Resect-Test-Refer –
Be Beforehand in the GAME

Steering Committee Authors

Dr Chandramohan K
RCC, Trivandrum

Dr Shubham Garg
Fortis Hospital, Delhi

Dr Somashekhar SP
Aster CMI, Bangalore

Dr Raj Nagarkar
HCG Manavata, Nashik

Dr Bivas Biswas
TMC, Kolkata

Dr Nambaru Lavanya
Sr Scientific Officer,
Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad

Table of Contents

A. Background

Epidemiology:

Cancer by the Numbers

As per the GLOBOCAN 2020 report, lung cancer is the fourth leading cause of cancer-associated deaths (7.8%) in India.[1] The National Cancer Registry Programme (NCRP) predicted a sharp rise in lung cancer cases and age-wise incidence rate in India by 2025 (Fig 1).[2]

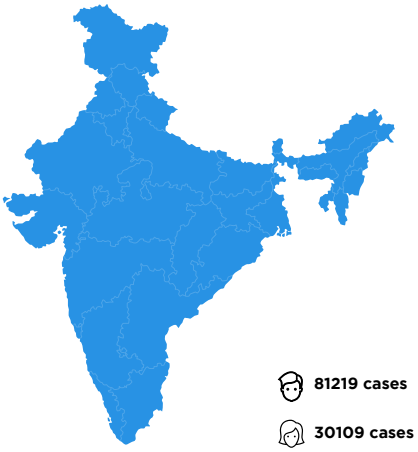


Figure 1: Projected estimates of lung cancer cases by the year 2025

Early-Stage Lung Cancer:

When Is Resectability an Option?

Early-stage non-small cell lung cancer (NSCLC) includes stage I-IIA (primary tumor size [T1-2], no lymph node involvement [N0], and no metastasis [M0]); stage IIB (primary tumor size [T1-2], N1 lymph node involvement, and no metastasis [M0]); stage IIIA and IIIB (primary tumor size [T1-4], N [1-2] lymph node involvement, and no metastasis [M0]).[3–5]

Stage I or II early-stage lung cancer is found in one-third of newly diagnosed cases.[6] Patients with stage I and II NSCLC are primarily treated by surgical resection. However, surgery is not universally prescribed for stage III patients, and there is no widely accepted definition for resectability.[7] On the basis of multidisciplinary approach, stage IIIA patients with no evidence of extrathoracic or distant metastases[8], and non-bulky (less than 3 cm), distinct, or single-level N2 involvement may undergo surgical resection.[9] The surgeon should aim for an en bloc R0 resection as incomplete resection would lead to a worse prognosis.[6]

Sixteen percent of estimated patients present with early-stage disease; however, this rate may rise in the future with the use of low-dose computed tomography (LDCT) screening.[10,11]

When Lung Cancer Returns:

A Call to Enhance Systemic Control

Survival in patients with early-stage lung cancer falls behind when compared to patients with breast, colon, and prostate cancer.[12] The likelihood of 5-year survival (Stage I–72%; Stage II–55%)[13] remains self-effacing as patients experience both loco-regional and metastatic relapse.[12] Even though surgery remains the mainstay of treating early-stage lung cancer, disease recurrence is between 30% and 50%. Recurrence factors for early-stage lung cancer are represented in Fig 2.[14] Postoperative relapse after complete resection is reported in almost half of the stage I-IIIA patients, and the possibility of finding a cure is substantially low. Hence, the majority of the patients experience disease recurrence leading to death.[15,16]

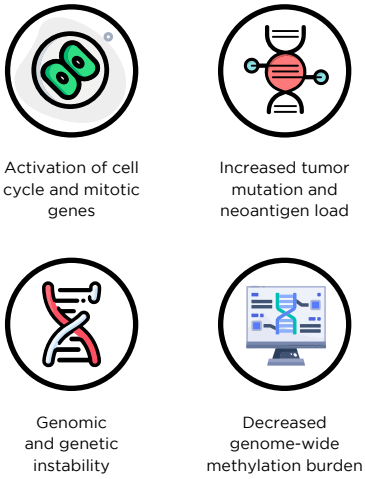


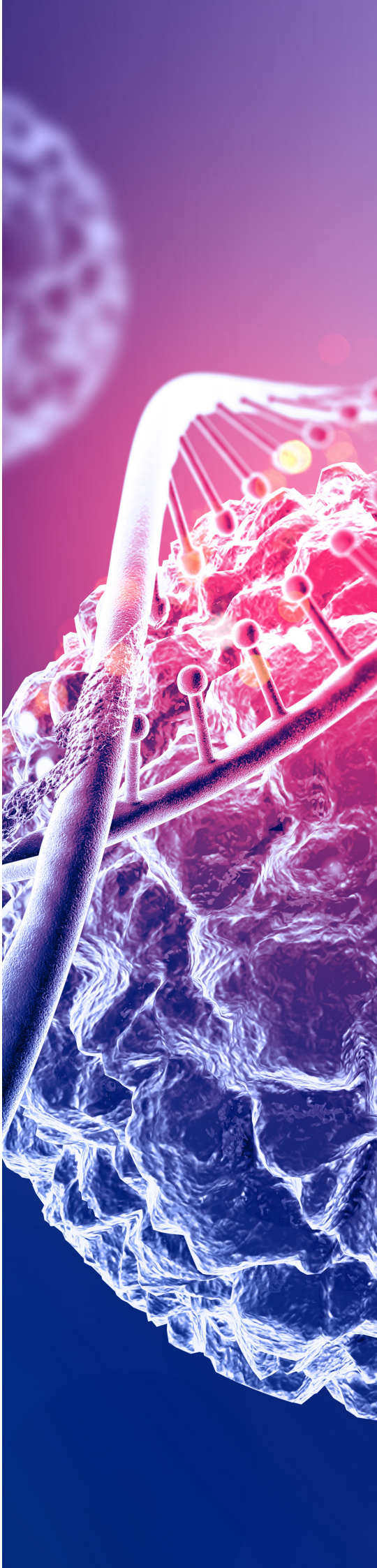
Figure 2: Recurrence factors for early- lung cancer

The Potential Pitfalls:

