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The Importance of Guideline-Recommended Biomarker Testing and Multidisciplinary Treatment in Resectable Stage IB-IIIA Non–Small Cell Lung Cancer

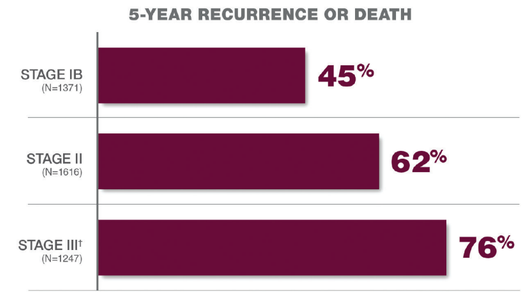
Disease recurrence rates remain high after surgery

Lung cancer accounts for 25% of all cancer deaths, making it by far the most lethal form of cancer.[1] Of the estimated 2.2 million new lung cancer cases diagnosed in 2020, approximately 80% to 85% were non–small cell lung cancer (NSCLC), which encompasses adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[2,3] Although early-stage NSCLC is considered potentially curable with surgical resection, disease recurrence rates remain unacceptably high.[4-6] Some patients with stage IB-III NSCLC—even with adjuvant treatment, including chemotherapy—can recur or die within 5 years after surgery.[6] **(Figure 1)**

Figure 1

Disease recurrence is a significant threat—some patients may experience disease recurrence or death within 5 years

Even when treated with adjuvant chemotherapy, some patients with stage IB-III NSCLC will have a recurrence or will have died within 5 years.[6*]



In a separate study, the 2016 IASLC database shows that 5-year survival rates in NSCLC are as follows: stage I, 68-92%; stage II, 53-60%; stage II, 13-36%; stage IV, 0-10%.[7‡]

*Pooled analysis of 5 randomized trials with 4584 patients; trials compared postoperative cisplatin-based chemotherapy vs no chemotherapy or cisplatin-based chemotherapy plus postoperative radiotherapy (administered sequentially) vs postoperative radiotherapy alone in patients with completely resected NSCLC.[6] †Resectable patients. ‡Based on the 8th edition of the AJCC tumor, node, and metastasis classification of lung cancer.[7]

NSCLC can recur as metastases throughout the body, with 68% of recurrences involving distant metastases.[8] The most common sites of recurrence include the brain, lung, bone, and liver.[8] This discussion focuses on the clinical rationale for guideline-recommended biomarker testing prior to selection of an adjuvant treatment plan.

EGFR mutations: an important driver of disease

EGFR mutations are a key biomarker in NSCLC, driving tumor growth across stages and impacting recurrence.[10-13] EGFR is a cell-signaling transmembrane protein that plays an important role in cell proliferation, leading to the unregulated growth and survival of tumor cells.[12]

Guideline recommendations for biomarker testing

One way to address high rates of disease recurrence is through the use of adjuvant treatment. To both identify potentially efficacious targeted therapies and avoid therapies unlikely to provide clinical benefit, the National Comprehensive Cancer Network® (NCCN®) recommends testing eligible patients with resectable NSCLC for targetable genomic alterations.[9] In recent years, NCCN updated the biomarker testing recommendations for resectable disease to include *EGFR* (resected stage IB-IIIA) and PD-L1 expression (resected stage II-IIIA).[9] Knowing the patient's complete molecular profile and PD-L1 status can help physicians make optimal treatment decisions for their patients.

Up to 1 in 5 patients with early-stage NSCLC may have an *EGFR* mutation, with 20% of stage I, 18% of stage II, and 18% of stage III patients having *EGFR* mutations, respectively.[10,11§] **(Figure 2)**

Patients with *EGFR*-mutated NSCLC face a greater risk of metastatic recurrence compared with patients without *EGFR*-mutated disease or with *EGFR* wild-type. One study found that when patients with *EGFR*-mutated disease had a recurrence, 97% had distant metastases, compared with 72% of those with wild-type *EGFR* (P=0.007).[14] Additionally, having an *EGFR* mutation doubles the risk that a patient will develop a metastasis to the central nervous system (odds ratio [OR]=1.99).[15] Notably, *EGFR* mutations commonly coexist with PD-L1 expression. Up to 57% of patients with stage IB-III resectable *EGFR*m NSCLC can also express at least 1% PD-L1.[16] **(Figure 3)**

Given these data, a multidisciplinary treatment approach with guideline-recommended biomarker testing is critical for eligible patients with resectable NSCLC.[9]

