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Review

Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment

Anuj A. Shukla*, Shreya Podder, Sana R. Chaudry, Bryan S. Benn and Jonathan S. Kurman

Division of Pulmonary & Critical Care, Medical College of Wisconsin, Milwaukee, WI, USA

*** Correspondence:** Email: ashukla@mcw.edu.

Abstract: Lung cancer is the most common cancer worldwide and is also one of the leading causes of cancer related deaths. The 5-year survival rate depends largely on stage at diagnosis. Multiple large randomized controlled trials have demonstrated the clinical utility of lung cancer screening. Low dose computed tomography is recommended for lung cancer screening in several guidelines. Lung cancer is often diagnosed at more advanced stages owing to the nonspecific symptoms with which it presents. Diagnosis relies primarily upon imaging and biopsy. Diagnosis and staging should be performed simultaneously, if possible, by performing a biopsy at the site that will confer the highest stage. Sufficient material should be obtained to allow for molecular testing. Liquid biopsy may have a complementary role in detecting actionable mutations in non-small cell lung cancer. Treatment is predicated upon stage and may involve surgery, targeted chemotherapy, radiation therapy, immunotherapy, or some combination thereof.

Keywords: non-small cell lung cancer; computed tomography; biopsy; endobronchial ultrasound; staging; chemotherapy; radiation; immunotherapy; targeted therapies

Abbreviations: CISNET: Cancer intervention and surveillance modeling network; CT: Computed tomography; ctDNA: Circulating tumor DNA; EBUS: Endobronchial ultrasound; EBUS-NA: Endobronchial ultrasound-guided needle aspiration; EGFR: Epidermal growth factor receptor; ESTS: European Society of Thoracic Surgeons; EUS-NA: Endoscopic ultrasound-guided needle aspiration; IASLC: International Association for the Study of Lung Cancer; LDCT: Low-dose computed tomography; NCCN: National Comprehensive Cancer Network; NELSON: Dutch-Belgian Randomized Lung Cancer Screening trial; NILE: Non-invasive versus invasive evaluation; NLST:

National Lung Cancer Screen Trial; NSCLC: Non-small cell lung cancer; PD-L1: Programmed cell death ligand; PET: Positron emission tomography; RCTs: Randomized controlled trials; RT: Radiation therapy; SEER: Surveillance, Epidemiology and End Results; TBNA: Transbronchial needle aspiration; TKI: Tyrosine kinase inhibitor; TNM: Tumor-node-metastasis; USPTF: United States Preventative Service Task Force; WHO: World Health Organization

1. Epidemiology and classification

Lung cancer is the most common cancer worldwide and the leading cause of cancer deaths in the United States. In 2018, lung cancer accounted for 14% of new cancers diagnosed in men and 13% of new cancers diagnosed in women [1]. In the last twenty years, the incidence and mortality rates of lung cancer for both men and women have declined in the United States [2]. Nevertheless, lung cancer remains a disease of considerable morbidity and mortality, and the 5-year survival rate has changed only minimally over the decades [1,2]. Cigarette smoking continues to be the single most important risk factor, with over 90% of lung cancer cases attributed to smoking [3]. Although smoking prevalence has decreased dramatically in the United States over the past few decades, tobacco use globally is on the rise and is likely to play a significant role in the increased incidence of lung cancer worldwide in the future. Other significant risk factors include age, environmental, behavioral, and genetic risk factors which not only play a role in tumorigenesis, but also in response to therapy. The predominant disease burden falls on minority populations, populations with low education levels, and the socioeconomically disadvantaged [3]. The median age of lung cancer diagnosis is 70 years old for both men and women [4]. Although primarily a disease that affects older populations, 10% of cases occur in patients less than 55 years of age [4]. An area of increasing interest and incidence is lung cancer in never smokers (LCINS). LCINS now accounts for 10–15% of lung cancer cases in the US and represents the seventh leading cause of cancer-related mortality [5,6]. LCINS primarily occurs in women and younger patients, with adenocarcinoma being the most common histologic subtype [6].

