ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

SPECIAL ARTICLE

Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

A. Zer[1], M.-J. Ahn[2], F. Barlesi[3], L. Bubendorf[4], D. De Ruysscher[5,6], P. Garrido[7], O. Gautschi[8,9], L. E. Hendriks[10], P. A. Jänne[11], K. M. Kerr[12], C. Mascaux[13], T. Mitsudomi[14], S. Peters[15], C. Rolfo[16], A. Sacher[17], S. Senan[18], P. Ugalde[19] & N. B. Leighl[17], on behalf of the ESMO Guidelines Committee*

[1]Department of Medical Oncology, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3]Gustave Roussy, University Paris-Saclay, Villejuif, France; [4]Institute of Pathology and Medical Genetics, University Hospital Basel, Basel, Switzerland; [5]Department of Radiation Oncology (Maastro), Research Institute for Oncology and Reproduction (GROW), Maastricht University Medical Center, Maastricht; [6]Department of Radiotherapy, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, The Netherlands; [7]Medical Oncology Department, Hospital Universitario Ramon y Cajal, IRYCIS, Madrid, Spain; [8]Department of Oncology, Cantonal Hospital of Lucerne, Lucerne; [9]Faculty of Medicine, University of Berne, Berne, Switzerland; [10]Department of Pulmonary Diseases, Research Institute for Oncology and Reproduction (GROW), Maastricht University Medical Center, Maastricht, The Netherlands; [11]Lowe Center for Thoracic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [12]Department of Pathology, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK; [13]Department of Pulmonology, Les Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [14]Department of Innovative Medicine, Faculty of Medicine, Izumi City General Hospital, Kindai University, Osaka, Japan; [15]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [16]Division of Medical Oncology, The Arthur G. James Comprehensive Cancer Center, Columbus, USA; [17]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; [18]Department of Radiation Oncology, Amsterdam University Medical Centres, Vrije University, Amsterdam, The Netherlands; [19]Division of Thoracic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

Available online 28 August 2025

Key words: diagnosis, early non-small-cell lung cancer (NSCLC), guideline, staging, treatment

INCIDENCE AND EPIDEMIOLOGY

Every year, >2.2 million people are diagnosed with lung cancer and >1.8 million people die of the disease,[1] making it the leading cause of cancer-related death in men and women worldwide. A reduction in male lung cancer mortality, including in some European Union countries, has been reported along with reduced smoking rates;[2] however, lung cancer mortality in European women continues to rise.[2]

Tobacco smoking, including second-hand exposure, remains the most important risk factor for lung cancer. Up to 30% of smokers develop lung cancer, and 90% of all lung cancer cases are caused by active smoking or second-hand exposure.[3,4] Other known risk factors include exposure to radon or asbestos, previous radiotherapy (RT) to the lungs and air pollution.

There are currently no specific recommendations for genetic counselling and germline testing for patients with lung cancer. A recent study in the United States, however, revealed that ∼15% of patients with lung cancer had pathogenic germline variants, most commonly *BRCA2*, followed by *CHEK2*, *ATM*, *TP53*, *BRCA1* and germline *EGFR* mutations.[5] To date, there are no recommendations for lung cancer screening in healthy carriers of these mutations.

Screening for lung cancer

Lung cancer screening using low-dose (LD) computed tomography (CT) has been implemented in many countries, based on the results of the National Lung Screening Trial (NLST)[6] and the NELSON trial.[7] These studies reported a relative reduction in lung cancer-related mortality of ≥20% in past and current smokers aged 50-74 years with a history of ≥15 pack years in the NELSON study and ≥30 pack years in the NLST.[6,7] LD-CT screening in the NLST increased lung cancer diagnosis by a factor of 2.7 and led to a 6.7% reduction in all-cause mortality, and in the NELSON trial, screening reduced the proportion of lung cancers diagnosed at stage IV (lung cancer identified in 0.86% of participants). In the United States, where lung cancer screening is publicly reimbursed, uptake remains low at ∼16%.[8] Improved implementation strategies and screening accuracy with multiomic biomarkers as well as identification of risk factors beyond smoking are needed.

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

☆Note: Approved by the ESMO Guidelines Committee: July 2017, last update August 2025. This publication supersedes the previously published version—*Ann Oncol.* 2017;28(suppl 4):IV1-IV21.

The single-arm TALENT study screened participants in Taiwan without a smoking history but with one or more risk factor, such as family history or exposure to passive smoking.[9] Screening identified lung cancer in 2.6% of participants, although the impact on mortality, cost effectiveness and external generalisability of the study findings need to be further defined.

Efforts to reduce the burden of lung cancer by prevention, smoking cessation and early detection are required at a global level.

Recommendations

- LD-CT screening through established screening programmes is recommended in current (>30 pack years) or former (<15 years since cessation) smokers aged 55-74 years [I, A].
- Patients with non-small-cell lung cancer (NSCLC) should receive optimal support for smoking cessation, including counselling and behavioural techniques as well as pharmacotherapy, to optimise treatment outcomes and reduce the risk of future malignancies [I, A].

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Pathological diagnosis is required in all patients with suspected lung cancer if feasible. Feasibility and diagnostic method should be determined by a multidisciplinary team (MDT) based on patient and tumour characteristics. Biomarker testing is also essential for treatment decision making in patients with stage IB-III NSCLC.

Surgical diagnosis should be limited to cases with small high-risk nodules, including those with negative positron emission tomography (PET)—CT findings and/or inability to obtain tissue by less invasive procedures.[10] Radiological criteria of small high-risk lesions requiring tissue diagnosis are defined in the Fleischner Society guidelines.[11]

Diagnostic procedures and sample requirements are presented in detail in the ESMO Clinical Practice Guideline (CPG) for metastatic non-oncogene-addicted NSCLC[12,13] and in Table 1.

Pathology

Many of the challenges surrounding the pathological diagnosis of NSCLC have been recently described in the ESMO CPGs for metastatic NSCLC.[12-15] Initial diagnostic steps are the same, regardless of disease stage. Pathologists should anticipate a possible diagnosis of lung cancer from the source and type of submitted sample, as well as the clinical context. The handling and processing of small samples, including tissue-sparing block cutting protocols, must facilitate diagnosis, permit all biomarker testing modalities and conserve sufficient tissue for anticipated diagnostic steps.[16-18]

In brief, pathological diagnosis on small biopsy and cytology-type samples follows the 2021 World Health Organization (WHO) classification guidance.[19] Small-cell carcinoma must be distinguished from non-small-cell tumour. All NSCLCs must be subtyped where possible using morphology; immunohistochemistry (IHC) is used when morphological subtyping is not possible and is usually limited to two markers (p40 and thyroid transcription factor 1; Table 1).[19] Unnecessary use of IHC is avoided to preserve tissue for biomarker testing. A limited range of possible diagnoses, with nomenclature, is available for small sample diagnosis.[19]

Diagnosis of surgically resected tumours also follows the 2021 WHO classification. In these specimens, the full range of diagnostic classification categories can be applied as appropriate.

Biomarkers

Programmed death-ligand 1. Validated and established programmed death-ligand 1 (PD-L1) tumour testing for stage II-III NSCLC helps to select adjuvant immunotherapy and may inform the potential benefit of neoadjuvant or perioperative chemotherapy (ChT) combined with immune checkpoint inhibitors (ICIs; ChT—ICI). The proportion of tumour cells (TCs) expressing PD-L1 should be reported, using categories of <1%, ≥1%-49% and ≥50% at a minimum.

Testing for *EGFR, ALK* and other oncogenic drivers. Testing for *EGFR*-sensitising mutations (exon 19 deletion, L858R point mutation) is carried out in stage IB (tumour >3 cm or other high-risk features), II or III (resectable or unresectable) NSCLC. This is based on recent evidence showing improved overall survival (OS) in patients with resected stage IB-III *EGFR*-mutated NSCLC (exon 19 deletion or L858R) with adjuvant osimertinib[20] and markedly improved progression-free survival (PFS) with third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) after chemoradiotherapy (CRT) for unresectable stage III *EGFR*-mutated NSCLC.[21,22] Similarly, *ALK* fusion testing in patients with stage II (tumour ≥4 cm)-IIIA resectable non-squamous NSCLC can identify patients who may derive benefit from adjuvant alectinib.[23] *EGFR* and *ALK* testing is also required when patients are being considered for neoadjuvant ChT—ICI, as positivity for *ALK* fusion or exon 19 deletion or L858R *EGFR* variants excludes this therapy option.

Although current data support testing of *EGFR* and *ALK* only, routine implementation of broad next-generation sequencing (NGS) in patients with stage II-III non-squamous NSCLC may be more pragmatic, although more time-consuming, and is likely to be beneficial in the future, as the number of targets with clinical significance is expected to increase.

Minimal residual disease evaluation. Post-operative detection of plasma circulating tumour DNA (ctDNA) after curative-intent treatment is a strong prognostic factor in early-stage and locally advanced NSCLC, including after induction ChT—ICI.[24-26] The sensitivity of current assays is, however, suboptimal, with a large proportion of false-negative results in patients who subsequently experience

Table 1. Work-up for diagnosis and staging

	Mandatory	Optional
General	Medical history Physical examination Assess comorbidities, weight loss and PS	
Imaging	FDG—PET and contrast-enhanced CT Brain MRI (for clinical stage II-III)	Contrast-enhanced brain CT if MRI not possible
Laboratory	CBC Chemistry profile	
Preoperative cardiopulmonary evaluation	FEV_1 DLCO CPET	
Tissue acquisition	Bronchoscopy EBUS or EUS CT-guided biopsy US-guided biopsy	Mediastinoscopy
Pathology	TTF-1 IHC staining p40 IHC staining *EGFR* molecular testing *ALK* molecular testing PD-L1 testing	

CBC, complete blood count; CPET, cardiopulmonary exercise testing; CT, computed tomography; DLCO, diffusing lung capacity for carbon monoxide; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; FEV_1, forced expiratory volume in the first second; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PS, performance status; TTF-1, thyroid transcription factor 1; US, ultrasound.

recurrence. Currently available assays are prognostic but not predictive of treatment outcomes and cannot be used for treatment de-escalation after curative-intent therapy at this time. Further technological advances are needed before clinical implementation.

In the neoadjuvant setting, preoperative ctDNA detection has been shown to be a poor prognostic factor.[27] ctDNA clearance after treatment with ChT with or without immunotherapy is associated with improved outcomes and higher pathological complete response (pCR) and major pathological response (MPR) rates.[27-30] Nevertheless, given the heterogeneity of the assays used, absence of optimal timepoints for ctDNA analysis during follow-up and the lack of data on how to manage ctDNA-positive cases during follow-up in the absence of radiographical evidence of recurrence, the current data do not support the use of ctDNA for minimal residual disease detection to select patients for (neo)adjuvant therapy intensification or treatment de-escalation outside of clinical trials.