Treatment outcomes of lung cancer remains at later stages; therefore, early detection is critical to improve the overall survival (OS). A study showed that patients with hilar node (N1) and mediastinal node (N2) involvement presented with an 11.6% (for 5 years) and 14.7% improvement in OS, respectively.[17]

Biomarker Testing:

Identification of actionable mutation (s) in advanced NSCLC patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer;[18] 5-year survival rates range from 15% to 50%, depending on the biomarker.[19] Lessons learned from the metastatic setting should be applied to surgically resectable NSCLC for better survival in early-stage disease.[20,16] When compared to patients with metastatic cancer at diagnosis, patients with localized cancer at diagnosis have a much improved 5-year survival rate (56.3% vs. 4.7%, respectively).[21,6]



B. Current Practices in Early-Stage Lung Cancer

Early-Stage Lung Cancer Diagnosis:

An estimated <1% of hospitals in India have dedicated interventional radiology setups to perform transthoracic sampling under CT or ultrasonogram image guidance.[22] Positron-emission tomography (PET)-guided transthoracic sampling is preferred for patients with inconclusive thoracic lesion results from previous sampling method.[23]

Is Invasive Mediastinal Staging a Preferred Option in India?

Mediastinal lymph node involvement is verified by invasive mediastinal imagingusing endobronchial ultrasound (EBUS), endoscopic ultrasound, and mediastinoscopy (for inconclusive endoscopic results) techniques.[17] In India, only a few centers prefer invasive mediastinal staging in all resectable patients irrespective of PET-CT scan results and others prefer if PET-CT scan shows N3 stage.[23]

Tissue Fixation for Successful Biomarker Testing

- Sample fixation and preservation is a crucial pre analytical step for optimal molecular testing.[24] Sample preservation is possible through a tissue-sparing technique such as the "one biopsy per block" approach and small sample cutting protocols.[25]
- For limited biopsies, fixation timing is between 6 and 12 hours, and for resected specimens, it is between 8 and 24 hours in 10% neutral-buffered formalin.[18]
- Majority (about 70%) of patients with NSCLC have advanced disease at the time of presentation, making curative surgery impractical. In these circumstances, fine-needle aspiration cytology (FNAC) is done. However, compared to surgical resection, they generate small samples. Currently, FNAC is not used directly for molecular diagnostic testing.[18]

Challenges with Tissue Biopsies

Tissue biopsies may present with inter-and intra tumor heterogeneity (for primary tumors and their metastases). The lack of adequate tissue for tumor characterization is also an important limitation.[26]

Molecular Testing in Early-Stage:

Ways to Guide Treatment

Management of NSCLC has taken a major shift in recent decades from chemotherapy to targeted therapies.[27] Personalized targeted therapies can be planned along with surgery with or without adjuvant or neoadjuvant chemotherapy for patients with early-stage lung cancer who pose a high risk for recurrence after surgical resection.[28]

Utility of Reflex-Ordered Testing in Early-Stage Lung Cancer

To make the process of molecular testing uniform and utilize a tissue to the maximum, reflex-ordered testing should be implemented in newly diagnosed early-stage lung cancer (Fig 3).[29]

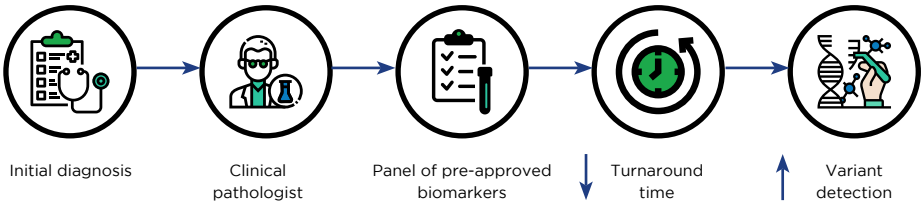


Figure 3: Benefits of reflex ordered testing

Dynamic Monitoring of EGFR Mutations:

Harnessing Advancements for Enhanced Monitoring

Epidermal growth factor receptor (EGFR)-mutated disease may be associated with a higher risk of metastatic recurrence. EGFR-mutated lung cancer had increased rates of metastatic recurrence compared with EGFR-wildtype disease (97% vs 68%; *P* = 0.007). Molecular testing may be a promising tool for risk stratification and surveillance after definitive management for early-stage disease. For risk assessment and surveillance after definitive treatment for early-stage disease, molecular testing may be a helpful approach.[6]

A US-based study documented significant reduction in the average turn around time for with and without reflex ordered molecular testing (52.6 days vs 26.5 days [2017] and 15.6 days [2018]; *P* = 0.0002) in patients with lung adenocarcinoma including patients with 10% stage II disease, and 16% stage I disease.[29] It concluded that reflex ordered testing of molecular biomarkers in lung adenocarcinoma led to significantly decreased turn around time in their hospital system and higher detection rates of targeted gene alterations.[29]

Mutation testing platforms for EGFR include NGS, droplet digital polymerase chain reaction (ddPCR), and real-time PCR [amplification refractory mutation system (ARMS-PCR)][30]. The results obtained from the Canadian study, for EGFR testing in early-stage lung cancer on tissue biopsies, have been depicted in Fig 4.[31]

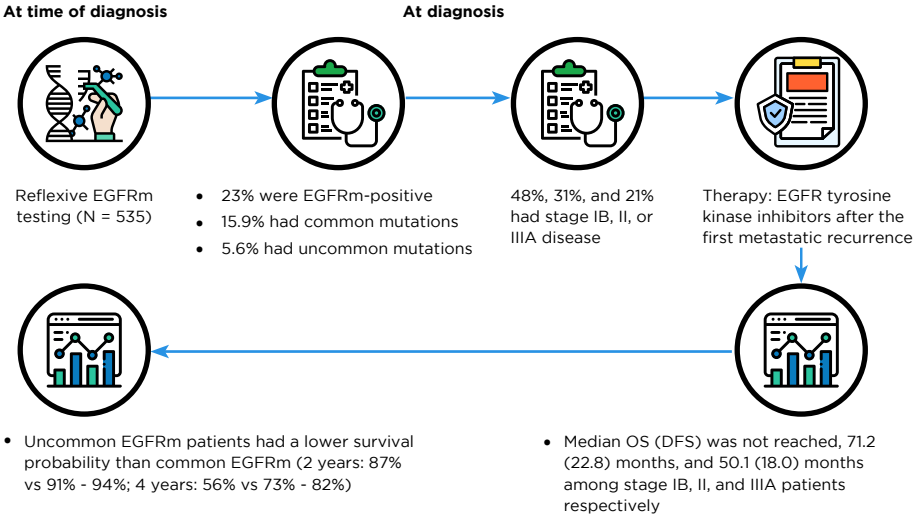


Figure 4: EGFR mutation prevalence, real-world treatment patterns, and outcomes among patients with resected, early-stage NSCLC