Non-small cell lung cancer (NSCLC) is the major histologic subtype of lung cancer and accounts for close to 80% of all lung cancers [7]. The World Health Organization (WHO) classifies NSCLC into three main types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [8]. Adenocarcinoma is the most common type of NSCLC and accounts for 40% of all lung cancers [8]. Adenocarcinomas arise from the alveolar epithelium and tend to express the cell markers TTF-1 and napsin-A [8]. Squamous cell carcinomas arise from the airway epithelium, typically centrally in large bronchi, and tend to express cell markers such as CK5, CK6, p40, and desmoglein-3 [9]. Large cell carcinomas comprise 5–10% of all lung cancers and are often a diagnosis of exclusion [8]. The incidence of large cell carcinomas is overall declining due to better immunophenotyping techniques, which are allowing large cell carcinomas to be re-classified as poorly differentiated adenocarcinomas or squamous cell carcinomas [8]. Notably, lung cancer is frequently not diagnosed until the advanced stages. The 5-year survival rate for NSCLC depends on the clinical stage at diagnosis and overall remains poor for advanced stages (Table 1).

Table 1. 5-year survival rate by clinical stage for NSCLC. Adapted from the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project [10].

Stage	5-year survival
IA	77–92%
1B	68%
IIA	60%
IIB	53%
IIIA	36%
IIIB	26%
IIIC	13%
IVA	10%
IVB	0%

2. Screening

Disease outcomes and survival rates for NSCLC depend on the clinical stage at diagnosis, raising the importance of early screening for NSCLC. Prior to the National Lung Screening Trial (NLST), screening tools using standard chest radiographs with or without sputum cytology failed to provide a robust mortality benefit in several clinical trials [11,12]. In 2011, the NLST randomized over 50,000 high risk patients between the ages of 55–74 to undergo either three annual low-dose screening computed tomography (LDCT) scans or single view chest radiographs as a screening modality for lung cancer. The results from this trial demonstrated a 20% relative reduction in mortality from lung cancer with LDCT and a 6.7% relative reduction in mortality of any cause compared to chest radiography [13]. This trial led to the United States Preventative Service Task Force (USPTF) recommending annual screening for lung cancer with LDCT in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years [14]. In 2020, the Dutch-Belgian lung cancer screening trial (NELSON) randomized over 13,000 high-risk men and 2,500 high-risk women between the ages of 50–74 to undergo volume-based LDCT or no screening at 1, 3, and 5.5-year intervals [15]. This trial was powered to detect a 25% reduction in lung cancer mortality over 10 years. The results demonstrated a cumulative rate ratio of death from lung cancer of 0.76 in men who underwent LDCT screening over 10 years, indicating a 24% mortality reduction compared to no screening. In the subgroup of women analyzed, the cumulative rate ratio of death was 0.67 in the LDCT group over 10 years, indicating a 33% mortality reduction compared to no screening [15]. In addition, about 50% of the lung cancers diagnosed in the screening arm were early stage and 65–70% were stages I-II. In contrast, 70% of the lung cancers diagnosed in the control arm were stages III-IV [15].

In March 2021, the USPTF updated their 2013 guidelines to recommend "annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery" [16]. This update was based on systematic review and modeling data from the Cancer Intervention and Surveillance Modeling

Network (CISNET) and is a grade B recommendation (recommends service, moderate-high certainty of net benefit) [16].

The potential harms of LDCT for lung cancer screening includes false positives leading to unnecessary diagnostic testing, overdiagnosis, radiation exposure, cost, and increased anxiety for patients. With the most recent USPTF recommendations, in conjunction with modeling data from CISNET, the goal will be to reduce false positive and overdiagnosis rates and help mitigate subsequent downstream complications [17]. Despite robust data for LDCT in high-risk populations, implementation of lung cancer screening programs has lagged due to resource availability and patient adherence.

Risk prediction models are also emerging as potential screening tools for lung cancer. These models combine radiographic features of lung nodules and relevant clinical history to calculate the risk of lung cancer and guide further evaluation. Although there is some evidence (mostly retrospective data) to suggest risk prediction models are superior to current screening recommendations, only the National Comprehensive Cancer Network (NCCN) guidelines support the use of these models in current clinical practice [18]. More research and validation are needed to evaluate the overall effectiveness and cost-effectiveness of risk-based lung cancer screening programs.