Recommendations

- In patients with clinical stage I-III lung cancer, a pathological diagnosis is recommended before any treatment decision [IV, A].
- Feasibility and diagnostic method [bronchoscopy with bronchial or transbronchial biopsy, endobronchial ultrasound (EBUS)-guided sampling or transthoracic biopsy] should be discussed by an MDT and based on patient and tumour characteristics [IV, A].
- Surgical diagnosis is recommended for small high-risk nodules that cannot be sampled by less invasive procedures, including those that are negative on PET—CT [IV, A].
- Pathological diagnosis should follow the 2021 WHO classification for lung tumours [IV, A].
- Molecular testing for *EGFR* mutations is recommended for patients with stage IB (>3 cm or high risk)-IIIC NSCLC to identify patients suitable for adjuvant or consolidation osimertinib [I, A; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A].
- Molecular testing for *ALK* alterations is recommended for patients with resectable stage II (≥4 cm)-IIIA NSCLC to identify patients suitable for adjuvant alectinib [I, A; ESCAT score: I-A].
- Tumour PD-L1 testing is recommended before treatment decision making in patients with stage II-III NSCLC being considered for pre- or perioperative ChT—ICI [IV, A].
- Tumour PD-L1 testing is recommended for all resected stage II-IIIA NSCLC cases if preoperative ChT—ICI was not administered, to inform adjuvant immunotherapy decisions [I, A].
- Recommended biomarker testing should be carried out as soon as possible as part of the preoperative evaluation [IV, A]. For markers requiring genomic sequencing, broad NGS testing can be recommended if feasible [V, B].
- ctDNA detection or clearance after curative-intent treatment is not recommended to guide treatment escalation or de-escalation outside of clinical trials [IV, E].

STAGING AND RISK ASSESSMENT

Staging is based on the ninth edition of the Union for International Cancer Control TNM (tumour—node—metastasis) Classification of Malignant Tumours (TNM9; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.08.003)[31] and the third edition of the International Association for the Study of Lung Cancer (IASLC) Staging Manual.[32] Staging information throughout this CPG refers to IASLC/TNM9, unless otherwise stated. IASLC has also provided recommendations on tumour measurement using CT.[33,34] If multiple lung lesions fulfil the criteria for separate primary tumours, each lesion should be evaluated and treated accordingly.[35]

Details on clinical and pathological staging are provided in Supplementary Material Section 1 and Figure S1, available at https://doi.org/10.1016/j.annonc.2025.08.003.

Risk assessment before treatment

Details on risk assessment before treatment are available in Supplementary Material Section 2 and Figure S2, available at https://doi.org/10.1016/j.annonc.2025.08.003.

Recommendations

- In non-metastatic NSCLC, detailed locoregional staging according to the IASLC/TNM staging system criteria and assessment of the cardiopulmonary fitness of the

patient should be carried out to determine the choice of treatment [III, A].
- For part-solid tumours, the size of the invasive component should be used to assign the T category for clinical staging [III, A].
- If multiple lung lesions fulfil the criteria for multiple primary tumours, these should be evaluated and treated accordingly [III, A].
- In case of multiple tumours with the same histological subtype, NGS analysis is recommended to distinguish between multiple individual primaries and intrapulmonary metastasis [III, A].
- Contrast-enhanced CT and PET [I, A] or PET—contrast-enhanced CT [I, A] are recommended for assessment of mediastinal and hilar lymph nodes (LNs). For patients with abnormal mediastinal and/or hilar LNs on CT and/or PET—CT, invasive mediastinal and hilar staging by representative endosonography is recommended [I, A].
- Pathological staging of surgically resected samples should be carried out to allow application of the IASLC/TNM staging system criteria [IV, A].
- Reporting of spread through air space can be recommended due to its role as a negative prognostic factor and possible incorporation in future TNM revisions [III, B].
- Needle aspiration under EBUS and/or endoscopic ultrasound guidance is recommended for pathological assessment of suspicious nodes [I, A].
- Screening for central nervous system (CNS) metastases by magnetic resonance imaging is recommended in patients with stage II-III NSCLC who are being considered for curative-intent therapy [III, A].
- The functional tolerance of patients being considered for curative-intent therapy should be assessed by an MDT [IV, A].
- Given the complexity of interstitial lung disease (ILD) diagnosis and treatment-related risks, it can be recommended that evaluation of patients with suspected or confirmed ILD should involve multidisciplinary ILD experts, whenever feasible, to guide therapeutic decision making [III, B].
- Patients being considered for surgery should undergo assessment of cardiac function, including recalibrated thoracic revised cardiac risk index and pulmonary function, to estimate the risk of operative morbidity [IV, A].
  - For patients with predicted post-operative (ppo)-forced expiratory volume in the first second (FEV_1) and ppo-diffusing capacity of the lung for carbon monoxide (DLCO) values $\geq$60% and no other major comorbidities, surgical resection should proceed with no further investigations [IV, A].
  - For patients with ppo-FEV_1 or ppo-DLCO values $<$30%, maximal oxygen consumption (VO_2 max) should be used to measure exercise capacity and predict post-operative complications [IV, A].
  - For patients with a VO_2 max $<$10 ml/kg per min, sublobar resection or non-surgical treatment options should be discussed [IV, A].

MANAGEMENT OF RESECTABLE STAGE I-III NSCLC

The cornerstone of treatment in fit patients with early-stage NSCLC is surgical resection with radical LN dissection (LND).[36] For patients who are unwilling to undergo surgery and those who are considered high risk, curative RT using stereotactic body RT (SBRT) or hypofractionated high-dose RT are alternatives. In addition to local therapy, systemic therapy for early-stage NSCLC is rapidly evolving, including ICIs and targeted therapies. Algorithms for the management of resectable stage I-III NSCLC are provided in Figures 1 and 2.

Surgery

While lobectomy with radical LND has been the gold-standard treatment for three decades, two multicentre randomised phase III trials (CALGB 140503[37] and JCOG0802/WJOG4607L[38]) recently demonstrated that sublobar resection (segmentectomy or wedge resection) is non-inferior to lobectomy with respect to disease-free survival (DFS) and OS when the tumour is peripheral and $\leq$2 cm (stage IA1-IA2). Locoregional recurrences were more frequent after sublobar resection than after lobectomy in both studies (13.4% versus 10.0%, respectively, in CALGB 140503 and 10.5% versus 5.4% in JCOG0802/WJOG4607L). No clinically relevant differences were observed in lung function between approaches in either study. Intraoperative confirmation of N0 disease is crucial during sublobar resection, as shown in both studies.[37,38] If N1 disease is found intraoperatively, sublobar resection is abandoned and lobectomy is carried out.

In patients with resectable stage IIIA or selected IIIB disease, multimodal therapy that includes neoadjuvant ChT—ICI followed by surgery may be appropriate (e.g. cT3 N1, cT3 N2a or cT1 N2b). Resectability should be determined by experienced thoracic surgeons in MDT consensus, using frameworks such as those proposed by the European Organisation for Research and Treatment of Cancer (EORTC)[39] and Society of Thoracic Surgeons (STS).[40] The role of surgery in multistation or bulky N2 disease remains under investigation.

Nodal status is among the most reliable prognostic indicators in patients with early-stage lung cancer and is essential for treatment decision making;[41] however, methods for optimal LN staging during surgery are controversial. To achieve complete resection (R0) there must be no tumour at the margin, the highest LN resected must be negative for cancer, and extracapsular tumour invasion must be absent.[42] Lymphadenectomy should include a minimum of six LN stations, three of which should be mediastinal, including the subcarinal station. The optimal strategy, in terms of sampling versus lymphadenectomy and a lobe-guided versus systematic approach, is unknown.

Preinvasive lesions, such as adenocarcinoma *in situ* or minimally invasive adenocarcinoma, often present as pure or part-solid ground-glass opacities, typically follow an indolent course and have an excellent prognosis. Sublobar

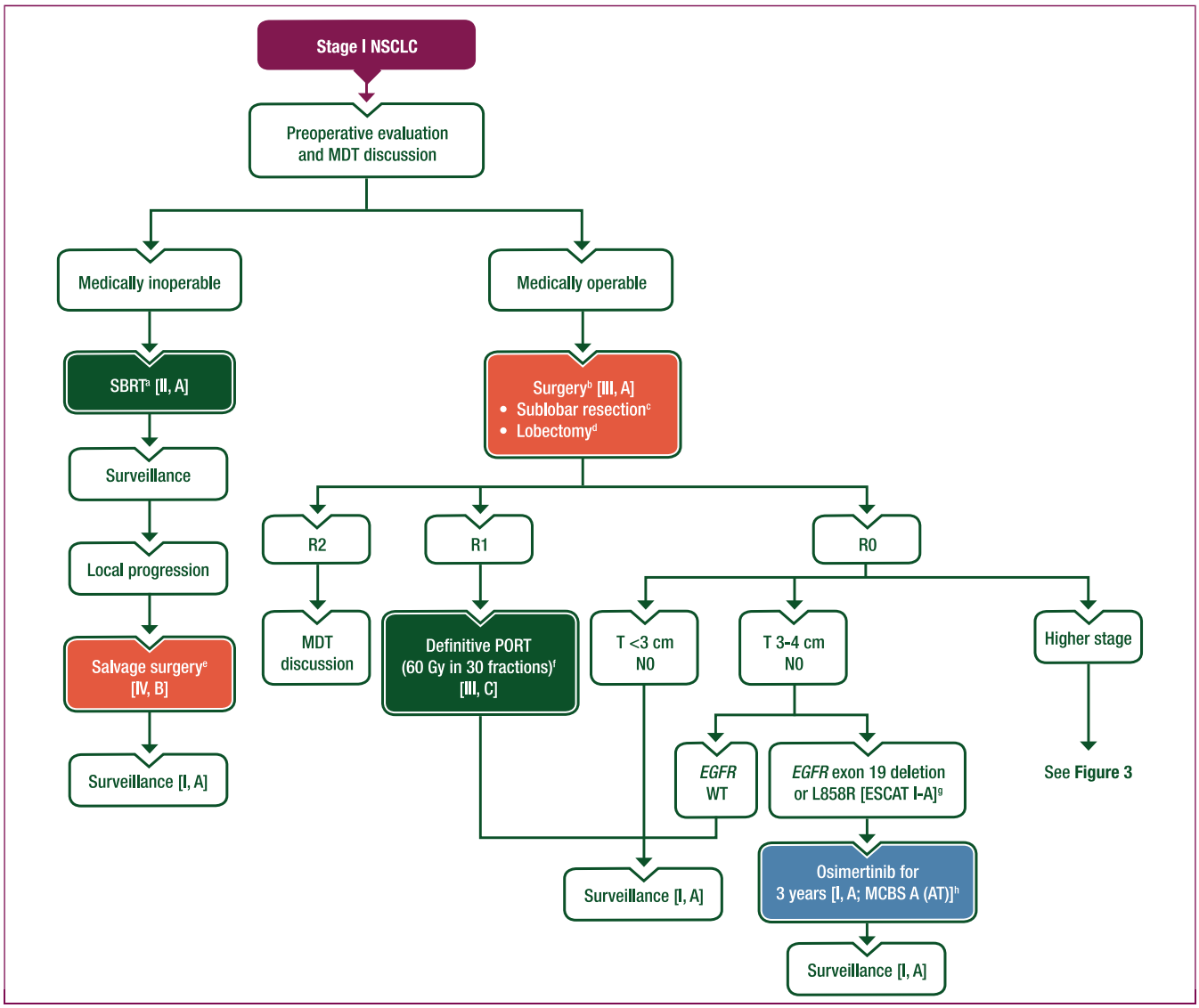

Figure 1. Management of stage I NSCLC.

Purple: algorithm title; orange: surgery; dark green: radiotherapy; blue: systemic anticancer therapy; white: other aspects of management.

CT, computed tomography; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; N, node; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; PORT, post-operative radiotherapy; R0, no tumour at the margin; R1, microscopic tumour at the margin; R2, macroscopic tumour at the margin; RATS, robotic-assisted thoracoscopic surgery; SBRT, stereotactic body radiotherapy; T, tumour; VATS, video-assisted thoracoscopic surgery; WT, wild type.

