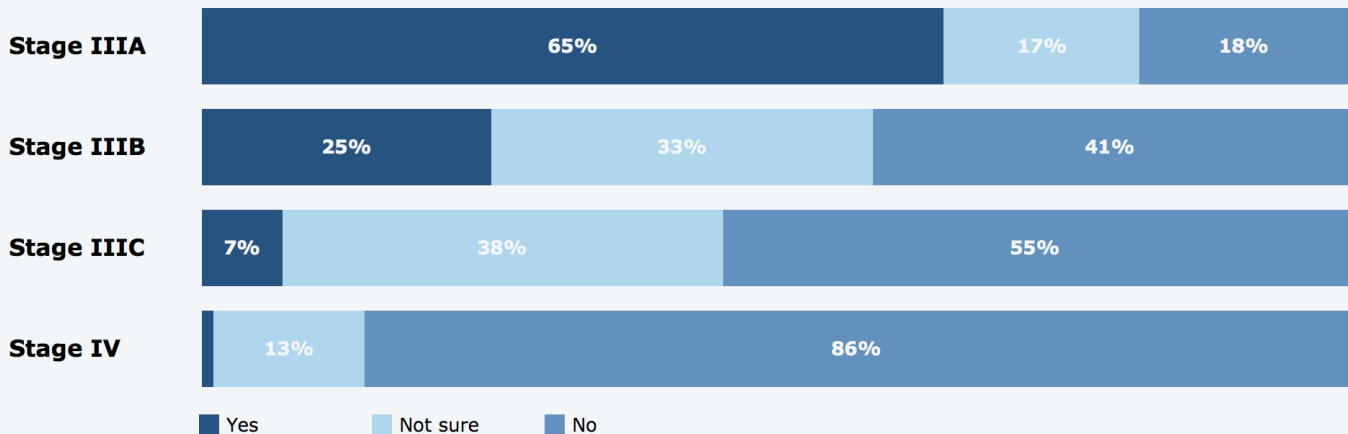


### Necessary Invasive Mediastinal Staging



**Awareness of curative therapies.** Knowledge about curative therapies is decidedly mixed among respondents—even at the unresectable stage III level. While a majority at this level (64%) is aware of curative therapies, awareness declines sharply with each succeeding gradation in stage. Of note, knowledge of therapies has a direct impact on the belief that unresectable stage III NSCLC is curable.

### Awareness Of Curative Therapies



**KEY  
TAKEAWAYS**

- Community-based pulmonologists play a key role in the diagnosis and staging of NSCLC.
- Community-based pulmonologists recognize the importance of NSCLC staging and typing, but this knowledge does not always translate into action.
- Pulmonologists' prognosis and patient refusal of treatment are key factors for lack of referral to an oncologist.
- While community-based pulmonologists say their treatment goal for patients with unresectable stage III NSCLC was curative intent, they do not always believe that a cure was possible.
- Community-based pulmonologists are not fully aware of curative therapies available for all NSCLC stages.
- Advancing knowledge regarding curative therapies for stage III unresectable NSCLC is critical in preparing pulmonologists for their counsel of patients who may initially refuse a referral to oncology or balk at the thought of undergoing chemotherapy and radiation.

**DISCUSSION**

Survey findings demonstrate that 40% of the surveyed community-based pulmonologists reported diagnosing five or more NSCLC cases per month. This highlights the important role that community-based centers and pulmonologists play in NSCLC diagnosis and cancer care, in general. Community-based centers offer the benefits of providing care at a lower cost and of usually being geographically closer to a patient than larger academic cancer centers.<sup>12,13</sup>

Most respondents of the survey agreed that clinical staging and typing are very important when evaluating a patient for NSCLC. Almost all surveyed pulmonologists accurately identified instances where mediastinal staging would be recommended (hilar lymph node involvement or mediastinal nodules). However, only 62% and 65% reported always typing or staging their patients with NSCLC, respectively. The disconnection between knowledge and action is surprising. While it is known that staging accuracy tends to decrease as stage increases and the difference between the clinical stage and the pathologic stage approaches 50%, this does not negate the necessity for staging.<sup>14,15</sup> Clinical upstaging may prevent a patient from receiving surgical resection that would be beneficial, while clinical understaging may result in treatment that is not beneficial to the patient.