3. Symptoms

Despite advances in screening, most lung cancers are still diagnosed in symptomatic patients [19]. The most common presenting symptoms include cough, dyspnea, chest pain, weight loss, loss of appetite, and hemoptysis, with the latter having the highest positive predictive value [19]. Diagnosis of lung cancer at the earliest stage is associated with better prognosis [20], so it is imperative physicians have a low threshold for initiation of diagnostic evaluation in high-risk patients, even in the presence of non-specific symptoms.

4. Diagnosis

The diagnosis of lung cancer involves a combination of imaging studies and tissue samples (Figure 1). For patients who are suspected to have lung cancer, a CT scan of the chest with contrast is recommended if the patient is eligible for treatment [20]. This scan can be extended to include the liver and adrenal glands for staging purposes if positron emission tomography (PET) scan is unavailable [20]. NSCLC can present in a variety of ways radiographically. It may be centrally or peripherally located and can invade adjacent structures. Tumor margins can also vary from smooth and/or lobulated to irregular or spiculated. The mass itself can be solid or have a central area of necrosis and cavitation [21]. In patients presenting with hemoptysis, bronchoscopy is required to rule out endobronchial malignancy even if a CT scan of the chest is unremarkable. Endobronchial lesions may not be readily identifiable on CT imaging.

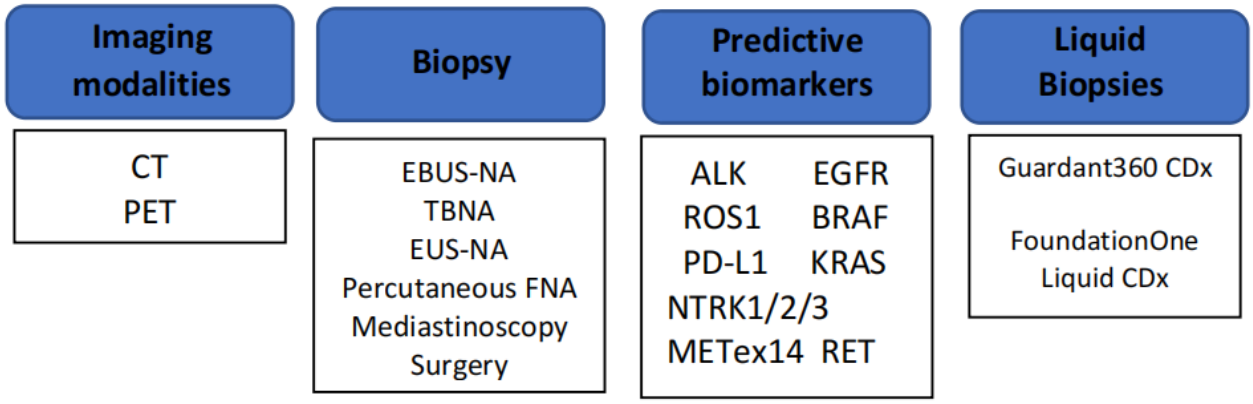

Figure 1. Summary of diagnostic tests used when evaluating lung cancer.

Staging plays an essential role in guiding treatment. The newest edition of tumor-node-metastasis (TNM) staging of NSCLC was released in 2018 and was developed through the analysis of an international database consisting of 100,000 patients [22]. Lung cancer staging and diagnosis should be performed concurrently whenever possible. This can be achieved with biopsy of the site that will confer the highest stage of malignancy. A malignant pleural effusion automatically confers stage IV disease. Patients with suspected lung cancer and a pleural effusion can undergo thoracentesis, though the diagnostic yield of initial thoracentesis for malignant pleural effusion in patients with NSCLC is about 66.7%, which is improved to 71.4% with second thoracentesis and 88.2% with pleural biopsy [23]. If there is extensive mediastinal involvement without extra-thoracic metastases, then tissue evaluation can be completed by bronchoscopy with transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided needle aspiration (EBUS-NA), endoscopic ultrasound-guided needle aspiration (EUS-NA), or mediastinoscopy. Of these, flexible bronchoscopy with EBUS-TBNA is most commonly utilized in the United States. With EBUS, complete assessment of the hilar and mediastinal nodes can be accomplished in a minimally invasive manner and acquire sufficient material for comprehensive molecular testing [24]. Acquiring tumor sample that preserves cellular context and tissue architecture is critical for diagnostic immunohistochemical assays [25]. Patients with early resectable disease (stage I or II) may benefit from proceeding directly to surgical resection. The sensitivity and specificity for detecting nodal disease by CT scan is 51–64% and 74–86% respectively [26], whereas for PET, the sensitivity and specificity of detecting diseased nodes are 58–94% and 76–96% respectively [27]. Current guidelines recommend invasive staging in all patients except those with a <3 cm nodule that is peripherally located in the lungs and without evidence of mediastinal/hilar nodal involvement on CT and PET [28]. In patients with suspicious extra-thoracic metastases, tissue confirmation by fine needle aspiration (FNA) or biopsy is recommended [29].