[a]SBRT is also recommended for patients with severe chronic obstructive pulmonary disease and elderly and/or frail patients [III, A] and can be recommended for subsets of patients with interstitial pulmonary fibrosis after multidisciplinary consultation and shared decision making with the patient [III, B].

[b]Anatomical resection is preferred over wedge resection [I, A]; three mediastinal and three hilar lymph node stations should be dissected [III, A]; VATS or RATS is recommended [I, A].

[c]Patients with a peripherally located, resectable tumour $\leq$2 cm and no nodal metastasis on both CT and PET imaging [I, A] and patients with pure ground-glass lesions [III, B].

[d]Patients with tumours >2 cm that have a solid appearance on CT [II, B].

[e]Same indications as for primary surgery, acknowledging higher operative risk.

[f]The sequence of PORT and any adjuvant systemic therapy should be defined individually by an MDT [III, A].

[g]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[112]

[h]ESMO-MCBS v2.0[113] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

resection, preferably wedge, may be appropriate in these cases[43,44] or observation alone may be appropriate if certain criteria are met.[11]

Patients presenting with multiple primary tumours should be assessed for curative-intent treatment. In 2016, the IASLC provided well-defined criteria to classify lung cancers with multiple sites into four patterns: synchronous multiple primary lung cancer, multifocal ground-glass or lepidic lung cancer, primary lung cancer with separate tumour nodules (intrapulmonary metastasis) and pneumonic-type lung cancer, all with different natural history and prognoses.[35] Although complete resection is recommended for multiple primary tumours in the American College of Chest Physicians guideline,[45] combinations of

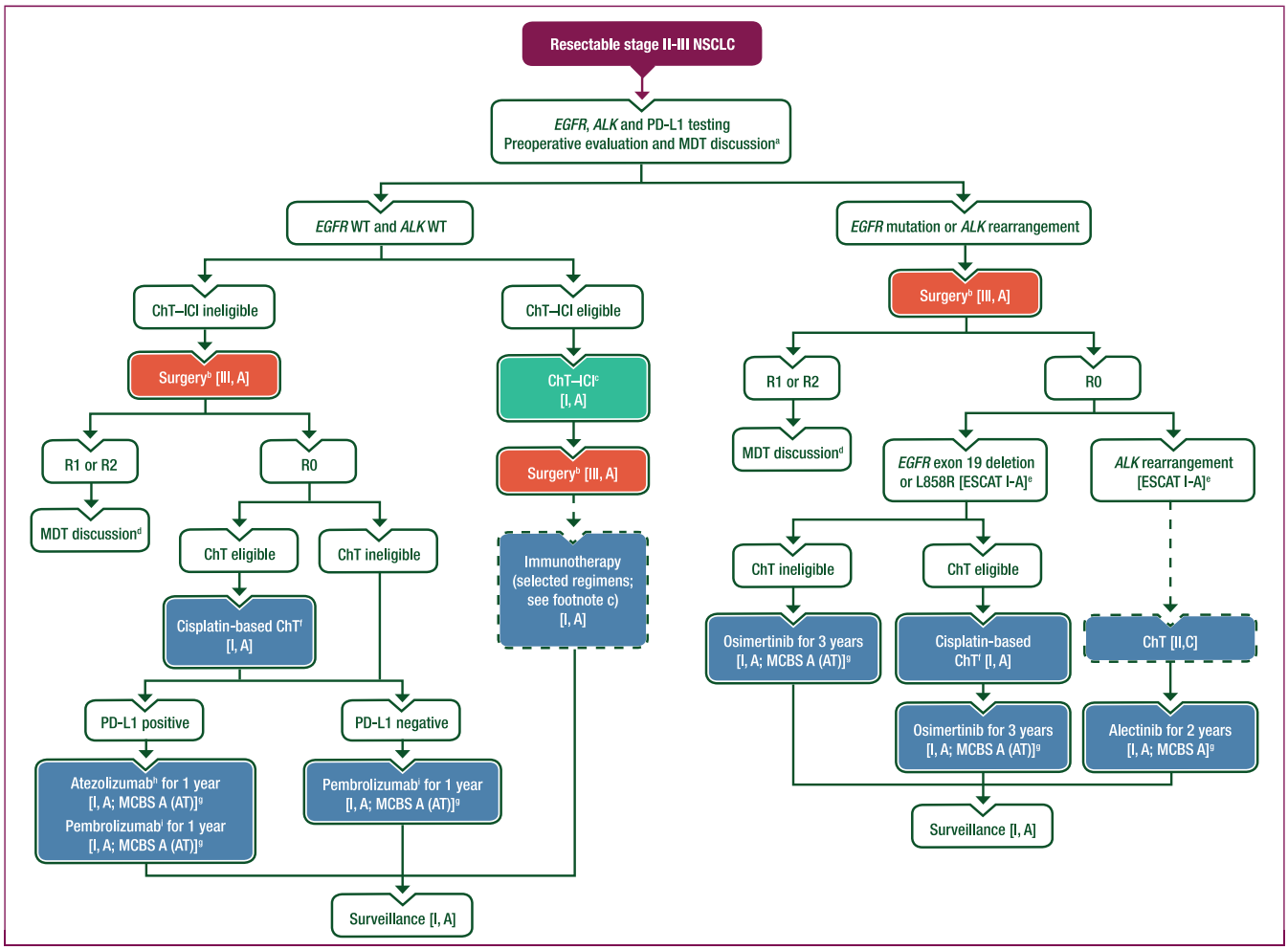

Figure 2. Management of resectable stage II-III NSCLC.

Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management; dashed lines: optional branches, colour used as described in the categories above.

ChT, chemotherapy; CRT, chemoradiotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; N, node; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PORT, post-operative radiotherapy; R0, no tumour at the margin; R1, microscopic tumour at the margin; R2, macroscopic tumour at the margin; RATS, robotic-assisted thoracoscopic surgery; SBRT, stereotactic body radiotherapy; TC, tumour cell; VATS, video-assisted thoracoscopic surgery; WT, wild type.

[a]SBRT is recommended for patients with severe chronic obstructive pulmonary disease and elderly and/or frail patients [III, A] and can be recommended for subsets of patients with interstitial pulmonary fibrosis after multidisciplinary consultation and shared decision making with the patient [III, B]. For patients with N2 disease, resectability and selection for neoadjuvant or perioperative systemic therapy versus concurrent definitive CRT should be discussed for each individual patient by an experienced MDT [V, A].

[b]Anatomical resection is preferred over wedge resection [I, A]; three mediastinal and three hilar lymph node stations should be dissected [III, A]; VATS or RATS is recommended for stage II tumours [I, A]; minimally invasive approaches may be considered for resectable stage III tumours, according to the surgeon's experience [V, C].

[c]Options: neoadjuvant nivolumab—ChT [I, A; ESMO-MCBS v2.0 score: A (AT); FDA approved, EMA approved for PD-L1 TC ≥1%]; neoadjuvant pembrolizumab—ChT followed by adjuvant pembrolizumab [I, A; ESMO-MCBS v2.0 score: A (AT)]; neoadjuvant durvalumab—ChT followed by adjuvant durvalumab [I, A; ESMO-MCBS v2.0 score: A (AT)]; neoadjuvant nivolumab—ChT followed by adjuvant nivolumab [I, A; ESMO-MCBS v2.0 score: A (AT); FDA approved, EMA approved for PD-L1 TC ≥1%]; neoadjuvant tislelizumab—ChT followed by adjuvant tislelizumab [I, A; ESMO-MCBS v2.0 score: A (AT); EMA approved, not FDA approved].

[d]In R1 and R2 resections, an MDT discussion is indicated for consideration of re-resection or incorporation of adjuvant ChT, PORT or definitive CRT.

[e]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[112]

[f]Carboplatin-based regimens can be recommended for patients who are not eligible for cisplatin (e.g. renal, neurological or other contraindication) [II, B].

[g]ESMO-MCBS v2.0[113] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[h]FDA approved for tumours with PD-L1 TC ≥1%, EMA approved for tumours with PD-L1 TC ≥50%.

[i]EMA and FDA approved after platinum-based ChT.

resection and SBRT have also proven effective;[46,47] thus, relevant decisions should be discussed in an MDT.

Minimally invasive surgery (MIS), either with video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracoscopic surgery (RATS), has become the standard approach. VATS achieves equivalent oncological outcomes with reduced morbidity compared with thoracotomy, as demonstrated in the VIOLET multicentre randomised controlled trial (RCT).[48] VATS has multiple advantages, including reduced incisional pain, better physical function

at 5 weeks, shorter hospital stay and fewer hospital readmissions.[48,49] Although the incidence of prolonged air leak and bleeding were higher after MIS in one randomised trial of early-stage lung cancer resection, this increase was not clinically relevant.[48] RATS and VATS demonstrate comparable outcomes for R0 resection, nodal upstaging and complication rates, as shown in multiple meta-analyses.[50,51] Lung cancer complete resection should meet all criteria defined by the IASLC, including negative resection margins, systematic or lobe-specific nodal dissection, and confirmation that the highest mediastinal node has been removed and is pathologically negative.[52] Given rapidly evolving multimodal treatments and heterogeneity within stage III disease, recent definitions of resectability proposed by the EORTC[53] and STS expert consensus survey[40] offer a framework for harmonising inclusion criteria across clinical trials, particularly when MDT interpretation of resectability varies. They recommend that surgery should be offered to patients with stage IIIA NSCLC diagnosed as cT3 N1, cT1-2 N2 single-station disease or cT4 N0-1 due to separate nodules or size, and to patients with stage IIIB NSCLC diagnosed as cT3 N2 or cT4 N2 due to separate nodules or size. N3 disease was defined as unresectable. Some stage IIIA cases classified as cT4 N0-1 due to infiltration may be considered potentially resectable, depending on the structure infiltrated. No consensus was reached on whether NSCLC with multiple-station N2 disease or bulky N2 disease (>2.5-3 cm) should be considered resectable. These definitions, however, are not intended to replace individualised, multidisciplinary assessment of resectability in routine practice.[39,40,52]

Patients with single-station N2 disease have better survival than those with multistation N2 disease. The recently revised TNM9 classification divides N2 into N2a (single) and N2b (multiple),[54] using data gathered before the introduction of immunotherapy. Patients with single-station, non-bulky N2 disease may be considered for neoadjuvant ChT—ICI followed by surgery. Selected patients with multistation N2 may also benefit from pre- or perioperative ChT—ICI followed by surgery; for example, in the CheckMate 77T study of perioperative ChT—ICI, patients undergoing successful resection of multiple N2 disease had similar outcomes to those with single N2 disease.[55] Thus, whether patients with potentially resectable bulky or multistation N2 disease are best managed with concurrent CRT followed by durvalumab or neoadjuvant or perioperative ChT—ICI followed by surgery remains controversial. This underscores the importance of individualised MDT discussion and further studies to refine risk stratification.