In a real-world study from Italy, reflex EGFR testing was done on 181 (80%) of the 225 surgical specimens, and 35 instances (19%) had EGFR mutations. The frequency of EGFR mutations was comparable across early-stage (I–III) and advanced-stage NSCLC. Reflex EGFR testing seems to be a reliable approach in all early-stage NSCLC at diagnosis or after surgery.[32]

Using modified Delphi methodology, an online survey was created by a scientific group constituting medical oncologists from hospitals distributed throughout Spain. About 84.4% of the panellists concurred that EGFR mutation testing had to be carried out after the surgery.[33]

Results of Targetable Mutations in Indian Patients with NSCLC

- The most common targetable mutations reported in Indian patients with NSCLC include EGFR, rearrangements in anaplastic lymphoma kinase (ALK), receptor tyrosine kinase encoded by ROS-1 gene, and overexpression of programmed cell death ligand-1 (PDL-1).[34] Other mutations that are gaining therapeutic importance include v-raf murine sarcoma viral oncogene homolog B1 (BRAF), mesenchymal-epithelial transition (MET), human epidermal growth factor receptor 2 (HER2), and Kirsten rat sarcoma viral oncogene homolog (KRAS).[21,34]

Proposed Molecular Testing Algorithm and Guidelines

A pragmatic molecular testing algorithm (Fig 5); (subjected to regional and institutional variations) and guideline recommendations proposed for stage I–III NSCLC patients is shown in Table 1.[35]

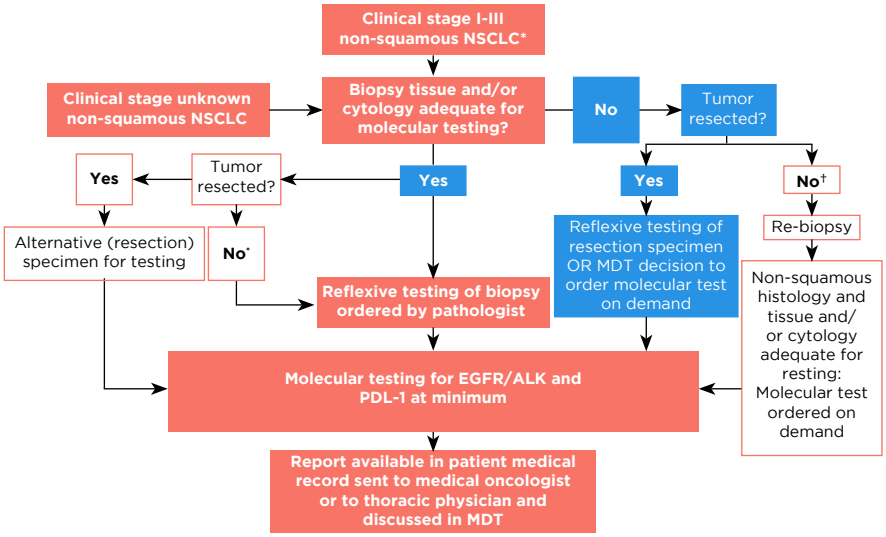


*Figure 5: Proposed algorithm for molecular testing in patients with stage I–III NSCLC (resectable and unresectable). *Patients with squamous cell carcinoma who have clinical characteristics associated with high probability of an oncogenic driver (never/minimal smokers and young age) may be included. †Patient not suitable for surgery (unresectable tumor/medically inoperable) or declines surgery.*

Guidelines	Recommendation for molecular testing	Recommendation for treatment with adjuvant agents
NCCN, 2023[36]	When adjuvant TKI therapy for NSCLC stage IB-IIIA is being considered, molecular screening for EGFR mutations should be carried out. Initial diagnostic biopsy specimens are also eligible for testing for this purpose.	On the basis of the results of clinical trials and FDA approval, the panel recommends osimertinib as an adjuvant therapy choice for eligible patients with completely resected (R0) stage IB - IIIA EGFR mutation-positive NSCLC who have undergone adjuvant chemotherapy in the past or who are not eligible for platinum-based chemotherapy. The NCCN panel stated that osimertinib is advised in these circumstances for the most prevalent EGFR mutations, exon 19 deletions, or L858R mutations.
Asia Area Consensus, 2022[37]	For nonmetastatic resectable NSCLC • Adenocarcinoma - EGFR and PD-L1 are not recommended as routine for Stage IA - EGFR to be analyzed by PCR for above stage IA - In case, tumor found either EGFR or PD-L1 mutation >1%, regional recommendations needs to be adopted • Squamous cell carcinoma: EGFR is not recommended as routine for stages IA to IIIA, and PD-L1 is not recommended for stage IA. Nonmetastatic unresectable NSCLC • When definitive chemoradiotherapy is considered, PD-L1 evaluation and EGFR mutation (adenocarcinoma only) and adhere to regional recommendations.	-
ESMO, 2022[38]	• EGFR mutation status should be determined. • Test methodology should cover mutations in exons 18-21, including those associated with resistance to some therapies. • In limited resources, the most common activating mutations (exon 19 deletion and exon 21 L858R point mutation) should be determined. • Testing for ALK, ROS-1, and NTRK rearrangements as well as BRAF V600 mutation status should be carried out.	-

Table 1: Guideline recommendations for molecular profiling in the early-stage lung cancer

Results from clinical trials for the implementation of targeted therapies in adjuvant and neoadjuvant settings advocate policymakers to fit in molecular testing into practice when managing patients with NSCLC at early stages.[39,40]

Benefits and Challenges of Molecular Testing in Early-Stage Disease in Indian Settings