5. Future direction of diagnostics

Although the least invasive diagnostic approach is preferred, it is important to have sufficient cellular material for biomarker testing. Liquid biopsy, which includes testing circulating tumor DNA (ctDNA), microRNA, and circulating tumor cells in plasma, serum, urine and cerebrospinal fluid, is

an attractive option for patients who are not candidates for invasive testing. A negative liquid biopsy does not rule out oncogenic alterations and tissue-based analysis is required for confirmation in these cases.

Liquid biopsies have many advantages. The non-invasive versus invasive evaluation (NILE) prospective study of 282 patients with previously untreated NSCLC showed that there was a 48% increase in rate of biomarker detection with ctDNA testing compared to tissue analysis alone with a faster turnaround time [30]. Liquid biopsies can also reduce sampling errors due to tumor heterogeneity and can be easily repeated [31]. These tests can be used to monitor disease progression, evolution, and development of resistance and co-mutations [31].

In 2020, the US Food and Drug Administration approved two liquid biopsy tests that use next generation sequencing, Guardant360 CDx (Guardant Health, Inc., California) and FoundationOne Liquid CDx (Foundation Medicine, Inc., Massachusetts), for patients with solid tumors, including lung cancer. The Guardant360 CDx assay is a companion diagnostic test for the identification of patients with NSCLC harboring an *EGFR* alteration who may benefit from treatment with osimertinib [32]. FoundationOne Liquid CDx is a comprehensive pan-tumor liquid biopsy test that can also be used as a companion diagnostic for patients with NSCLC who have *EGFR* mutation and may benefit from gefitinib, osimeritinib and erlotinib [33]. Assessing ctDNA clearance of *EGFR* mutation has also been shown to predict outcomes [34] and progression-free survival in patients with *EGFR*-mutant NSCLC [35].

6. Treatment

The treatment of lung cancer is dependent upon several primary factors including tumor histology, stage, and patient related factors. Generally, patients with stage I, II and III NSCLC are treated with curative intent using surgery, chemotherapy, radiation, or a combination of these modalities. Adjuvant chemotherapy is indicated for pathological stage II disease and in some instances stage IB disease. Definitive radiation therapy can be used as an alternate method for patients who would otherwise be surgical candidates based on clinical stage but are either poor candidates or refuse surgical intervention. Historically, postoperative radiation was reserved for individuals with pathologically confirmed lymph node metastases or positive margins post resection. More recent data have called into question the utility of postoperative radiation, even with positive margins [36,37]. For patients with stage III disease involving mediastinal lymph nodes or positive margins, sequential adjuvant chemotherapy and postoperative RT are indicated. Immunotherapy may be added for unresectable stage III disease.

6.1. Management of stage I and II NSCLC

Surgical resection remains the cornerstone of treatment for stage I and II NSCLC; however, significant developments have occurred in routine management. Data demonstrate better outcomes when these procedures are performed at academic institutions or high-volume centers with specialty trained surgeons [38]. For patients with clinical stage I disease, a minimally invasive approach such as video-assisted thoracic surgery or robotic assisted thoracoscopic surgery is preferred to open thoracotomy (grade 2C recommendation) [38]. The procedure of choice has been a lobectomy, the data for which is predominately derived from the Lung Cancer Study Group trial 801 showing an