RT

For patients who are medically inoperable, curative RT should be considered. The preferred curative-intent RT for patients with peripherally located stage I NSCLC is SBRT. Long-term control rates of ≥90% with <5% grade 3-5 toxicity have consistently been reported in RCTs, with superiority over conventionally fractionated RT.[56,57] In a pooled analysis of two small RCTs, SBRT yielded superior OS compared with lobectomy.[58] In the prospective STARS study, which included 80 patients who were fit to undergo lobectomy, the 5-year local recurrence rate after SBRT was 6.3%, regional failure rate was 12.5% and distant metastasis rate was 8.8%.[59] The 5-year OS and PFS rates were 87% and 77%, respectively, which were comparable with outcomes in a prospectively registered cohort of patients with clinical stage I NSCLC who underwent VATS lobectomy with mediastinal LND at the same institution. Details on the tolerability of SBRT are available in Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2025.08.003. SBRT should be delivered with state-of-the-art equipment and techniques.[60] In case of local recurrence or a new primary tumour after SBRT in an operable patient, surgery is an option.[61]

Post-operative RT. Post-operative RT (PORT) was investigated in the Lung ART RCT, which randomised 501 patients with NSCLC and proven N2 involvement who had undergone complete resection to receive PORT (54 Gy in 27-30 fractions) or no PORT.[62] Patients with extracapsular invasion of the LNs but with pathologically negative resection margins were included. Extracapsular invasion was inconsistently reported and was missing in one-third of patients. The 3-year DFS rate was 47% [95% confidence interval (CI) 40% to 54%] with PORT versus 44% (95% CI 37% to 51%) without PORT. Median DFS was 30.5 months (95% CI 24-49 months) in the PORT group and 22.8 months (95% CI 17-37 months) in the control group [hazard ratio (HR) 0.86, 95% CI 0.68-1.08, $P = 0.18$]. Mediastinal relapses were observed in 14% of patients in the PORT group and in 28% of patients in the control arm. The most common grade 3-4 adverse event was pneumonitis (5% in the PORT group versus <1% in the control group). Late grade 3-4 cardiopulmonary toxicity was reported in 11% of patients in the PORT group versus 5% of patients in the control group. Three treatment-related deaths occurred, all in the PORT group: two patients died from pneumonitis (partly related to RT and infection) and one patient died due to sepsis that was deemed to be ChT related. An RCT in China reported similar results.[63] Based on these data, PORT is not used after complete resection of NSCLC.

No RCT has evaluated PORT after resection with microscopic tumour at the margin (R1). In a retrospective study including 3395 patients from the National Cancer Database with stage II or III NSCLC who underwent lobectomy or pneumonectomy with a positive surgical margin, PORT was associated with improved OS.[64] The estimated 5-year OS rate was 32.4% with PORT versus 23.7% without PORT (HR 0.80, 95% CI 0.70-0.92, $P < 0.001$). Most patients received 60 Gy in 30 fractions, although the dose and fractionation varied. The optimal timing and sequencing of PORT in relation to systemic treatment are unclear. In a cohort of 277 patients from the National Cancer Database with R1 resection or resection with macroscopic tumour at the margin (R2) regardless of nodal involvement, there was

no clear association between OS and administration of adjuvant ChT before or concurrently with PORT.[65] The vast majority (94%) of these patients had an R1 resection, and the median OS was 38.5 months (95% CI 31.1-46.9 months). These data were obtained before the era of immunotherapy and targeted agents.

The role of PORT following incomplete resection after neoadjuvant ChT—ICI is unclear, as is the role of PORT in relation to adjuvant immunotherapy.

Systemic therapy

Despite advances in strategies for local treatment, 25%-50% of patients with stage I-II NSCLC will experience recurrence and die of their disease.[66] Neoadjuvant, adjuvant and perioperative systemic therapy with ICIs and targeted therapy have resulted in improved DFS or event-free survival (EFS).[20,28,67-69] To date, adjuvant ICI trials have not demonstrated improved OS, whereas one neoadjuvant and one perioperative ChT—ICI trial have reported improved OS.[69-73] Adjuvant treatment with an EGFR TKI after initial resection also improves OS in patients with resected *EGFR*-mutated NSCLC.[74]

Recommendations for neoadjuvant or perioperative therapy versus initial surgery followed by adjuvant therapy require MDT discussion and consideration of multiple factors, including tumour stage, resectability, patient preference, performance status (PS), comorbidities, biomarkers (*EGFR*, *ALK*, PD-L1) and local expertise.

Adjuvant ChT. Adjuvant cisplatin-based ChT is the standard of care (SoC) after complete resection of stage II-III NSCLC, with a 5-year survival benefit with cisplatin-based regimens reported in the LACE meta-analysis.[75] Agents combined with cisplatin include vinorelbine, docetaxel and gemcitabine in squamous-cell NSCLC or pemetrexed in non-squamous NSCLC.[76,77] Data on carboplatin in the adjuvant setting are sparse. The CALGB 9633 study, which compared adjuvant carboplatin—paclitaxel with observation in patients with resected stage IB NSCLC [TNM seventh edition (TNM7)], reported a survival benefit in those with tumours $\geq$4 cm.[78]

Data suggest a detrimental effect of adjuvant ChT in patients with resected stage IA NSCLC;[75] however, the benefit for patients with stage I NSCLC with high-risk features (including visceral pleural invasion, lymphovascular invasion or high-grade histology) is unknown.[79,80]

Adjuvant ICI therapy. The phase III IMpower010 study evaluated 1 year of atezolizumab versus observation after four cycles of cisplatin-based ChT in patients with completely resected stage IB (T $\geq$4 cm)-IIIA NSCLC (TNM7).[81] The study reported a significant DFS benefit with atezolizumab in patients with stage II (T $\geq$5 cm)-IIIA disease with PD-L1 TC $\geq$1% (5-year HR 0.70, 95% CI 0.55-0.91) and a trend for improved OS (HR 0.77, 95% CI 0.56-1.06).[70,81-83] The benefit was greater in patients with PD-L1 TC $\geq$50% (5-year OS HR 0.47, 95% CI 0.28-0.77).[70,81-83] The phase III PEARLS/KEYNOTE-091 study evaluated 1 year of pembrolizumab versus placebo in patients with resected stage IB-IIIA NSCLC (TNM7) and demonstrated improved DFS with pembrolizumab (HR 0.76, 95% CI 0.63-0.91).[71] Adjuvant durvalumab did not improve DFS compared with placebo after resection in patients with stage IB-IIIA NSCLC (T $\geq$4 cm, TNM7), although differences in the patient population may have contributed to the negative result.[72]

Adjuvant targeted therapy. In patients with resected *EGFR*-mutated (exon 19 deletion, L858R) NSCLC [stage IB with high-risk features, T $\geq$3 cm or stage II-IIIA (TNM7)], adjuvant osimertinib for up to 3 years improved OS (HR 0.49, 95% CI 0.34-0.70), DFS (HR 0.27, 95% CI 0.21-0.34) and CNS DFS (HR 0.24, 95% CI 0.14-0.42 in stage II-IIIA) versus placebo.[20,74] Adjuvant ChT was more frequently administered to patients aged $\leq$70 years (66%) and those with higher disease stage [stage II or IIIA (76%) versus stage IB (26%)].[20,84] OS was also improved in patients who received adjuvant osimertinib without prior ChT use (HR 0.47, 95% CI 0.25-0.83), most commonly patients with stage IB disease.[20,74,84] In patients with resected stage IB (T $\geq$4cm)-IIIA *ALK*-rearranged NSCLC (TNM7), adjuvant alectinib for 2 years improved DFS (HR 0.24, 95% CI 0.13-0.43) and CNS DFS (HR 0.22, 95% CI 0.08-0.58) compared with four cycles of adjuvant platinum-based ChT.[23] OS data have not been reported and the study did not include standard adjuvant ChT for all patients in its design.

Whether patients with other genomically defined subsets of NSCLC, for which highly effective therapies exist in the metastatic setting, should undergo targeted adjuvant therapy following surgical resection with or without adjuvant ChT is currently unknown. MDT discussion and participation in ongoing clinical trials should be encouraged to further define the role of targeted therapies in the early-stage setting. Perioperative studies of targeted therapies are also ongoing with some promising preliminary data.[85]

Neoadjuvant and perioperative therapy. Data from randomised trials suggest that neoadjuvant ChT yields similar survival benefit to adjuvant ChT.[86] The addition of ICIs to ChT in the neoadjuvant and perioperative setting has resulted in a paradigm shift in the management of patients with stage II-III resectable NSCLC [TNM eighth edition (TNM8)].[28,67-69,87]

In the phase III CheckMate 816 trial, patients with resectable NSCLC (T $\geq$4 cm or node positive, without *EGFR* or *ALK* mutations) were randomised to three cycles of neoadjuvant platinum-based ChT with or without nivolumab.[28] The addition of nivolumab improved pCR rate (24% versus 2.2% with ChT alone) and EFS (HR 0.63, 97% CI 0.43-0.91), and significantly improved OS (HR 0.72, 95% CI 0.52-0.99, 5-year OS rate 65.4% versus 55.0%).[28,88] In an exploratory analysis, pCR after treatment was associated with a 5-year OS rate of 95.3%.[88] In the KEYNOTE-671 trial, patients with resectable stage II-IIIB NSCLC (TNM8) were randomised to neoadjuvant pembrolizumab or placebo plus four cycles of cisplatin-based ChT, followed by post-operative pembrolizumab or placebo for up to 13 cycles.[68] Pembrolizumab

significantly improved EFS (HR 0.58, 95% CI 0.46-0.72), pCR rates (18.1% versus 4% with placebo, $P < 0.0001$) and OS (HR 0.72, 95% CI 0.56-0.93, one-sided $P = 0.0052$, 3-year OS 71% versus 64% with placebo).[68,89] Other perioperative studies include the AEGEAN study which randomised patients with resectable NSCLC (excluding those requiring pneumonectomy or with T4 disease) to either four cycles of neoadjuvant ChT—durvalumab followed by adjuvant durvalumab every 4 weeks for 12 cycles, or neoadjuvant ChT followed by adjuvant placebo.[67] Durvalumab was associated with significant improvements in pCR rate (17.2% versus 4.3% with neoadjuvant ChT, $P = 0.00004$) and EFS (HR 0.68, 95% CI 0.53-0.88; $P = 0.004$).[67,90] CheckMate 77T randomised patients with resectable stage II-IIIB NSCLC (TNM8) to either four cycles of neoadjuvant nivolumab—ChT followed by surgery and adjuvant nivolumab for 1 year, or four cycles of neoadjuvant placebo—ChT followed by surgery and adjuvant placebo for 1 year.[69] Nivolumab was associated with significant improvements in EFS (HR 0.59, 95% CI 0.45-0.79) and pCR rates (25.3% versus 4.7%; odds ratio 6.64, 95% CI 3.40-12.97).[69,91] Survival data for these latter studies are pending. RATIONALE-315 randomised patients with resectable stage II-IIIA NSCLC to four cycles of neoadjuvant tislelizumab—ChT or placebo—ChT followed by surgery and adjuvant tislelizumab or placebo for 1 year.[92] Tislelizumab was associated with a significant improvement in the rate of MPR (56% versus 15% with placebo, $P < 0.0001$) and EFS (HR 0.56, 95% CI 0.40-0.79).

There have been no direct comparisons between neoadjuvant and perioperative ChT—ICI approaches in patients with NSCLC. pCR and MPR are strongly associated with better outcomes across studies, while PD-L1 expression and ctDNA clearance are associated with higher rates of pCR and MPR. Further studies are needed to define which patients require only neoadjuvant ChT—ICI versus continued ICI after resection; for example, in the setting of pCR after neoadjuvant ChT—ICI. Patients with residual viable tumour after neoadjuvant ChT—ICI or persistent ctDNA in plasma have poor EFS and OS across studies. Additional approaches to improve outcomes are needed. Discussion of these challenging scenarios by MDT is encouraged along with clinical trials addressing opportunities for treatment de-escalation and intensification.

Superior sulcus tumours. Information on the management of superior sulcus tumours is provided in Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2025.08.003.