Benefits: In case of disease recurrence, "banked" molecular data can help one decide about the next treatment decision faster. Other advantages include identifying actionable genetic alterations in large numbers of patients, using of targeted therapies or immunotherapy, assisting in decision - making for clinician.[35]

Challenges: Data for genetic alterations that predict poor response to immunotherapy and risk prognosis for disease relapse in stage I-III resected NSCLC remain limited.[35]

Liquid Biopsy versus Tissue biopsy in Early-Stage Lung Cancer

Liquid biopsy is a non invasive test for the biomarker test in lung cancer; however, there is no much data available about the utility of liquid biopsy in early-stage lung cancer[41,42]. Liquid biopsy has the potential to improve patient care for early-stage NSCLC. It offers advantages in terms of speed, ease of access, and enhanced detection of biomarkers when compared to tissue biopsy. Additionally, liquid biopsy could be utilized for screening, diagnosis, and prognosis. It can optimize therapeutic management by addressing challenges of tumor heterogeneity, monitoring tumor burden, and detecting minimal residual disease (MRD), that is the presence of tumor-specific ctDNA, post-operatively.[43]

Standard Of Care For Early-Stage Lung Cancer:

The Vision and Mission

The SOC and the possibility of targeted therapy in early-stage lung cancer management have been represented in Fig 6[17].

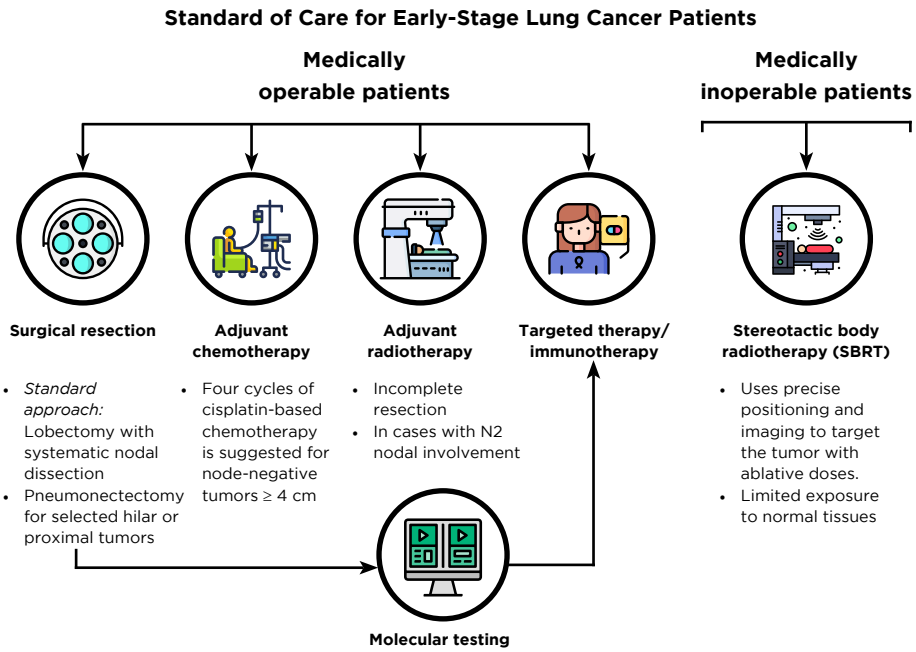


Figure 6: SOC for early-stage lung cancer

Neoadjuvant – Immunotherapy

The use of neoadjuvant nivolumab along with chemotherapy has significantly improved event-free survival than chemotherapy alone (31.6 months with nivolumab plus chemotherapy and 20.8 months with chemotherapy; hazard ratio [HR], 0.63; 97.38% confidence interval [CI], 0.43 - 0.91; $P = 0.005$)[39] with greater benefits observed in Stage III A patients rather than Stage IB and II.

Underutilized Curative Treatment:

Delayed Resection

Although resection is the SOC in early-stage disease, only 1.5% to 5.3% of patients are either eligible or undergo surgery in India[23].

Considerable delay (more than 4 months) in the initiation of treatment from diagnosis was documented, which may be due to overlapping symptoms and radiological assessment with tuberculosis, and lack of awareness[23].

Knowing the Instruments:

Front Lines of Thoracic Surgery

Lobectomy with mediastinal lymph node dissection is preferred for stage I or II and stage IIIA NSCLC patients for its better survival rates and reduced locoregional recurrence[23,44].Sublobar resections are preferred for ground-glass nodule (GGN)–dominant small-sized lung cancers[44,45].

Minimally invasive procedures such as video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracoscopic surgery (RATS) have demonstrated to reduce postoperative complications and shorten the length of hospitalization. The perioperative benefits of VATS may make it superior to thoracotomy.[46,44].

Adopting a minimally invasive approach (monoportal, multi portal, and robotic VATS, awake surgery) wherever available and applicable offer both diagnostic and therapeutic advances by improving surgical precision and reducing mortality.

Adjuvant Chemotherapy

Adjuvant chemotherapy improves survival by 4% at 5 years than surgery alone in patients with resected early-stage NSCLC.[47] Though adjuvant chemotherapy showed no survival benefit in stage-IA patients[48], a significant advantage was observed in high-risk stage IB patients and selected patients with tumors ≥4 cm[49]. Hence adjuvant platinum-based chemotherapy was recommended for stage II-III radically resected NSCLC patients.[49]

Adjuvant TKIs

In phase II SELECT trial, erlotinib treatment (for 2 years) after adjuvant chemotherapy (+/- radiotherapy) showed improvement in 2-year disease-free survival (DFS, 88%) in early-stage NSCLC patients.[50] An updated meta-analysis by Zhao (2022) showed that adjuvant EGFR-TKIs significantly prolonged DFS (HR, 0.46; 95% CI, 0.29–0.72) in patients with early-stage EGFRm-positive NSCLC, but had no impact on OS[3]. The phase III ADAURA trial showed significant DFS in the osimertinib group than placebo (HR, 0.20; 99.12% CI, 0.14–0.30; $P < 0.001$) in EGFR-mutated (EGFRm) completely resected stage IB–IIIA disease, with or without standard adjuvant chemotherapy.[35] The 5-year OS was 88% in the osimertinib group and 78% in the placebo group (overall HR for death, 0.49; 95.03% CI, 0.34 - 0.70; $P < 0.001$).[51]

The use of adjuvant TKIs alone or in combination with chemotherapy can benefit patients by improving DFS, OS, and quality of life and may be considered in EGFRm positive NSCLC Stage IB-IIIA.