improved disease related death rate and lower chance of locoregional recurrence [39]. There was a threefold increase in the rate of local recurrence (5.4 versus 1.9 percent) and a trend toward lower survival rates with limited resection compared with lobectomy [40]. Limited resections, otherwise known as sublobar resections, entail the removal of one or more segments (segmentectomy) or a nonanatomic wedge resection. Limited resections are reserved for patients unable to tolerate a complete lobectomy either owing to poor pulmonary reserve, multiple comorbid conditions or those with predominately ground-glass lesions measuring <2 cm in diameter. Data remain limited and conflicting regarding the use of limited resection versus lobectomy in older adults. An analysis of the Surveillance, Epidemiology and End Results (SEER) database showed similar survival outcomes with patients over the age of 71 with lobectomy and limited resection [41]. However, subsequent studies have yielded different results with worse outcomes in those treated with wedge resection [42]. Recently, a phase III randomized controlled trial (RCT) showed that segmentectomy was not only non-inferior to lobectomy for stage IA NSCLC, but it may have better survival benefits [43]. The optimal extent of lymph node assessment is uncertain. The European Society of Thoracic Surgeons (ESTS) guidelines recommend complete and systematic lymph node dissection with node specific sampling reserved for small peripheral T1 lesions [44]. There is no significant role for adjuvant chemotherapy in stage I NSCLC, except for certain stage IB lesions with high-risk characteristics. The role of adjuvant chemotherapy has been established for stage II NSCLC. In addition, immunotherapy with atezolizumab is now approved for adjuvant disease (stage II and IIIA) for patients whose tumors have programmed cell death-ligand 1 (PD-L1) expression with a 33–52% risk reduction of disease recurrence depending on the level of PD-L1 expression [45].

Although surgical resection remains preferred for early-stage NSCLC, this time-honored norm is based upon relatively low-quality evidence. It remains unclear if stereotactic body radiation therapy (SBRT) may be a safer, more effective treatment. As such, there are ongoing phase III studies comparing surgery to SBRT for stage I NSCLC [46]. Individuals who are not surgical candidates at the time of diagnosis owing to comorbidity, poor pulmonary reserve or advanced age are managed with definitive radiation therapy (RT) either in the form of SBRT or conventional fractionation. SBRT has been confirmed in RCTs to be superior to conventional RT in this setting [46,47].

6.2. Management of stage III NSCLC

Stage III lung cancer encompasses a heterogenous group of tumors, patients with varying prognosis and nodal status, and is otherwise referred to as locally advanced disease. General schematic management is not ideal, and outcomes depend on an interdisciplinary and multidisciplinary strategy. Overall prognosis is poor, so optimal local control with the addition of systemic therapy is crucial. Like stage I and II disease, the key component of stage III N0 or N1 disease entails surgery. Definitive radiation is a feasible option for those who are not surgical candidates. Unlike lower stage disease, however, recurrent extra-thoracic disease is common. Therefore, systemic therapy is added to initial local treatment. RT consists of once-daily fractionation totaling a dose of 60–66 Gy; further dose escalation is not advised. Sequential timing of therapy, with radiation following chemotherapy, has been established by observational data from the National Cancer Database [48].

In patients with infiltrative stage III (N2, N3) NSCLC, combination platinum-based chemotherapy and RT are recommended (Grade 1A) [38]. A highly selective subset of patients is eligible for induction chemoradiation or chemotherapy prior to surgery. Although there are no prospective randomized data to define the context of this subset, factors that deem candidates more favorable include single station N2 disease, lesions <3 cm prior to induction, surgical excision needing only single lobectomy, and response to induction. Patients who have T4 disease, progressive disease despite induction, extracapsular nodal involvement, multi-station lymph node involvement, active heart disease, poor functional status or pulmonary reserve are not considered tobe candidates for induction therapy. In N3 disease, definitive concurrent chemoradiation has been shown to be superior by several RCTs [49]. The prognosis of unresectable stage III lung cancer remains suboptimal, although recent data have shown that the addition of the PD-L1 antibody durvalumab improves 5-year survival with up to 33% not developing any relapse at 5 years [50]. Additional immunotherapy is an option for patients treated with chemoradiation whose disease has not shown evidence of progression, and durvalumab is approved for this indication. A nonrandomized phase II study suggests a benefit of pembrolizumab with concurrent chemoradiation in unresectable stage III disease, but further study is required prior to adoption of this approach [51].