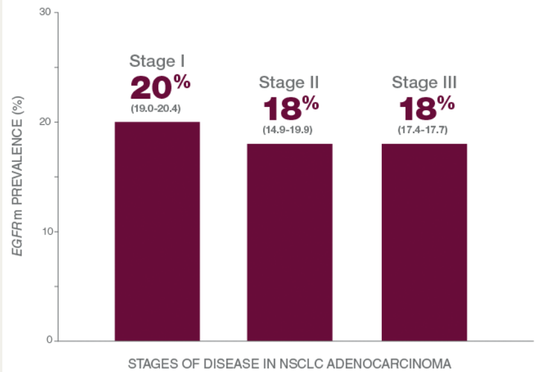
A multidisciplinary treatment approach for guideline-recommended testing and treatment

It has been my experience that multidisciplinary care is paramount in treating NSCLC. Working with a multidisciplinary team can lead to lower rates of disease recurrence, shorter times to diagnosis, and more complete staging evaluations.[17-19‖¶#] Patients presented at multidisciplinary tumor boards are more likely to receive guideline-recommended therapy compared with cases not reviewed at tumor boards.[19] At our institution, we engage a full multidisciplinary team, including a surgeon and a medical oncologist, for every patient with resectable NSCLC. We also have a shared decision-making visit as early as possible with patients regarding their options and eligibility for postsurgical treatment.

Guideline-recommended testing can help to determine optimal treatment options for patients, which can include chemotherapy, immunotherapy, radiation with or without chemotherapy, or targeted therapy.[9] These approaches help ensure every eligible patient receives guideline-recommended *EGFR* and PD-L1 expression testing and is referred to a medical oncologist.

Figure 2

PREVALENCE OF *EGFR*m DISEASE IN NSCLC ADENOCARCINOMA[10,11§]



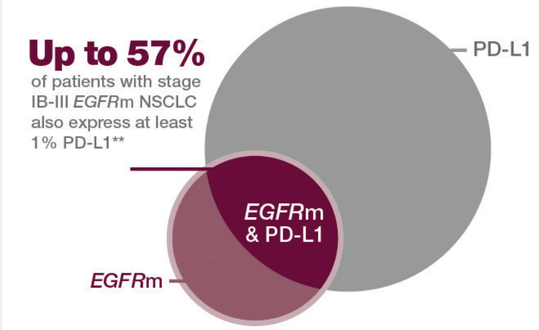
§Prevalence of *EGFR* mutations in NSCLC adenocarcinoma was based on data from 2 references: Sholl et al (2015) performed mutation analysis on 1007 specimens with confirmed diagnosis of lung adenocarcinoma with *EGFR* sensitizing mutations (exon 19 deletions, *EGFR* L858R mutations, *EGFR* G719X mutations, *EGFR* L861Q mutations) and other *EGFR* mutations (any 1 or more mutations in *EGFR* other than exon 19 deletions, L858R mutations, G719X mutations, or L861Q mutations); D'Angelo et al (2012) analyzed tumor specimens from a cohort of 1118 patients with stage I-III surgically resected lung adenocarcinomas with *EGFR* exon 19 deletions and L858R mutations only.[10,11,13,20]

Conclusion

Rates of recurrence after complete resection remain high in resectable NSCLC.[6] NCCN recommends that eligible patients be tested for biomarkers to identify potentially effective treatments.[9] Knowing *EGFR* and PD-L1 expression status before deciding on a postsurgical treatment plan is critical and now guideline recommended.[9] Biomarker testing is an essential part of care—and referring patients to a medical oncologist helps ensure they get the testing and the care they need.[17,19] Pulmonologists should continue to follow up with patients even after referral to a medical oncologist to ensure continuity of treatment and assess for pulmonary-related toxicity associated with treatment and disease progression.[17] By working together with a multidisciplinary team, pulmonologists can help ensure every patient receives guideline-recommended biomarker testing and, ultimately, the optimal adjuvant treatment plan for their disease.[17,19]

Figure 3

OVERLAP OF *EGFR* MUTATIONS AND PD-L1 EXPRESSION[16]



**EGFR mutation status and PD-L1 expression overlap were examined in a retrospective analysis of 319 patients with *EGFR*m NSCLC across all stages. *EGFR* mutations included exon 19 deletions (n=145), exon 21 L858R mutations (n=121), exon 19 nondeletions (n=26), exon 21 non-L858R mutations (n=3), exon 18 mutations (n=12), and exon 20 mutations (n=8). One patient had both exon 18 and exon 20 mutations and 3 patients had other mutations. PD-L1 expression ≥1% was observed in 86 out of 150 patients with stage IB-IIIA *EGFR*m NSCLC.[16]

Footnotes

‖Nemesure et al (2020) found that recurrence rates were significantly lower at 3 years in patients enrolled in a multidisciplinary team (MDT) program compared with those not enrolled in an MDT program (OR=0.51 [95% CI: 0.32, 0.79]) in a retrospective, longitudinal analysis of data from a lung cancer clinical registry. These data were only significant for patients with stage I lung cancer.[17]