Immune Checkpoint Inhibitor Therapy

Trials engaging immune checkpoint inhibitors (ICIs) in the neoadjuvant setting have shown impressive major pathologic response (MPR) and pathologic complete response (CR) rates without delaying surgery. Also, adjuvant immunotherapy has shown a promising increase in disease-free OS[52]. Table 2 and 3 show the clinical trials in the pipeline to investigate ICIs as neoadjuvant or adjuvant therapy in early-stage lung cancer.[39,53,54]

Study name	ICIs (ongoing clinical trial phase)	Primary endpoints	Treatment conditions
As neo adjuvant therapy in patients with resectable stage II, IIIA, or IIIB (N2) NSCLC			
NCT03425643 (KEYNOTE-671)	Pembrolizumab (III)	Event-free survival (EFS), and OS	Pembrolizumab plus chemotherapy, and then surgery followed by adjuvant pembrolizumab
NCT03456063 (IMpower030)	Atezolizumab (III)	**Independent review facility (IRF)-assessed EFS**	Atezolizumab plus chemotherapy versus placebo plus chemotherapy, and then surgery followed by adjuvant atezolizumab
As adjuvant therapy after resection and adjuvant chemotherapy in patients with Stage IB/II-IIIA NSCLC			
NCT02504372 (PEARLS)	Pembrolizumab (III)	**Disease-free survival (DFS)**	Adjuvant pembrolizumab or placebo for 1 year
NCT02595944 (ANVIL)	Nivolumab (III)	DFS and OS	Adjuvant pembrolizumab or observation for 1 year
NCT02273375 (BR31)	Durvalumab (III)	**Compare DFS for patients with NSCLC that is PD-L1 expression TC ≥25% vs patients without common activating EGFR mutations or ALK gene rearrangements**	Adjuvant durvalumab or placebo for 1 year

Table 2: Ongoing clinical trial of ICIs in patients with early-stage, resectable NSCLC[38,55]

Name of the study	Status	Study type	Study design	Outcomes
IMpower010 (NCT02486718)[40]	On-going	Randomized, multicenter, open-label, and phase 3	Compared atezolizumab with best supportive care after adjuvant platinum-based chemotherapy	• Median follow-up (stage II–IIIA): 32·2 months (IQR, 27·4–38·3) • DFS: Improved with atezolizumab compared with the best supportive care, especially in cells expressing 1% or more PD-L1 (HR, 0·66; 95% CI, 0·50-0·88; *P* = 0·0039)
Checkmate 816 (NCT02998528)[39]	On-going	Open-label, phase 3, randomized patients with stage IB to IIIA resectable NSCLC	Compared nivolumab + platinum-based chemotherapy with only platinum-based chemotherapy	• Median event-free survival: 31.6 months (95% CI, 30.2 - not reached) with nivolumab+ chemotherapy versus 20.8 months (95% CI, 14.0 - 26.7) with chemotherapy alone (HR for disease progression, recurrence, or death, 0.63; 97.38% CI, 0.43 - 0.91; *P* = 0.005). • Pathological complete response: 24.0% (95% CI, 18.0 - 31.0) and 2.2% (95% CI, 0.6 - 5.6), respectively (odds ratio, 13.94; 99% CI, 3.49 - 55.75; *P* < 0.001).

Table 3: Approved therapies in patients with resectable NSCLC

C. Multidisciplinary Team Approach in Early-Stage Lung Cancer

The Multidisciplinary Team:

Why It Matters?

Multidisciplinary team (MDT) involvement in early-stage disease may maximize treatment options in patients with borderline operable conditions (due to comorbidities) and those with multifocal lung changes. It may also increase the cure rate in patients taking SOC therapy and the number of individuals recruited for clinical trials.[55]

Multidisciplinary treatment included patients, health care professionals, and the community.[56] Additionally, the choice of management options from radiotherapy and resection to targeted or systemic therapy would require the involvement of multiple specialties to decide the optimal treatment strategy and care for patients with lung cancer.[57]

The 2023 NCCN Guidelines mentions that pulmonology, chest radiology, medical oncology, radiation oncology, and thoracic surgery specific-divisions are to be included in an MDT approach, especially during diagnosis for suspected lung cancer stages Stage IB (peripheral T2a, N0), Stage I (central T1abc–T2a, N0), Stage II (T1abc–2ab, N1; T2b, N0), Stage IIB (T3, N0), and Stage IIIA (T3, N1), NO-1.[60,38] A medical oncologist may be consulted to evaluate patients with pathologic stage II or higher illness or high-risk features. For stage IIIA NSCLC patients who are considered resectable, a radiation oncologist may be consulted.

The thoracic surgical oncologist must be evaluated for curative local therapy, especially for stage I and II; a multidisciplinary review with a radiation. The oncologist is advised when stereotactic ablative radiotherapy (SABR) is being explored for high-risk or patients with borderline operable conditions.[36]

A considerable population of patients diagnosed with early-stage NSCLC would eventually receive SBRT in place of surgery.[58]

Any patient with operable stage I NSCLC being considered for SBRT should be evaluated by a thoracic surgeon, preferably in a multidisciplinary setting to reduce specialty bias.[59]

Evidence to Support the importance of MDT in Lung Cancer Care[60]

Author name	Type of study	Outcome
Senter *et al.*, 2016[61]	Retrospective post test design with comparison group	Improved median survival in patients associated with the multidisciplinary clinic (MDC) and non-MDC patient group
Bilfinger *et al.*, 2018[62]	Retrospective post-test design with comparison group	Increased short - and long-term OS for all stages in MDC patients
Rogers *et al.*, 2017[63]	Retrospective pre and post test study	Reduced mortality in patients who underwent multidisciplinary meeting (MDM) before treatment
Stone *et al.*, 2018[64]	Retrospective cohort study	Improvement in patient survival for all stages at 1, 2, and 5 years who underwent MDM, except stage IIIB
Tamburini *et al.*, 2018[65]	Retrospective pre-and post test audit	Significantly improved 1-year survival in MDM group versus pre-MDM patients