6.3. Management of stage IV NSCLC

Cure is not possible with stage IV NSCLC, but significant advances have been made in terms of palliation, survival and quality of life. Key factors that influence management include the presence of high level of PD-L1 expression, presence of a driver mutation (eg, epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], c-ROS oncogene 1 [ROS1], BRAF, etc.), degree of disease burden, and histology (squamous vs. nonsquamous). For patients with tumor PD-L1 expression 50% or higher, pembrolizumab was associated with significantly longer progression free survival and overall survival compared to platinum-based chemotherapy [52]. Consequently, pembrolizumab or atezolizumab monotherapy is generally preferred over chemotherapy; however, combination therapy can be used with rapid disease progression. For patients with PD-L1 expression less than 50%, combination concurrent chemotherapy/pembrolizumab is recommended. The choice of chemotherapeutic agent is based on the histological type of NSCLC. In patients with a good performance status (ECOG score of 0 or 1), a platinum-based chemotherapy regimen is recommended (Grade 1A) [38]. In those patients with a good functional status, a two-drug combination is standard. The addition of a third agent provides no survival benefit and increases the risk of toxicity and is therefore not recommended. Patients with known EGFR mutations benefit from tyrosine kinase inhibitors (TKIs) (gefitinib or erlotinib) based on improved response and progression free survival compared to platinum-based therapy. Certain driver mutations, including KRAS, NTRK1/2/3, METex14 skipping, ALK, ROS, and RET, now have approved therapies [53]. Local consolidation therapy with SBRT can be used in patients with oligometastatic disease [54].

7. Targeted therapy

Over the past two decades treatment has evolved from empiric use of cytotoxic agents to more effective and specific molecular treatment. The incorporation of tumor genotyping has transformed

the management of lung cancer by allowing targeted therapy, leading to significant response when mutations in these pathways exist.

7.1. EGFR mutation

EGFR TKIs include osimertinib, erlotinib, gefitinib, and afatinib. These are indicated as initial monotherapy in those with an activating mutation in EGFR. In RCTs, osimertinib showed superior efficacy and progression free survival compared to standard EGFR TKIs and is now considered first-line management. Treatment is continued in the absence of toxicity or disease progression. EGFR TKIs are not combined with platinum-based chemotherapy as initial management because of risk of toxicity [55].

7.2. ALK fusion oncogene positive

For patients with advanced NSCLC with tumor positivity for the ALK fusion oncogene, ALK TKIs is the preferred treatment of choice [56]. Agents include alectinib, certinib and brigatinib. Alectinib is considered first line therapy and continued until evidence of disease progression or toxicity occurs.

7.3. Other mutations

Various other driver mutations have been identified including ROS1, BRAF, RET, TRK, MET and KRAS with specific inhibitors present for most of these mutations. They should be incorporated when indicated for specific patients [57,58].

8. Special considerations

There are several circumstances that merit special consideration in terms of management. These include patients with pancoast tumors, T4, N0, N1, and M0 central tumors, chest wall involvement, additional pulmonary nodules, synchronous and metasynchronous primary lung cancers and a solitary metastasis. In patients with a potentially resectable pancoast tumor with good performance status, it is suggested that concurrent chemoradiotherapy be given prior to resection (Grade 2B) [38]. In patients with tumor invading the chest wall or T4 disease, the recommendation is to achieve complete surgical resection. Mediastinal lymph node involvement or metastasis at the time of diagnosis is a contraindication to surgery, and definitive chemoradiation becomes the modality of choice. In patients who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is suggested, provided the patient has adequate pulmonary reserve and there is no N2 nodal involvement (Grade 2C) [38].

Patients with postoperative positive microscopic resection margins have a worse prognosis than those with negative margins. While postoperative RT is not recommended for stage I or II disease, data show improved survival for those with positive surgical margins (R1) in stage II or III disease [59]. The incidence of local recurrence following surgery for stage I or stage II NSCLC varies from 6 to 55 percent [40]. ctDNA tests are available now via an FDA breakthrough designation and can be used to track minimal residual disease (MRD), which may be able to predict

the likelihood of disease recurrence [60]. Patients with local recurrence without evidence of metastases are candidates for repeat resection. When surgical intervention is not an option, management consists of either chemotherapy or RT.

Although data are limited for older patients with advanced disease, phase III trials have suggested that chemotherapy alone, in the absence of driver mutations, prolongs survival. Age itself should not be a deterrent to systemic therapy, but treatment is not recommended in this population if they have a poor functional status (ECOG 3-4). Supportive care is preferred in this situation.

Authors' contributions

All authors participated in the conception and writing of this manuscript.

Conflict of interest

All authors have no conflicts of interest.

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