¶In a single-center study using tumor registry data to identify all cases of stage III NSCLC seen at Lehigh Valley Health Network between March 2010 and 2013, Friedman et al (2016) compared the care received by patients seen in the thoracic multidisciplinary clinic (MDC) vs the care received by patients not seen in the thoracic MDC: 88.5% of patients (46 of 52 patients) seen in the MDC were treated according to the institutional clinical pathway for stage III NSCLC vs 35.1% of patients (20 of 57 patients) seen outside of the MDC (P<0.001). In addition, Friedman et al found that patients seen in the MDC started therapy within a mean of 19.85 ± 13.8 days as opposed to those not seen in the MDC, who started therapy within a mean of 29.09 ± 27.3 days (P=0.043); and that patients seen in the MDC were more likely to undergo pathologic staging of the mediastinum, with 57.7% of patients (30 of 52 patients) seen in the MDC receiving pathologic staging of the mediastinum vs 24.5% of patients (14 of 57 patients) not seen in the MDC (P<0.001).[19]

#Freeman et al (2015) found in a retrospective analysis of 12,354 propensity-matched patients with stage I, II, or III lung cancer followed from 2008 to 2013, 88% (5382 of 6627) of patients whose care was coordinated in an MDC received care that was within the standards of the NCCN Guidelines® vs 71% (4705 of 6627) of patients whose care was not coordinated in an MDC (P<0.0001); patients in the MDC cohort had a significantly shorter mean interval from the initial pathologic diagnosis to the initiation of treatment compared with patients in the non-MDC cohort (19 ± 8 days vs 32 ± 11 days; P<0.0001); and 91% of patients (6031 of 6627) in the MDC cohort received a complete staging evaluation vs 67% of patients (4572 of 6627) in the non-MDC cohort (P<0.0001).[18]

NCCN=National Comprehensive Cancer Network® (NCCN®)

References

1. American Cancer Society. Key statistics for lung cancer. https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Accessed August 16, 2021.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. American Cancer Society. What is lung cancer? https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed May 21, 2021.
4. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. *Transl Lung Cancer Res.* 2014;3(4):242-249.
5. Lackey A, Donington JS. Surgical management of lung cancer. *Semin Intervent Radiol*. 2013;30(2):133-140.
6. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559.
7. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39-51.
8. Chouaid C, Danson S, Andreas S, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung Cancer*. 2018;124:310-316.
9. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2022. ©National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed September 2, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
10. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: the lung cancer mutation consortium experience. *J Thorac Oncol*. 2015;10(5):768-777 [supplementary appendix].
11. D'Angelo SP, Janjigian YY, Ahye N, et al. Distinct clinical course of *EGFR*-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. *J Thorac Oncol*. 2012;7(12):1815-1822.
12. Black RC, Khurshid H. NSCLC: an update of driver mutations, their role in pathogenesis and clinical significance. *R I Med J* (2013). 2015;98(10):25-28.
13. Sholl LM, Aisner DL, Varella-Garcia M, et al; LCMC Investigators. Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: The Lung Cancer Mutation Consortium experience. *J Thorac Oncol*. 2015;10(5):768-777.
14. Galvez C, Jacob S, Finkelman BS, et al. The role of EGFR mutations in predicting recurrence in early and locally advanced lung adenocarcinoma following definitive therapy. *Oncotarget*. 2020;11(21):1953-1960.
15. Li L, Luo S, Lin H, et al. Correlation between EGFR mutation status and the incidence of brain metastases in patients with non-small cell lung cancer. *J Thorac Dis*. 2017;9(8):2510-2520.
16. Cho JH, Zhou W, Choi YL, et al. Retrospective molecular epidemiology study of PD-L1 expression in patients with EGFR-mutant non-small cell lung cancer. *Cancer Res Treat*. 2018;50(1):95-102.
17. Nemesure B, Albano D, Bilfinger T. Lung cancer recurrence and mortality outcomes over a 10-year period using a multidisciplinary team approach. *Cancer Epidemiol*. 2020;68:101804.
18. Freeman RK, Ascioti AJ, Dake M, Mahidhara RS. The effects of a multidisciplinary care conference on the quality and cost of care for lung cancer patients. *Ann Thorac Surg*. 2015;100(5):1834-1838.
19. Friedman EL, Kruklitis RJ, Patson BJ, Sopka DM, Weiss MJ. Effectiveness of a thoracic multidisciplinary clinic in the treatment of stage III non-small-cell lung cancer. *J Multidiscip Healthc*. 2016;9:267-274.
20. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006.