Table 4: Role of MDT on patient outcomes with lung cancer

MDT Involvement in Early-Stage Lung Cancer Treatment

A real-world setting showed that only 54% of patients with stage I disease underwent surgery and 24% received no treatment, therefore, demanding the need for MDT in decision-making for improving patient survival.[55,66] In stage II disease, evaluation of the patient's pathology reports, preoperative staging, and surgical reports by the MDT team would favor patient selection for adjuvant therapy and also aid in clinical decision-making in complete resection.[67]

Paving the Way Forward:

The key recommendations for early-stage NSCLC treatment strategy have been mentioned in Fig 7.[68]

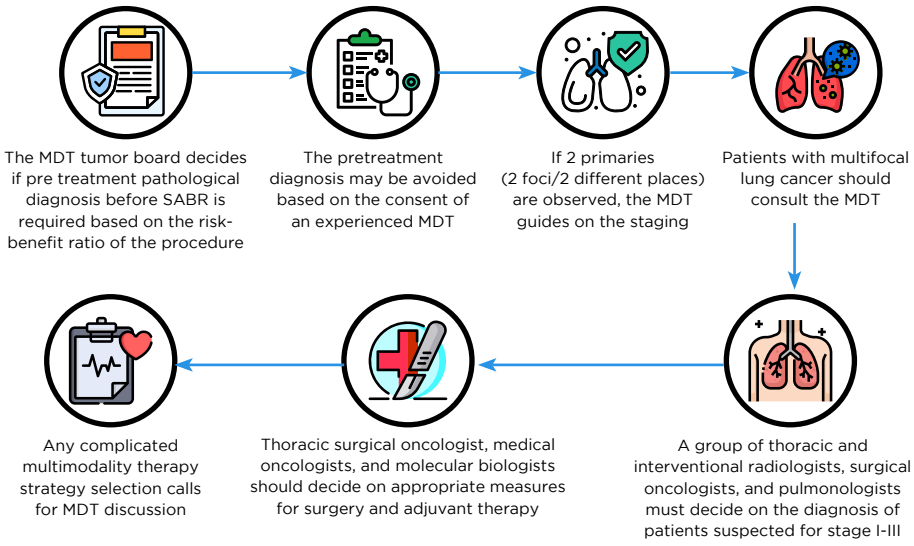


Figure 7: Key recommendations for a multidisciplinary approach to lung cancer

D. Implications of RESECT-TEST-REFER

Testing in patients with early-stage lung cancer would help in deciding adjuvant therapy better. If the patient is EGFRm positive, they can be treated with osimertinib. On the other hand, mutation status would also help identify the right candidates for immunotherapy.[40,69]

Conclusions

- It is important that right candidates receive the right treatment. Biomarker testing is one such guiding tool for appropriate treatment of early-stage NSCLC.
- All cases should be discussed MDT teams to guide appropriate treatment decisions, considering patient preferences.
- All patients undergoing surgery should undergo biomarker testing at least for EGFR/ ALK and PDL-1 to guide appropriately for targeted therapy or exclude these patients before deciding immunotherapy. This may be done in diagnostic or resected sample.