Recommendations

Surgery

- Surgery should be offered to all patients with operable stage I and II NSCLC who are willing to accept procedure-related risks [III, A].
- Sublobar resection is recommended for patients with a peripherally located, resectable tumour $\leq$2 cm and no nodal metastases on both CT and PET imaging [I, A].
- Anatomical resection is preferred over wedge resection [I, A].
- Sublobar resection can be recommended for pure ground-glass lesions [III, B].
- Lobectomy can be recommended as the standard surgical treatment of tumours >2 cm that have a solid appearance on CT [II, B].
- Three mediastinal and three hilar LN stations should be dissected to conform with IASLC specifications for staging [III, A].
- VATS or RATS is recommended in patients with stage I-II tumours [I, A].
- Minimally invasive approaches may be considered for resectable stage III tumours, according to the surgeon's experience [V, C].
- For patients with multifocal lung cancer, complete resection is recommended whenever possible [III, B].
  - Multidisciplinary tumour board discussion is recommended for all patients with multifocal lung cancer [III, A].
- For patients with N2 disease, resectability and selection for neoadjuvant or perioperative systemic therapy versus concurrent definitive CRT should be discussed for each individual patient by an experienced MDT [V, A].

RT

- SBRT is recommended as the non-surgical treatment of choice for stage I NSCLC [II, A].
- SBRT is also recommended for patients with severe chronic obstructive pulmonary disease and elderly and/or frail patients [III, A].
- SBRT can be recommended for subsets of patients with interstitial pulmonary fibrosis after multidisciplinary consultation and shared decision making with the patient [III, B].
- Salvage surgery after SBRT can be offered, if feasible, using the same indications as for primary surgery, acknowledging that surgery may be more difficult with higher operative risk [IV, B].
- For patients with central or ultracentral tumours, curative-intent RT using more fractionated schedules is recommended [II, A].
- PORT cannot be recommended after R0 resection, including for patients with extracapsular nodal involvement if the surgical resection margins are negative [I, D].
- PORT (60 Gy in 30 fractions) may be recommended after R1 resection, following MDT discussion [III, C].
  - The sequence of PORT and adjuvant systemic therapy should be defined individually by an MDT [III, A].

Systemic therapy

- Optimal sequencing of systemic therapy (neoadjuvant, perioperative or adjuvant) should be defined by an MDT before treatment decision making, including biomarker testing for *EGFR, ALK* and PD-L1 at a minimum [V, A].

- For *EGFR* and *ALK* wild-type disease:
  - Neoadjuvant or perioperative ChT—ICI is recommended for resectable stage II-III NSCLC without *EGFR* or *ALK* alterations [I, A]:
    - Neoadjuvant nivolumab—ChT [I, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v2.0 score: A (AT); Food and Drug Administration (FDA) approved, European Medicines Agency (EMA) approved for PD-L1 TC ≥1%].
    - Neoadjuvant pembrolizumab—ChT followed by adjuvant pembrolizumab [I, A; ESMO-MCBS v2.0 score: A (AT)].
    - Neoadjuvant durvalumab—ChT followed by adjuvant durvalumab [I, A; ESMO-MCBS v2.0 score: A (AT)].
    - Neoadjuvant nivolumab—ChT followed by adjuvant nivolumab [I, A; ESMO-MCBS v2.0 score: A (AT); FDA approved, EMA approved for PD-L1 TC ≥1%].
    - Neoadjuvant tislelizumab—ChT followed by adjuvant tislelizumab [I, A; ESMO-MCBS v2.0 score: A (AT); EMA approved, not FDA approved].
  - Adjuvant cisplatin-based ChT is recommended for patients with completely resected *EGFR* and *ALK* wild-type, stage II-III NSCLC who are not eligible for ChT—ICI [I, A].
    - Carboplatin-based regimens can be recommended for patients who are not eligible for cisplatin (e.g. renal, neurological or other contraindication) [II, B].
  - Adjuvant atezolizumab for 1 year is recommended following cisplatin-based ChT for patients with resected stage II-IIIA (T ≥5 cm) NSCLC with PD-L1 TC ≥1% and without *EGFR* or *ALK* alterations [I, A; ESMO-MCBS v2.0 score: A (AT); FDA approved for PD-L1 TC ≥1%, EMA approved for PD-L1 TC ≥50%].
  - Adjuvant pembrolizumab for 1 year is recommended for patients with resected stage II-IIIA (T ≥4 cm) NSCLC without *EGFR* or *ALK* alterations, regardless of PD-L1 expression [I, A; ESMO-MCBS v2.0 score: A (AT); EMA and FDA approved after platinum-based ChT].
- For *EGFR*-mutated disease:
  - Adjuvant osimertinib for 3 years (after ChT as appropriate) is recommended for completely resected *EGFR*-mutated (exon 19 deletion or L858R) stage IB-IIIA NSCLC [I, A; ESMO-MCBS v2.0 score: A (AT); ESCAT score: I-A].
  - Adjuvant cisplatin-based ChT before targeted therapy is recommended for patients with stage II-III disease who are eligible for ChT [I, A]. Carboplatin-based regimens can be recommended for patients who are not eligible for cisplatin [II, B].
- For *ALK*-rearranged disease:
  - Adjuvant alectinib for 2 years is recommended for completely resected *ALK* fusion-positive stage II-IIIA (T ≥4 cm) NSCLC [I, A; ESMO-MCBS v2.0 score: A; ESCAT score: I-A].
  - Adjuvant ChT before targeted therapy may be considered [II, C].
- Neoadjuvant CRT followed by surgery can be recommended for patients with superior sulcus tumours (T3-4 N0-1) after MDT discussion [III, B].

MANAGEMENT OF UNRESECTABLE STAGE III NSCLC

Several phase III trials and an individual patient data meta-analysis reported that concurrent CRT improved 5-year OS rates in unresectable stage III NSCLC by ∼4% compared with sequential CRT, but was associated with higher rates of reversible oesophagitis.[93] Addition of surgery to concurrent CRT,[94,95] induction or consolidation ChT[96-98] and RT dose escalation >60 Gy in 30 fractions[99] have not resulted in improved survival. RT doses >60 Gy or equivalent may even be detrimental, with higher mortality partly due to more cardiac deaths.[99]

The current SoC was established in the PACIFIC trial, which randomised 713 patients with unresectable stage III NSCLC without disease progression following concurrent CRT to 1 year of durvalumab or placebo in a 2 : 1 ratio.[100] Durvalumab was initiated within 42 days of CRT completion. Durvalumab was associated with improved 5-year OS rate (42.9% versus 33.4% with placebo) and median PFS (16.9 months versus 5.6 months with placebo; HR 0.55, 95% CI 0.45-0.68).[100-102] Although pre-planned subgroup analyses suggested the survival benefit was irrespective of PD-L1 expression levels (stratified as <25% and ≥25%), a *post hoc* exploratory analysis did not demonstrate benefit in patients with PD-L1 expression <1%.[103]

Preliminary results from studies exploring the use of immunotherapy concurrently with definitive CRT have suggested a lack of benefit compared with the PACIFIC regimen, as well as increased toxicity.[104,105]

A subgroup analysis of patients with *EGFR*-sensitising mutations or *ALK* rearrangements in the PACIFIC study suggested a lack of benefit with consolidation durvalumab in these patients (PFS HR 0.91, 95% CI 0.39-2.13; OS HR 1.02, 95% CI 0.39-2.63).[106] Furthermore, the use of TKIs after immunotherapy is associated with increased rates of severe immune-related toxicity.[107] Thus, an ESMO expert consensus statement recommended avoiding the use of durvalumab in patients with unresectable stage III *EGFR*-mutated NSCLC following concurrent CRT.[108]

In the LAURA study, 216 patients with *EGFR*-mutated unresectable stage III NSCLC without progression after CRT were randomised (2 : 1) to receive osimertinib or placebo until disease progression.[21] The primary endpoint was met with a median PFS of 39.1 months with osimertinib versus 5.6 months with placebo (HR 0.16, 95% CI 0.10-0.24) and a decreased risk of CNS metastasis with osimertinib. OS data were immature. The risk of RT- or drug-related pneumonitis was ∼10% higher in the osimertinib arm. A confirmatory trial from China of aumolertinib, another third-generation EGFR TKI, demonstrated similar results.[22]

In recent studies using contemporary RT techniques,[60] concurrent CRT was associated with ~8% temporary grade 3 oesophagitis and 5% high-grade pneumonitis.[99] Supportive care measures implemented before starting concurrent CRT include smoking cessation and advice on diet and physical exercise,[109] as well as supportive care during and following treatment.

As concurrent CRT is associated with higher toxicity than sequential CRT, the sequential approach is an option for frail patients or those with substantial comorbidities. The addition of durvalumab after sequential CRT was studied in the non-randomised PACIFIC-6 study.[110] Nearly all patients had a WHO PS 0-1. Median PFS was 10.9 months. Due to the lack of a control group, the role of durvalumab after sequential CRT is uncertain. Nevertheless, consolidation immunotherapy after sequential CRT was evaluated in a phase III Chinese study (GEMSTONE-301), which randomised patients who were not progressing following concurrent or sequential CRT to sugemalimab (a programmed cell death protein 1 inhibitor) versus placebo.[111] Sugemalimab was effective (PFS HR 0.64, 95% CI 0.48-0.85) and well tolerated.[111]

An algorithm for the management of unresectable stage III NSCLC is provided in Figure 3. Patients who are not candidates for radical RT with or without systemic therapy should be managed according to the ESMO CPGs for metastatic NSCLC.[12-15]

Recommendations

- Concurrent CRT is recommended for patients with stage IIIA-C NSCLC deemed unresectable by an MDT [I, A].
- An RT dose of 60 Gy in once-daily fractions is recommended for concurrent CRT [I, A].
- In patients who are not fit for concurrent CRT, sequential CRT or RT alone is recommended as an alternative [I, A].
- Concurrent or sequential platinum-based doublet ChT for two to three cycles is recommended [preferably cisplatin—etoposide or carboplatin—paclitaxel (all histologies) or cisplatin—pemetrexed (non-squamous histology)] [I, A].
- Osimertinib consolidation is recommended after concurrent or sequential CRT in patients with *EGFR*-mutated unresectable stage III NSCLC without disease progression [I, A; ESMO-MCBS v2.0 score: 4; ESCAT score: I-A].
- Durvalumab consolidation for 1 year (initiated within 42 days after the end of CRT) is recommended after concurrent CRT in patients with *EGFR* wild-type, stage III NSCLC without disease progression [I, A; ESMO-MCBS v2.0 score: 4; FDA approved, EMA approved for PD-L1 TC $\geq$1%].
- Durvalumab consolidation for 1 year (initiated within 42 days after the end of CRT) can also be recommended after sequential CRT in patients with *EGFR* wild-type, stage III NSCLC without disease progression [III, B; EMA approved for tumours with PD-L1 TC $\geq$1%, not FDA approved].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Patients with early-stage and locally advanced NSCLC who are treated with curative intent are at risk of treatment-related complications, cancer recurrence and new primary malignancies. Patients treated with surgical resection with or without neoadjuvant ChT—ICI are at risk of postoperative complications, including respiratory failure, pneumonia, pneumothorax and cardiac complications, particularly within the first 30 days after surgery. The likelihood of readmission due to treatment-related complications is associated with resection type, age, neoadjuvant therapy and preoperative comorbidities. Readmission due to treatment-related complications in resected patients is associated with a significant increase in 90-day mortality. Curative CRT is also associated with a risk of complications, including infection, oesophagitis, pneumonitis, cytopenias, cardiac toxicity and hepatotoxicity. As such, careful clinical monitoring of patients after treatment is essential to identify and manage potential early treatment-related complications. The increasing use of immunotherapy and targeted therapy in early-stage disease also necessitates careful monitoring for late complications of these treatments, which may occur later in the surveillance period.