This survey addressed the need for histologic subtyping, but the questions did not specifically address the knowledge surrounding molecular biomarkers. However, biomarker subtyping is becoming more important as several targeted therapies are available. Some reported barriers to molecular subtyping include long turnaround times for results, the need for repeated biopsies, concerns regarding Medicare reimbursements, and patient health status.<sup>16</sup> Additionally, some practitioners are reluctant to order testing because of the patient's clinical characteristics (smoker status, ethnicity, gender, etc) and because the frequency of therapy-targeted mutations is rare.<sup>17</sup> When molecular subtyping is utilized and driver mutations are identified, patients with adenocarcinomas can benefit from precision genomic-based therapies that have been shown to increase patient survival.<sup>16</sup> As key players in NSCLC patient care, community-based centers need to streamline both staging and molecular subtyping practices. There should be education around the importance of accurate staging, and clear institutional guidelines should be implemented to overcome logistical barriers to staging and subtyping. This will ensure timely development and execution of optimal treatment plans for patients with NSCLC.

It is encouraging to note that the majority of pulmonologists referred their patients with unresectable stage III disease to oncologists for consultations regarding treatment. Multidisciplinary care is recommended for cancer management, and patients referred to oncologists are more likely to receive treatment according to the recommended guidelines.<sup>18</sup> Additionally, referred patients have an increased chance of being able to participate in clinical trials. Among pulmonologists surveyed, almost 25% did not refer patients with unresectable stage III disease to an oncologist. A variety of reasons were given, such as advanced age and disabilities/limitations. Similar reasons for lack of referral to oncologists have been given in previous studies.<sup>18</sup> Furthermore, the multidisciplinary care approach raises concerns regarding delays in diagnosis and treatment.<sup>19</sup> In this survey, there were two prominent reasons for lack of referral: (1) patient refusal of additional treatment and (2) pulmonologist's prognosis. These reasons highlight the fact that a sense of therapeutic nihilism still exists despite recent advances in the management of unresectable NSCLC. In fact, many of the surveyed pulmonologists were hesitant to discuss with patients that unresectable stage III NSCLC could potentially be cured. The overall outlook about curing unresectable stage III NSCLC was poor. A little more than half of the survey respondents said curative intent was their treatment goal. However, they did not believe that unresectable stage III NSCLC can be cured.

As major contributors to the diagnosis and staging of NSCLC, community-based pulmonologists have the important role of explaining the disease and its prognosis to patients with newly diagnosed disease. Therefore, pulmonologists' perception on whether or not unresectable stage III NSCLC can be cured likely impacts patient outlook and willingness to undergo treatment. Lack of knowledge of curative therapies was not cited as a barrier for referral, but the level of knowledge was not evaluated in this study. To shift the outlook regarding curative treatments for unresectable stage III NSCLC, there needs to be an increase in knowledge about emerging treatment options with curative potential. The NSCLC treatment landscape is rapidly evolving, and the possibility for a cure for unresectable stage III NSCLC now exists.

## EDUCATIONAL OPPORTUNITIES

- Education around the importance of staging and histologic and biomarker subtyping.
- Education around curative therapies available for all stages of stage III NSCLC.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
2. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med*. 2008;359(13):1367-1380.
3. Pozo-Rodriguez F, Martin de Nicolas JL, Sanchez-Nistal MA, et al. Accuracy of helical computed tomography and [18F] fluorodeoxyglucose positron emission tomography for identifying lymph node mediastinal metastases in potentially resectable non-small-cell lung cancer. *J Clin Oncol*. 2005;23(33):8348-8356.
4. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e211S-e250S.
5. Ettinger DS, Wood DE, Akerley W, et al. Non-small cell lung cancer, Version 6.2015. *J Natl Compr Canc Netw*. 2015;13(5):515-524.
6. Leighl NB, Rekhtman N, Biermann WA, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the study of lung cancer/association for molecular pathology guideline. *J Clin Oncol*. 2014;32(32):3673-3679.
7. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Mol Diagn*. 2018;20(2):129-159.
8. Gandara DR, Hammerman PS, Sos ML, Lara PN, Jr., Hirsch FR. Squamous cell lung cancer: from tumor genomics to cancer therapeutics. *Clin Cancer Res*. 2015;21(10):2236-2243.
9. Jain NA, Otterson GA. Immunotherapy in inoperable stage III non-small cell lung cancer: a review. *Drugs Context*. 2019;8:212578.
10. Gordan L, Blazer M, Saundankar V, Kazzaz D, Weidner S, Eaddy M. Cost differential of immuno-oncology therapy delivered at community versus hospital clinics. *Am J Manag Care*. 2019;25(3):e66-e70.
11. Hayes J, Hoverman RJ, Brow ME, et al. Cost differential by site of service for cancer patients receiving chemotherapy. *Am J Manag Care*. 2015;21(3):e189-196.
12. Navani N, Fisher DJ, Tierney JF, Stephens RJ, Burdett S, Group NM-aC. The accuracy of clinical staging of stage I-IIIa non-small cell lung cancer: an analysis based on individual participant data. *Chest*. 2019;155(3):502-509.