References

1. IARC, WHO. India GLOBOCON 2020. Accessed Aug 31, 2023. Available from: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
2. Nath A, Sathishkumar K, Das P, Sudarshan KL, Mathur P. A clinicoepidemiological profile of lung cancers in India – Results from the National Cancer Registry Programme. *Indian J Med Res.* 2022;155(2):264-272. doi:10.4103/ijmr.ijmr_1364_21
3. Zhao P, Zhen H, Zhao H, Zhao L, Cao B. Efficacy and safety of adjuvant EGFR-TKIs for resected non-small cell lung cancer: a systematic review and meta-analysis based on randomized control trials. *BMC Cancer.* 2022;22:328. doi:10.1186/s12885-022-09444-0
4. Lababede O, Meziane MA. The eighth edition of tnm staging of lung cancer: reference chart and diagrams. *Oncologist.* 2018;23(7):844-848. doi:10.1634/theoncologist.2017-0659
5. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg.* 2018;8(7):709-718. doi:10.21037/qims.2018.08.02
6. 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. doi:10.18632/oncotarget.27602
7. Lackey A, Donington J. Surgical management of lung cancer. *Semin Interv Radiol.* 2013;30(02):133-140. doi:10.1055/s-0033-1342954
8. Shamji FM, Beauchamp G. Assessment of operability and resectability in lung cancer. *Thorac Surg Clin.* 2021;31(4):379-391. doi:10.1016/j.thorsurg.2021.07.008
9. Brascia D, De Iaco G, Schiavone M, et al. Resectable IIIA-N2 non-small-cell lung cancer (NSCLC): In Search for the Proper Treatment. *Cancers.* 2020;12(8):2050. doi:10.3390/cancers12082050
10. Seer_CSR_2021.pdf. Accessed Aug 31, 2023. Available from: https://seer.cancer.gov/csr/
11. Bethesda, MD National Cancer Institute_2015.pdf. Accessed Aug 31, 2023. Available from: https://seer.cancer.gov/archive/csr/1975_2015/
12. Lovly CM. Expanding horizons for treatment of early-stage lung cancer. *N Engl J Med.* 2022;386(21):2050-2051. doi:10.1056/NEJMe2203330
13. Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non–small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. *J Thorac Cardiovasc Surg.* 2014;147(2):747-753. doi:10.1016/j.jtcvs.2013.10.001
14. Kratz JR, Li JZ, Tsui J, et al. Genetic and immunologic features of recurrent stage I lung adenocarcinoma. *Sci Rep.* 2021;11:23690. doi:10.1038/s41598-021-02946-0
15. Imai H, Onozato R, Kaira K, et al. Course of postoperative relapse in non small cell lung cancer is strongly associated with post progression survival. *Thorac Cancer.* 2021;12(20):2740-2748. doi:10.1111/1759-7714.14119
16. Sugimura H, Nichols FC, Yang P, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg.* 2007;83(2):409-418. doi:10.1016/j.athoracsur.2006.08.046
17. Coakley M, Popat S. Management of lung cancer. *Medicine (Baltimore).* 2020;48(4):273-278. doi:10.1016/j.mpmed.2020.01.003
18. Majeed U, Manochakian R, Zhao Y, Lou Y. Targeted therapy in advanced non-small cell lung cancer: current advances and future trends. *J Hematol OncolJ Hematol Oncol.* 2021;14:108. doi:10.1186/s13045-021-01121-2
19. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw JNCCN.* 2022;20(5):497-530. doi:10.6004/jnccn.2022.0025
20. Gentzler RD, Riley DO, Martin LW. Striving toward improved outcomes for surgically resectable non-small cell lung cancer: the promise and challenges of neoadjuvant immunotherapy. *Curr Oncol Rep.* 2020;22(11):109. doi:10.1007/s11912-020-00969-w
21. Lung and Bronchus Cancer — Cancer Stat Facts.pdf. Accessed Aug 31, 2023. Available from: https://seer.cancer.gov/statfacts/html/lungb.html
22. Madhusudhan KS, Srivastava DN, Sharma S, Sharma S. Interventional Radiology in India. *Am J Roentgenol.* 2018;211(4):730-735. doi:10.2214/AJR.18.19777
23. Singh N, Agrawal S, Jiwnani S, et al. Lung Cancer in India. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* 2021;16(8):1250-1266. doi:10.1016/j.jtho.2021.02.004
24. Stojši J. *Precise Diagnosis of Histological Type of Lung Carcinoma: The First Step in Personalized Therapy.* IntechOpen; 2018. doi:10.5772/intechopen.75316
25. Penault-Llorca F, Kerr KM, Garrido P, et al. Expert opinion on NSCLC small specimen biomarker testing — Part 1: Tissue collection and management. *Virchows Arch.* 2022;481(3):335-350. doi:10.1007/s00428-022-03343-2
27. Chen YY, Chen YS, Huang TW. Prognostic impact of EBUS TBNA for lung adenocarcinoma patients with postoperative recurrences. *Diagnostics.* 2022;12(10):2547. doi:10.3390/diagnostics12102547
26. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer. *Chest.* 2013;143(5):e142S-e165S. doi:10.1378/chest.12-2353
27. Mitsudomi T, Tan D, Yang JCH, et al. Expert consensus recommendations on biomarker testing in metastatic and non-metastatic non-small cell lung cancer in Asia. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* Published online November 12, 2022:S1556-0864(22)01905-0. doi:10.1016/j.jtho.2022.10.021
28. Wang X, Janowczyk A, Zhou Y, et al. Prediction of recurrence in early stage non-small cell lung cancer using computer extracted nuclear features from digital H&E images. *Sci Rep.* 2017;7(1):13543. doi:10.1038/s41598-017-13773-7
29. Anand K, Phung TL, Bernicker EH, Cagle PT, Olsen RJ, Thomas JS. Clinical utility of reflex ordered testing for molecular biomarkers in lung adenocarcinoma. *Clin Lung Cancer.* 2020;21(5):437-442. doi:10.1016/j.cllc.2020.05.007
30. Li C, He Q, Liang H, et al. Diagnostic accuracy of droplet digital PCR and amplification refractory mutation system PCR for detecting EGFR mutation in cell-free DNA of lung cancer: a meta-analysis. *Front Oncol.* 2020;10:290. doi:10.3389/fonc.2020.00290
31. Sara Kuruvilla M, Liu G, Syed I, et al. EGFR mutation prevalence, real-world treatment patterns, and outcomes among patients with resected, early-stage, non-small cell lung cancer in Canada. *Lung Cancer.* 2022;173:58-66. doi:10.1016/j.lungcan.2022.08.023
32. Pasello G, Lorenzi M, Pretelli G, et al. Diagnostic-therapeutic pathway and outcomes of early stage nsclc: a focus on EGFR testing in the real-world. *Front Oncol.* 2022;12:909064. doi:10.3389/fonc.2022.909064
33. Isla D, Felip E, Garrido P, et al. A Delphi consensus panel about clinical management of early-stage EGFR-mutated non-small cell lung cancer (NSCLC) in Spain: a Delphi consensus panel study. *Clin Transl Oncol.* 2023;25(1):283-291. doi:10.1007/s12094-022-02941-5
34. Prabhash K, Advani SH, Batra U, et al. Biomarkers in non-small cell lung cancers: indian consensus guidelines for molecular testing. *Adv Ther.* 2019;36(4):766-785. doi:10.1007/s12325-019-00903-y
35. Aggarwal C, Bubendorf L, Cooper WA, et al. Molecular testing in stage I-III non-small cell lung cancer: Approaches and challenges. *Lung Cancer Amst Neth.* 2021;162:42-53. doi:10.1016/j.lungcan.2021.09.003