Details on surveillance are available in Supplementary Material Section 5, available at https://doi.org/10.1016/j.annonc.2025.08.003.

Recommendations

- Patients with NSCLC treated with curative intent should undergo surveillance for treatment-related complications, detection of disease recurrence and development of a new primary lung cancer [I, A].
- Surveillance can be recommended at a minimum of every 6 months for 2 years, then annually until 5 years from definitive therapy with visits comprising history, physical examination, bloodwork and preferably contrast-enhanced chest CT scan including the adrenals [I, B].
- Follow-up with 3-6-monthly CT scans for 3 years can be recommended in patients at high risk of recurrence who are potential candidates for salvage therapy, then annually until 5 years from definitive therapy, as above [III, B].
  - The frequency of the follow-up visits can be tailored to the individual patient for those not suitable for salvage treatment or those with additional risk factors [V, B].
- Selective use of [^{18}F]2-fluoro-2-deoxy-D-glucose—PET can be recommended when recurrence after SBRT or CRT is suspected based on serial chest CT scans [III, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/guidelines/esmo-guidelines-methodology). All recommendations provided are based on

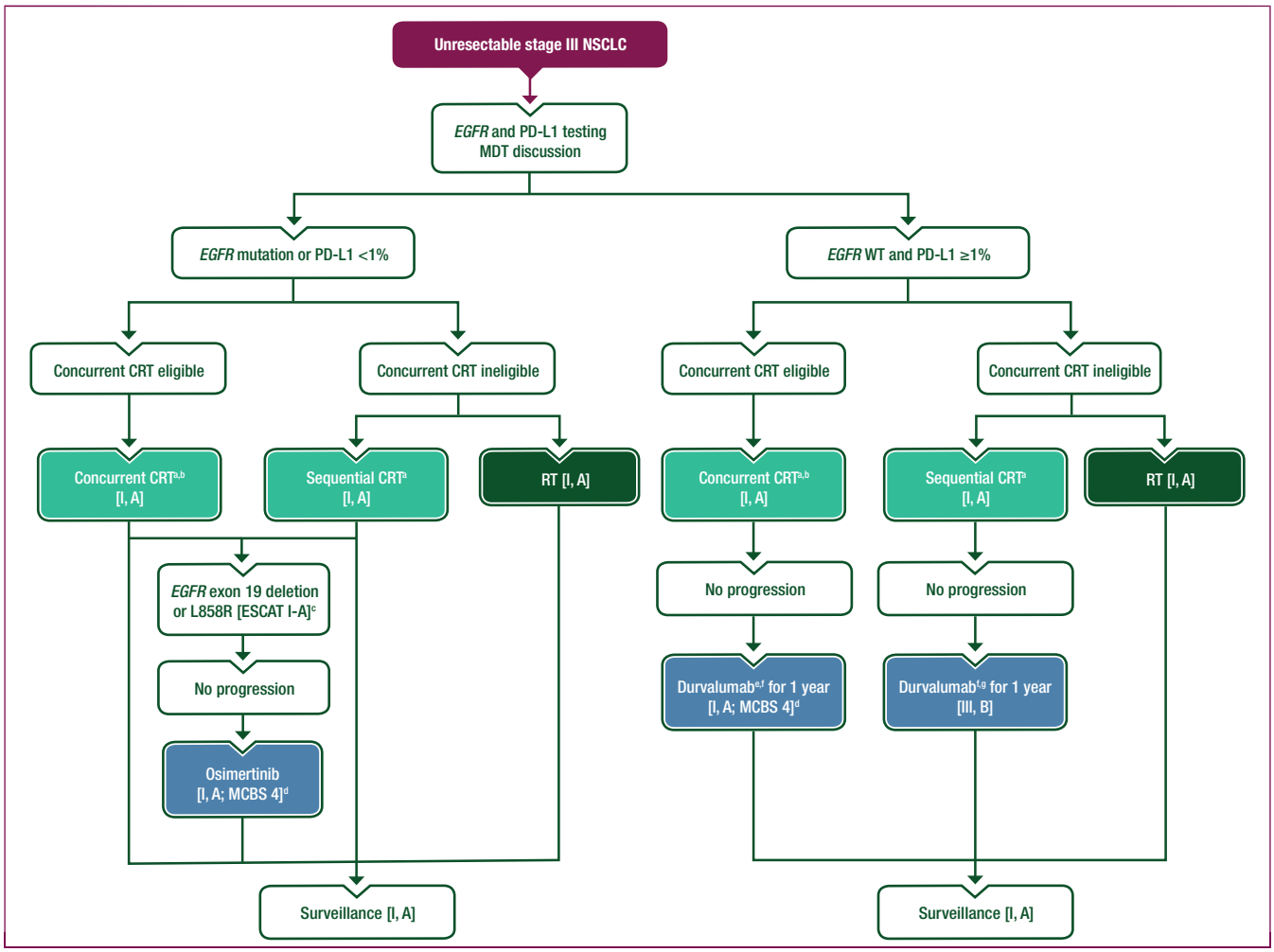

Figure 3. Management of unresectable stage III NSCLC.
Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management.
ChT, chemotherapy; CRT, chemoradiotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; RT, radiotherapy; TC, tumour cell; WT, wild type.
[a]Platinum-based doublet ChT for two to three cycles is recommended [preferably cisplatin—etoposide or carboplatin—paclitaxel (all histologies) or cisplatin—pemetrexed (non-squamous histology)] [I, A].
[b]RT dose of 60 Gy in once-daily fractions [I, A].
[c]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[112]
[d]ESMO-MCBS v2.0[113] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]FDA approved, EMA approved for tumours with PD-L1 TC ≥1%.
[f]Durvalumab should be initiated within 42 days after the end of CRT [I, A].
[g]EMA approved for tumours with PD-L1 TC ≥1%, not FDA approved.

current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[112] ESMO-MCBS v2.0[113] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/guidelines/esmo-mcbs). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.08.003.[114] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Guideline Updates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-early-stage-and-locally-advanced-non-small-cell-lung-cancer.

ACKNOWLEDGEMENTS

Manuscript editing support was provided by Sammi Cham, Ioanna Ntai and Claire Bramley (ESMO Guidelines staff) and Angela Corstorphine and Sian-Marie Lucas of Kstorfin Medical Communications Ltd (KMC); this support was funded by ESMO. Nathan Cherny, member of the ESMO-MCBS Working Group, and Urania Dafni, Giota Zygoura, Georgia Dimopoulou and Tereza Dellaporta of Frontier Science Foundation Hellas, provided review and validation of the ESMO-MCBS scores. Nicola Latino and Francesca Chiovaro (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scores and Angela Corstorphine and Sian-Marie Lucas of KMC provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO.

FUNDING

No external funding has been received for the preparation of this guideline. Production costs have been covered by ESMO from central funds.

DISCLOSURE

AZ reports personal fees for advisory board membership from AstraZeneca and Johnson & Johnson; personal fees for consultancy from BeiGene and Gilead; personal fees as an invited speaker from Merck Sharp & Dohme (MSD), Pfizer and Roche; personal fees as a safety review committee member from Beyond Air; and institutional funding as local principal investigator (PI) for AbbVie, AstraZeneca, Gilead, Johnson & Johnson and MSD. MJA reports personal fees for advisory board membership from Alpha Pharmaceutical, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Daiichi Sankyo, Genexin, Janssen, Merck, MSD, Roche, Takeda, Voronoi and Yuhan. FB reports institutional fees for advisory board membership from AbbVie, ACEA, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Eisai, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Ignyta, Merck, Mirati, MSD, Novartis, Pfizer, Pierre Fabre, Sanofi Aventis, Seattle Genetics, Summit Therapeutics and Takeda; and non-remunerated activities as PI for AstraZeneca, BMS, F. Hoffmann-La Roche Ltd, Innate Pharma, Merck, Mirati and Pierre Fabre. LB reports personal stocks/shares in Novartis and Roche; institutional fees for advisory board membership from AstraZeneca, Bayer, BMS, Daiichi Sankyo, Janssen, Pfizer and Takeda; institutional fees as an invited speaker from Amgen, AstraZeneca, Eli Lilly and Thermo Fisher; an institutional research grant from GlaxoSmithKline (GSK), Systems Oncology and Thermo Fisher; institutional funding as local PI from Roche; institutional fees for consultancy from Swiss Rockets AG; and institutional funding from Novartis. DDR reports institutional fees for advisory board membership from AstraZeneca and BMS; institutional fees as an invited speaker from AstraZeneca; institutional fees as a steering committee member from AstraZeneca and Philips Health; institutional research grants from AstraZeneca, BMS and Varian; institutional funding as coordinating PI from AstraZeneca and BMS; institutional funding from BeiGene and Olink; and institutional fees for consultancy from Eli Lilly. PG reports personal fees for advisory board membership from Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, BMS, Daiichi Sankyo, GSK, Johnson & Johnson, MSD, Novartis, Pfizer, PharmaMar, Pierre Fabre, Regeneron, Roche and Sanofi; personal fees as an invited speaker from Amgen, Johnson & Johnson and Eli Lilly; institutional funding as local PI from Amgen, Apollomics, Array Biopharma, AstraZeneca, BeiGene, BMS, Eli Lilly, Janssen, Novartis, Pfizer and Roche; non-remunerated leadership roles for Asociación Española Contra el Cáncer, ESMO, Spanish Federation of Medical Societies, IASLC and Sociedad Española de Oncología Médica; non-remunerated advisory roles for the King Hussein Cancer Award (Board of Directors) and the Ministerio de Sanidad (Spanish National Health Advisory Board); and a non-remunerated role as a steering committee member for IO Biotech. PG's spouse reports personal fees for advisory board membership from AbbVie, Boehringer Ingelheim, Gebro, Johnson & Johnson, Nordic Pharma Ltd and Sanofi; and personal fees as an invited speaker from Amgen, Boehringer Ingelheim, Galapagos, GP Pharm, Johnson & Johnson, Nordic Pharma Ltd and Pfizer. PG's son reports employment at Teva Pharmaceuticals. OG reports institutional travel expenses/grants from Amgen, AstraZeneca and Roche; and institutional funding as local PI from Eli Lilly, Loxo and Nuvalent. LEH reports personal fees as an invited speaker from Benecke, Medimix, MEDtalks and VJOncology; personal fees for membership of the committee responsible for revising the Dutch guidelines on NSCLC, brain metastases and leptomeningeal metastases from Kennisinstituut voor Medisch Specialisten; institutional fees for advisory board membership from AbbVie, Amgen, AnHeart, AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Summit and Takeda; institutional fees as an invited speaker from AstraZeneca, Bayer, GSK, High5 Oncology, Lilly, MSD, Pfizer and Sanofi; institutional funding from Janssen for an educational webinar and Takeda for a podcast; institutional funding as steering committee member from AbbVie; institutional funding as local PI from Amgen, AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Daiichi Sankyo, Gilead, GSK, Merck Serono, Mirati, MSD, Novartis, Pfizer, Roche and Takeda; institutional research grants from AstraZeneca, Boehringer Ingelheim, Gilead, Merck, Novartis, Pfizer, Roche and Takeda; and non-remunerated roles as vice chair of the scientific committee for the Dutch Thoracic Group, chair of the EORTC NSCLC for Lung Cancer group and past secretary and current chair of the Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose Studies Foundation. PAJ reports personal fees for advisory board membership from AbbVie, Accutar Biotech, Allorion Therapeutics, AstraZeneca, Bayer, Biocartis, Blueprint Medicines, Boehringer Ingelheim, Chugai Pharmaceuticals, Daiichi Sankyo, Dizal Pharma, Duality Biologics, Eli Lilly, Eisai, Frontier Medicines, GSK, Hongyun Biotechnology, Merus, Mirati Therapeutics, Myris Therapeutics, Novartis, Nuvalent, Pfizer, Roche/Genentech, Sanofi, Silicon Therapeutics,