13. Heineman DJ, Daniels JM, Schreurs WH. Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy. *Ther Adv Med Oncol*. 2017;9(9):599-609.
14. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: gaps and opportunities. *Clin Lung Cancer*. 2017;18(6):651-659.
15. Arney J, Helm A, Crook T, Braun UK, Chen GJ, Hayes TG. Utilization of genomic testing in advanced non-small cell lung cancer among oncologists in the Veterans Health Administration. *Lung Cancer*. 2018;116:25-29.
16. Goulart BH, Reyes CM, Fedorenko CR, et al. Referral and treatment patterns among patients with stages III and IV non-small-cell lung cancer. *J Oncol Pract*. 2013;9(1):42-50.
17. Kedia SK, Ward KD, Digney SA, et al. 'One-stop shop': lung cancer patients' and caregivers' perceptions of multidisciplinary care in a community healthcare setting. *Transl Lung Cancer Res*. 2015;4(4):456-464.



**Doug Arenberg, MD,  
FCCP**  
University of Michigan

Doug Arenberg, MD, FCCP, is a rabid Chicago Cubs fan and believes ketchup has no place on a hot dog. He is currently a Professor of Medicine in the Division of Pulmonary & Critical Care Medicine at the University of Michigan. He is the Medical Director of the Lung Nodule Clinic and Lung Cancer Screening Program. For CHEST, he has served as member and Chair of the Thoracic Oncology NetWork Steering Committee and is currently Associate Editor for the Thoracic Oncology Section of the journal *CHEST*®.

## ADVISORY WORK GROUP



**Nancy Collop, MD, FCCP**  
Emory University



**Clayton Cowl, MD, MS, FCCP**  
Mayo Clinic  
*CHEST Clinical Perspectives*™  
Chair



**Nicola Hanania, MD, MS,  
FCCP**  
Baylor College of Medicine



**Lisa Moores, MD, FCCP**  
Walter Reed Medical Center



**M. Patricia Rivera, MD, FCCP**  
University of North Carolina  
at Chapel Hill



**Gerard Silvestri, MD, MS,  
FCCP**  
Medical University  
of South Carolina



### *CHEST Clinical Perspectives™ Series*

Through this series of groundbreaking white papers, you will find thorough summaries of insights and opinions gathered from key opinion leaders on the most critical issues in chest medicine.

If you would like to participate in future studies, please contact [CHESTAnalytics@chestnet.org](mailto:CHESTAnalytics@chestnet.org).

Sponsored by AstraZeneca



The American College of Chest Physicians ("CHEST") and its officers, regents, executive committee members, members, related entities, employees, representatives, and other agents (collectively, "CHEST Parties") are not responsible in any capacity for, do not warrant and expressly disclaim all liability for, any content whatsoever in any CHEST publication or other product (in any medium) and the use or reliance on any such content, all such responsibility being solely that of the authors or the advertisers, as the case may be. By way of example, without limiting the foregoing, this disclaimer of liability applies to the accuracy, completeness, effectiveness, quality, appearance, ideas, or products, as the case may be, of or resulting from any statements, references, articles, positions, claimed diagnosis, claimed possible treatments, services, or advertising, express or implied, contained in any CHEST publication or other product. Furthermore, the content should not be considered medical advice and is not intended to replace consultation with a qualified medical professional. Under no circumstances, including negligence, shall any CHEST Parties be liable for any DIRECT, INDIRECT, INCIDENTAL, SPECIAL or CONSEQUENTIAL DAMAGES, or LOST PROFITS that result from any of the foregoing, regardless of legal theory and whether or not claimant was advised of the possibility of such damages. The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or an infrequently employed drug. Some drugs and medical devices presented in this publication may have US Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health-care provider to ascertain the FDA status of each drug or device planned for use in his or her clinical practice.

Copyright © 2019 by the American College of Chest Physicians®

*CHEST Clinical Perspectives™* is a trademark of the American College of Chest Physicians.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means—electronic, mechanical, photocopied, recorded, otherwise—without the prior written permission of the copyright owner.