36. NCCN 2023.pdf. Accessed Aug 31, 2023. Available from: https://www.nccn.org/guidelines/recently-published-guidelines
37. Mitsudomi T, Tan D, Yang JCH, et al. Expert consensus recommendations on biomarker testing in metastatic and nonmetastatic NSCLC in asia. *J Thorac Oncol.* Published online November 2022:S1556086422019050. doi:10.1016/j.jtho.2022.10.021
38. Hendriks LE, Kerr K, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* Published online January 2023:S0923753422047810. doi:10.1016/j.annonc.2022.12.009
39. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med.* 2022;386(21):1973-1985. doi:10.1056/NEJMoa2202170
40. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet.* 2021;398(10308):1344-1357. doi:10.1016/S0140-6736(21)02098-5
41. Tang Y, Qiao G, Xu E, Xuan Y, Liao M, Yin G. Biomarkers for early diagnosis, prognosis, prediction, and recurrence monitoring of non-small cell lung cancer. *OncoTargets Ther.* 2017;10:4527-4534. doi:10.2147/OTT.S142149
42. Shen H, Jin Y, Zhao H, et al. Potential clinical utility of liquid biopsy in early-stage non-small cell lung cancer. *BMC Med.* 2022;20(1):480. doi:10.1186/s12916-022-02681-x
43. Vandekerckhove O, Cuppens K, Pat K, et al. Liquid biopsy in early-stage lung cancer: current and future clinical applications. *Cancers (basel).* 2023;15(10):2702. doi:10.3390/cancers15102702
44. Raman V, Yang CFJ, Deng JZ, D'Amico TA. Surgical treatment for early stage non-small cell lung cancer. *J Thorac Dis.* 2018;10(Suppl 7):S898-S904. doi:10.21037/jtd.2018.01.172
45. Kato H, Oizumi H, Suzuki J, Suzuki K, Takamori S. Indications and technical details of sublobar resections for small-sized lung cancers based on tumor characteristics. *Mini-Invasive Surg.* 2021;5:5. doi:10.20517/2574-1225.2020.98
46. Ujiie H, Gregor A, Yasufuku K. Minimally invasive surgical approaches for lung cancer. *Expert Rev Respir Med.* 2019;13(6):571-578. doi:10.1080/17476348.2019.1610399
47. Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev.* Published online March 2, 2015. doi:10.1002/14651858.CD011430
48. Luna J, Sotoca A, Fernández P, Miralles C, Rodríguez A. Recent advances in early stage lung cancer. *J Clin Transl Res.* 2021;7(2):163-174.
49. Indini A, Rijavec E, Bareggi C, Grossi F. Novel treatment strategies for early-stage lung cancer: the oncologist's perspective. *J Thorac Dis.* 2020;12(6):3390-3398. doi:10.21037/jtd.2020.02.46
50. Pennell NA, Neal JW, Chaft JE, et al. Select: a phase II trial of adjuvant erlotinib in patients with resected epidermal growth factor receptor–mutant non–small-cell lung cancer. *J Clin Oncol.* 2019;37(2):97-104. doi:10.1200/JCO.18.00131
51. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med.* 2023;389(2):137-147. doi:10.1056/NEJMoa2304594
52. Shukla N, Hanna N. Neoadjuvant and adjuvant immunotherapy in early-stage non-small cell lung cancer. *Lung Cancer Auckl NZ.* 2021;12:51-60. doi:10.2147/LCTT.S277717
53. Zhou F, Qiao M, Zhou C. The cutting-edge progress of immune-checkpoint blockade in lung cancer. *Cell Mol Immunol.* 2021;18(2):279-293. doi:10.1038/s41423-020-00577-5
54. Wakelee HA, Altorki NK, Zhou C, et al. IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2021;39(15):8500-8500. doi:10.1200/JCO.2021.39.15_suppl.8500
55. Popat S, Navani N, Kerr KM, et al. Navigating diagnostic and treatment decisions in non-small cell lung cancer: expert commentary on the multidisciplinary team approach. *Oncologist.* 2021;26(2):e306-e315. doi:10.1002/onco.13586
56. Göker E, Altwairgi A, Al-Omair A, et al. Multi-disciplinary approach for the management of non-metastatic non-small cell lung cancer in the Middle East and Africa: Expert panel recommendations. *Lung Cancer.* 2021;158:60-73. doi:10.1016/j.lungcan.2021.05.025
57. Guirado M, Sanchez-Hernandez A, Pijuan L, Teixido C, Gómez-Caamaño A, Cilleruelo-Ramos Á. Quality indicators and excellence requirements for a multidisciplinary lung cancer tumor board by the Spanish Lung Cancer Group. *Clin Transl Oncol.* 2022;24(3):446-459. doi:10.1007/s12094-021-02712-8
58. Arvold ND. Involvement of radiation oncologists in multidisciplinary decision-making for early-stage lung cancer. *JAMA Netw Open.* 2022;5(3):e224849. doi:10.1001/jamanetworkopen.2022.4849
59. Moghanaki D, Simone CB, Rimner A, et al. The value of collaboration between thoracic surgeons and radiation oncologists while awaiting evidence in operable stage i non–small cell lung cancer. *J Thorac Cardiovasc Surg.* 2018;155(1):429-431. doi:10.1016/j.jtcvs.2017.09.001
60. Heinke MY, Vinod SK. A review on the impact of lung cancer multidisciplinary care on patient outcomes. *Transl Lung Cancer Res.* 2020;9(4):1639-1653. doi:10.21037/tlcr.2019.11.03
61. Senter J, Hooker C, Lang M, Voong KR, Hales RK. Thoracic multidisciplinary clinic improves survival in patients with lung cancer. *Int J Radiat Oncol.* 2016;96(2):S134. doi:10.1016/j.ijrobp.2016.06.326
62. Bilfinger TV, Albano D, Perwaiz M, Keresztes R, Nemesure B. Survival outcomes among lung cancer patients treated using a multidisciplinary team approach. *Clin Lung Cancer.* 2018;19(4):346-351. doi:10.1016/j.cllc.2018.01.006
63. Rogers MJ, Matheson L, Garrard B, et al. Comparison of outcomes for cancer patients discussed and not discussed at a multidisciplinary meeting. *Public Health.* 2017;149:74-80. doi:10.1016/j.puhe.2017.04.022
64. Stone E, Rankin N, Kerr S, et al. Does presentation at multidisciplinary team meetings improve lung cancer survival? Findings from a consecutive cohort study. *Lung Cancer.* 2018;124:199-204. doi:10.1016/j.lungcan.2018.07.032
65. Tamburini N, Maniscalco P, Mazzara S, et al. Multidisciplinary management improves survival at 1 year after surgical treatment for non-small-cell lung cancer: a propensity score-matched study. *Eur J Cardiothorac Surg.* 2018;53(6):1199-1204. doi:10.1093/ejcts/ezx464
66. Phillips I, Sandhu S, Lüchtenborg M, Harden S. Stereotactic ablative body radiotherapy versus radical radiotherapy: comparing real-world outcomes in stage I lung cancer. *Clin Oncol.* 2019;31(10):681-687. doi:10.1016/j.clon.2019.07.013
67. Hardavella G, Frille A, Theochari C, et al. Multidisciplinary care models for patients with lung cancer. *Breathe Sheff Engl.* 2020;16(4):200076. doi:10.1183/20734735.0076-2020
68. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28:iv1-iv21. doi:10.1093/annonc/mdx222
69. Herbst RS, Wu YL, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: Updated Results From the Phase III Randomized ADAURA Trial. *J Clin Oncol.* 2023;41(10):1830-1840. doi:10.1200/JCO.22.02186