Syndax, Takeda Oncology, TOLREMO, Transcenta and Voronoi; personal licensing fees or royalties from intellectual property from Lab Corp; personal stocks/shares in Allorion Therapeutics, Frontier Medicines and Gatekeeper Pharmaceuticals; and institutional research grants from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, PUMA, Revolution Medicines and Takeda Oncology. KMK reports personal fees for advisory board membership from AbbVie, Amgen, AstraZeneca, Bayer, Debiopharm, Diaceutics, Jannsen, Merck Serono, MSD, Novartis, Pfizer, Regeneron, Roche, Roche Diagnostics/Ventana and Sanofi; personal fees as an invited speaker from Amgen, AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Merck Serono, MSD, Novartis, Pfizer, Prime Oncology, Roche and Roche Diagnostics/Ventana; a non-remunerated leadership role for IASLC; and a non-remunerated membership with the UK Lung Cancer Consortium. CM reports personal fees for advisory board membership from AstraZeneca, BMS, Daiichi Sankyo, Janssen, Kephren, MSD, Novartis, Pfizer, Regeneron, Roche, Sanofi and Takeda; and personal fees as an invited speaker from Amgen, AstraZeneca, BMS, Janssen, MSD, Pfizer and Roche. TM reports personal fees for advisory board membership from AstraZeneca, Boehringer Ingelheim, BMS, Janssen, Ono and Regeneron; personal fees as an invited speaker from Amgen, AstraZeneca, Bayer, Chugai, Daiichi Sankyo, Eli Lilly, Merck Biopharma, MSD, Novartis, Ono, Pfizer, Taiho, Takeda; an institutional research grant from Bridge Bio; non-remunerated activities as PI for AstraZeneca and BMS; and a non-remunerated leadership role as president (2021-2023) for the IASLC. SP reports personal fees for an editorial role as associate editor for *Annals of Oncology* and an editorial role as deputy editor for *Lung Cancer*; institutional fees for advisory board membership from AbbVie, Amgen, Arcus, AstraZeneca, Bayer, BeiGene, Bio Invent, Biocartis, Blueprint Medicines, Boehringer Ingelheim, BMS, Daiichi Sankyo, Debiopharm, Eli Lilly, F-Star, Foundation Medicine, Genzyme, Gilead, GSK, HUTCHMED, Illumina, Incyte, IQVIA, iTeos, Janssen, Merck Serono, Mirati, MSD, Novartis, Novocure, Nuvalent, Nuvation Bio, Nykode, Pfizer, PharmaMar, Phosplatin Therapeutics, Regeneron, Roche/Genentech, Sanofi, Seattle Genetics, Takeda, Vaccibody; institutional fees as an invited speaker from AstraZeneca, Boehringer Ingelheim, BMS, Ecancer, Eli Lilly, Fishawack, Illumina, Imedex, Medscape, Mirati, MSD, Novartis, OncologyEducation, PER, Pfizer, Prime, RMEI Medical Education, Roche/Genentech, RTP, Sanofi and Takeda; institutional funding as coordinating PI for AstraZeneca; institutional fees as a board of directors member for Galenica (Swiss network of pharmacies); institutional fees as a steering committee member from AstraZeneca, BeiGene, BMS, iTeos, Mirati, MSD, PharmaMar, Phosplatin Therapeutics and Roche/Genentech; institutional fees for role as trial chair from GSK and Roche/Genentech; non-remunerated activities as PI for European Thoracic Oncology Program (ETOP), EORTC/Swiss Group for Clinical Cancer Research (SAKK); non-remunerated leadership roles for Ballet Béjart Lausanne Foundation, ESMO, ETOP/International Breast Cancer Study Group (IBCSG) Partners, Oncosuisse, SAKK and Swiss Academy of Multidisciplinary Oncology; non-remunerated membership with American Association for Cancer Research, American Society of Clinical Oncology, ASMAC/VSAO, Association of Swiss Physicians Foederatio Medicorum Helveticorum Switzerland, IASLC, SAKK; and non-remunerated affiliation with Swiss political activities. CR reports personal fees for advisory board membership from AbbVie, Affrontiamo il cancro. Insieme (AIRC), Boehringer Ingelheim, F. Hoffmann-La Roche, Janssen, NeoGenomics, Novartis, Novocure and Touch Oncology; personal fees as an invited speaker from HPM Education, IDEOlogy Health, Merck and Roche; personal research grants from AstraZeneca, Lung Cancer Research Foundation, OncoHost and Thermo Fisher; institutional fees for advisory board membership from AstraZeneca, Imagene, MedStar, OneCell and Regeneron; institutional fees as an invited speaker from COR2ED; institutional research grants from AstraZeneca, Lung Cancer Research Foundation and Thermo Fisher; non-renumerated leadership roles as a scientific board member for the European School of Oncology, deputy chair on the educational committee for the IASLC, vice president for the International Society of Liquid Biopsy and educational chair for the Oncology Latin American Association; a non-renumerated role as editor-in-chief for *Critical Reviews in Oncology Hematology*; a non-renumerated role as an associate editor for *ESMO Open*; a non-renumerated role as ESMO Faculty Group/Speciality and Faculty Coordinator for metastatic NSCLC for ESMO; and non-renumerated analysis of liquid biopsies in a lung cancer trial for Guardant Health. AS reports personal travel expenses/grants from Amgen, Genentech-Roche and Merck; institutional funding as local PI from Amgen, BridgeBio, CRISPR Therapeutics, GSK, Hotspot Therapeutics, Iovance, Eli Lilly, Merck, Pfizer and Spectrum; institutional funding as coordinating PI from AstraZeneca and Genentech-Roche; and non-remunerated advisory roles for Amgen, Genentech-Roche and Merck. SS reports institutional fees for advisory board membership from AstraZeneca, Eli Lilly and MSD; an institutional research grant as a PhD student from AstraZeneca; institutional funding as PI from Varian Medical Systems; and a non-remunerated advisory role as a scientific advisory committee member (2013-March 2025) for ETOP and IBCSG. PU reports personal fees for advisory board membership from AstraZeneca and Medtronic; and personal fees as an invited speaker from AstraZeneca, BMS, Johnson & Johnson, MSD and Roche. NBL reports personal travel expenses/grants from AstraZeneca, Guardant Health, Janssen, MSD and Sanofi; institutional research grants from AstraZeneca, Inivata/NeoGenomics, Janssen, Eli Lilly, MSD, Novartis and Pfizer; and a non-remunerated role as a data safety monitoring board member for Daiichi Sankyo and Mirati.

REFERENCES

1. 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.

2. Santucci C, Mignozzi S, Levi F, et al. European cancer mortality predictions for the year 2025 with focus on breast cancer. *Ann Oncol*. 2025;36(4):460-468.
3. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(suppl 5):e1S-e29S.
4. Samet JM, Wiggins CL, Humble CG, et al. Cigarette smoking and lung cancer in New Mexico. *Am Rev Respir Dis*. 1988;137(5):1110-1113.
5. Sorscher S, LoPiccolo J, Chen E, et al. Landscape of pathogenic germline variants in patients with lung cancer. *J Clin Oncol*. 2022;40 (suppl 36):388570.
6. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.
7. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382(6):503-513.
8. Henderson LM, Su IH, Rivera MP, et al. Prevalence of lung cancer screening in the US, 2022. *JAMA Netw Open*. 2024;7(3):e243190.
9. Chang GC, Chiu CH, Yu CJ, et al. Low-dose CT screening among never-smokers with or without a family history of lung cancer in Taiwan: a prospective cohort study. *Lancet Respir Med*. 2024;12(2):141-152.
10. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(suppl 5):e93S-e120S.
11. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*. 2017;284(1):228-243.
12. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):358-376.
13. Hendriks L, Cortiula F, Mariamidze E, et al. ESMO non-oncogene-addicted metastatic non-small-cell lung cancer living guideline, v1.2 January 2025. Available at https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-non-oncogene-addicted-metastatic-non-small-cell-lung-cancer. Accessed April 14, 2025.
14. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):339-357.
15. Hendriks L, Cortiula F, Mariamidze E, et al. ESMO oncogene-addicted metastatic non-small-cell lung cancer living guideline, v1.2 January 2025. Available at https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-oncogene-addicted-metastatic-non-small-cell-lung-cancer. Accessed April 14, 2025.
16. Kerr KM, Bubendorf L, Lopez-Rios F, et al. Optimizing tissue stewardship in non-small cell lung cancer to support molecular characterization and treatment selection: statement from a working group of thoracic pathologists. *Histopathology*. 2024;84(3):429-439.
17. 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.
18. Penault-Llorca F, Kerr KM, Garrido P, et al. Expert opinion on NSCLC small specimen biomarker testing - Part 2: analysis, reporting, and quality assessment. *Virchows Arch*. 2022;481(3):351-366.
19. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. *J Thorac Oncol*. 2022;17(3):362-387.
20. 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.
21. Lu S, Kato T, Dong X, et al. Osimertinib after chemoradiotherapy in stage III EGFR-mutated NSCLC. *N Engl J Med*. 2024;391(7):585-597.
22. Yu J, Meng X, Ge H, et al. PL04.13 Aumolertinib maintenance after chemoradiotherapy in stage III non-small-cell lung cancer: interim results of the phase III study (POLESTAR). *J Thorac Oncol*. 2024;19 (suppl 10):S6-S7.
23. Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in resected ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2024;390(14):1265-1276.
24. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.
25. Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. *Cancer Discov*. 2017;7(12):1394-1403.
26. Xia L, Mei J, Kang R, et al. Perioperative ctDNA-based molecular residual disease detection for non-small cell lung cancer: a prospective multicenter cohort study (LUNGCA-1). *Clin Cancer Res*. 2022;28(15):3308-3317.
27. Tran HT, Heeke S, Sujit S, et al. Circulating tumor DNA and radiological tumor volume identify patients at risk for relapse with resected, early-stage non-small-cell lung cancer. *Ann Oncol*. 2024;35 (2):183-189.
28. 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.
29. Provencio M, Serna-Blasco R, Nadal E, et al. Overall survival and biomarker analysis of neoadjuvant nivolumab plus chemotherapy in operable stage IIIA non-small-cell lung cancer (NADIM phase II trial). *J Clin Oncol*. 2022;40(25):2924-2933.
30. Reck M, Gale D, Zhu Z, et al. LBA49 Associations of ctDNA clearance (CL) during neoadjuvant Tx with pathological response and event-free survival (EFS) in pts with resectable NSCLC (R-NSCLC): expanded analyses from AEGEAN. *Ann Oncol*. 2024;35(suppl 2):S1239.
31. Union for International Cancer Control. *TNM Classification of Malignant Tumours*. 9th ed. Oxford, UK: John Wiley & Sons, Ltd; 2025.
32. International Association for the Study of Lung Cancer. Staging Manual in Thoracic Oncology. 3rd ed. Published 2024. Available at https://www.iaslc.org/research-education/publications-resources-guidelines/staging-manual-thoracic-oncology-3rd-edition. Accessed February 24, 2025.
33. Detterbeck FC, Marom EM, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic type of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol*. 2016;11(5):666-680.
34. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11(8):1204-1223.
35. Detterbeck FC, Nicholson AG, Franklin WA, et al. The IASLC Lung Cancer Staging Project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol*. 2016;11(5):639-650.
36. Rosen JE, Keshava HB, Yao X, et al. The natural history of operable non-small cell lung cancer in the National Cancer Database. *Ann Thorac Surg*. 2016;101(5):1850-1855.
37. Altorki N, Wang X, Kozono D, et al. Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. *N Engl J Med*. 2023;388(6):489-498.
38. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399(10335):1607-1617.
39. Houda I, Bahce I, Dickhoff C, et al. An international and multidisciplinary EORTC survey on resectability of stage III non-small cell lung cancer. *Lung Cancer*. 2025;199:108061.
40. Kim SS, Cooke DT, Kidane B, et al. The Society of Thoracic Surgeons expert consensus on the multidisciplinary management and

resectability of locally advanced non-small cell lung cancer. *Ann Thorac Surg*. 2025;119(1):16-33.
41. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10(12):1675-1684.
42. Xie H, Dai C, Gu C, et al. Validation of the proposed International Association for the Study of Lung Cancer residual tumor classification to upgrade extracapsular extension of tumor in nodes from R0 to incomplete resection. *J Thorac Oncol*. 2024;19(1):130-140.
43. Liu S, Wang R, Zhang Y, et al. Precise diagnosis of intraoperative frozen section is an effective method to guide resection strategy for peripheral small-sized lung adenocarcinoma. *J Clin Oncol*. 2016;34(4):307-313.
44. Yu Y, Jian H, Shen L, et al. Lymph node involvement influenced by lung adenocarcinoma subtypes in tumor size ≤3 cm disease: a study of 2268 cases. *Eur J Surg Oncol*. 2016;42(11):1714-1719.
45. Kozower BD, Larner JM, Detterbeck FC, et al. Special treatment issues in 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(suppl 5):e369S-e399S.
46. Benzaquen J, Bondiau PY, Otto J, et al. Comparison of outcome after stereotactic ablative radiotherapy of patients with metachronous lung versus primary lung cancer. *Radiat Oncol*. 2023;18(1):97.
47. Dong B, Chen R, Zhu X, et al. Comparison of stereotactic body radiation therapy versus surgery for multiple primary lung cancers after prior radical resection: a multicenter retrospective study. *Clin Transl Radiat Oncol*. 2023;40:100601.
48. Lim E, Batchelor TJP, Dunning J, et al. Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer. *NEJM Evid*. 2022;1(3):EVIDoa2100016.
49. Bendixen M, Jorgensen OD, Kronborg C, et al. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol*. 2016;17(6):836-844.
50. Zhou Q, Huang J, Pan F, et al. Operative outcomes and long-term survival of robotic-assisted segmentectomy for stage IA lung cancer compared with video-assisted thoracoscopic segmentectomy. *Transl Lung Cancer Res*. 2020;9(2):306-315.
51. Ma J, Li X, Zhao S, et al. Robot-assisted thoracic surgery versus video-assisted thoracic surgery for lung lobectomy or segmentectomy in patients with non-small cell lung cancer: a meta-analysis. *BMC Cancer*. 2021;21(1):498.
52. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer*. 2005;49(1):25-33.
53. Dingemans AM, Remon J, Hendriks L, et al. OA06.05 Consensual definition of stage III NSCLC resectability: EORTC-Lung Cancer Group initiative with other scientific societies. *J Thorac Oncol*. 2023;18(11):S57-S58.
54. Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project for lung cancer: proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2024;19(5):766-785.
55. Provencio M, Awad MM, Spicer J, et al. Clinical outcomes with perioperative nivolumab (NIVO) by nodal status among patients (pts) with stage III resectable NSCLC: results from the phase 3 CheckMate 77T study. *J Clin Oncol*. 2024;42(suppl 17):LBA8007.
56. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol*. 2019;20(4):494-503.
57. Nyman J, Hallqvist A, Lund JA, et al. SPACE - a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol*. 2016;121(1):1-8.
58. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637.
59. Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol*. 2021;22(10):1448-1457.
60. De Ruysscher D, Faivre-Finn C, Moeller D, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol*. 2017;124(1):1-10.
61. Afshari S, Anker CJ, Kooperkamp HZ, et al. Trends and outcomes of salvage lobectomy for early-stage non-small cell lung cancer. *Am J Clin Oncol*. 2023;46(6):271-275.
62. Le Pechoux C, Pourel N, Barlesi F, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (lung ART): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(1):104-114.
63. Hui Z, Men Y, Hu C, et al. Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-C randomized clinical trial. *JAMA Oncol*. 2021;7(8):1178-1185.
64. Wang EH, Corso CD, Rutter CE, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer. *J Clin Oncol*. 2015;33(25):2727-2734.
65. Francis S, Orton A, Stoddard G, et al. Sequencing of postoperative radiotherapy and chemotherapy for locally advanced or incompletely resected non-small-cell lung cancer. *J Clin Oncol*. 2018;36(4):333-341.
66. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10(7):990-1003.
67. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med*. 2023;389(18):1672-1684.
68. Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med*. 2023;389(6):491-503.
69. Cascone T, Awad MM, Spicer JD, et al. Perioperative nivolumab in resectable lung cancer. *N Engl J Med*. 2024;390(19):1756-1769.
70. Felip E, Wakelee HA, Vallieres E, et al. OA01.04 IMpower010 5-y subgroup analysis and relapse patterns: phase 3 study of atezolizumab vs BSC in stage II-IIIA NSCLC. *J Thorac Oncol*. 2024;19(suppl 10):S8-S9.
71. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. 2022;23(10):1274-1286.
72. Goss G, Darling GE, Westeel V, et al. LBA48 CCTG BR.31: a global, double-blind placebo-controlled, randomized phase III study of adjuvant durvalumab in completely resected non-small cell lung cancer (NSCLC). *Ann Oncol*. 2024;35(suppl 2):S1238.
73. Spicer J, Girard N, Provencio M, et al. Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. *J Clin Oncol*. 2024;42(suppl 17):LBA8010.
74. 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.
75. 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.

76. Kreuter M, Vansteenkiste J, Fischer JR, et al. Three-year follow-up of a randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine (the TREAT study). *J Thorac Oncol*. 2016;11(1):85-93.
77. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003;21(16):3016-3024.
78. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26(31):5043-5051.
79. Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline. *J Clin Oncol*. 2007;25(34):5506-5518.
80. Shen ZQ, Feng KP, Fang ZY, et al. Influence of adjuvant chemotherapy on survival for patients with completely resected high-risk stage IB NSCLC. *J Cardiothorac Surg*. 2024;19(1):1.
81. 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.
82. Felip E, Altorki N, Zhou C, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol*. 2023;34(10):907-919.
83. Wakelee HA, Altorki NK, Zhou C, et al. IMpower010: final disease-free survival (DFS) and second overall survival (OS) interim results after $\geq$5 years of follow up of a phase III study of adjuvant atezolizumab vs best supportive care in resected stage IB-IIIA non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2024;42(suppl 17):LBA8035.
84. Wu Y, John T, Grohe C, et al. OA06.04 Postoperative chemotherapy use and outcomes from ADAURA: osimertinib as adjuvant therapy for resected EGFR mutated NSCLC. *J Thorac Oncol*. 2021;16(3):S113-S114.
85. He J, Tsuboi M, Weder W, et al. Neoadjuvant osimertinib for resectable EGFR-mutated non-small cell lung cancer. *J Clin Oncol*. 2025;43(26):2875-2887.
86. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. 2014;383(9928):1561-1571.
87. Spicer JD, Gao S, Liberman M, et al. LBA56 Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2023;34(suppl 2):S1297-S1298.
88. Forde PM, Spicer JD, Provencio M, et al. Overall survival with neoadjuvant nivolumab plus chemotherapy in lung cancer. *N Engl J Med*. 2025;393(8):741-752.
89. Spicer JD, Garassino MC, Wakelee H, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;404(10459):1240-1252.
90. Heymach JV, Harpole D, Mitsudomi T, et al. OA13.03 Perioperative durvalumab for resectable NSCLC (R-NSCLC): updated outcomes from the phase 3 AEGEAN trial. *J Thorac Oncol*. 2024;19(10):S38-S39.
91. Provencio Pulla M, Awad M, Cascone T, et al. LBA50 Perioperative nivolumab (NIVO) v placebo (PBO) in patients (pts) with resectable NSCLC: clinical update from the phase III CheckMate 77T study. *Ann Oncol*. 2024;35(suppl 2):S1239-S1240.
92. Yue D, Wang W, Liu H, et al. Perioperative tislelizumab plus neoadjuvant chemotherapy for patients with resectable non-small-cell lung cancer (RATIONALE-315): an interim analysis of a randomised clinical trial. *Lancet Respir Med*. 2025;13(2):119-129.
93. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28(13):2181-2190.
94. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-386.
95. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol*. 2015;33(35):4194-4201.
96. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2016;34(9):953-962.
97. Vokes EE, Herndon JE 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol*. 2007;25(13):1698-1704.
98. Tsujino K, Kurata T, Yamamoto S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. *J Thorac Oncol*. 2013;8(9):1181-1189.
99. Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG Oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J Clin Oncol*. 2020;38(7):706-714.
100. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-1929.
101. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.
102. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40(12):1301-1311.
103. Peters S, Dafni U, Boyer M, et al. Position of a panel of international lung cancer experts on the approval decision for use of durvalumab in stage III non-small-cell lung cancer (NSCLC) by the Committee for Medicinal Products for Human Use (CHMP). *Ann Oncol*. 2019;30(2):161-165.
104. Bradley JD, Sugawara S, Lee KHH, et al. LBA1 Durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: final results from PACIFIC-2. *Ann Oncol*. 2024;9(suppl 3):1-12.
105. De Ruysscher D, Ramalingam S, Urbanic J, et al. CheckMate 73L: a phase 3 study comparing nivolumab plus concurrent chemoradiotherapy followed by nivolumab with or without ipilimumab versus concurrent chemoradiotherapy followed by durvalumab for previously untreated, locally advanced stage III non-small-cell lung cancer. *Clin Lung Cancer*. 2022;23(3):e264-e268.
106. Naidoo J, Antonia S, Wu YL, et al. Brief Report: Durvalumab after chemoradiotherapy in unresectable stage III EGFR-mutant NSCLC: a post hoc subgroup analysis from PACIFIC. *J Thorac Oncol*. 2023;18(5):657-663.
107. Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol*. 2019;30(5):839-844.
108. Passaro A, Leighl N, Blackhall F, et al. ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer. *Ann Oncol*. 2022;33(5):466-487.

109. De Ruysscher D, Faivre-Finn C, Nackaerts K, et al. Recommendation for supportive care in patients receiving concurrent chemotherapy and radiotherapy for lung cancer. *Ann Oncol*. 2020;31(1):41-49.
110. Garassino MC, Mazieres J, Reck M, et al. Durvalumab after sequential chemoradiotherapy in stage III, unresectable NSCLC: the phase 2 PACIFIC-6 trial. *J Thorac Oncol*. 2022;17(12):1415-1427.
111. Zhou Q, Chen M, Jiang O, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2022;23(2):209-219.
112. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902.
113. Cherny NI, Oosting SF, Dafni U, et al. ESMO-Magnitude of Clinical Benefit Scale version 2.0 (ESMO-MCBS v2.0). *Ann Oncol*. 2025;36(8):866-908.
114. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144 [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18(3):421].