ASCO special articles

Management of Stage III Non–Small-Cell Lung Cancer: ASCO Guideline

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abstract

PURPOSE To provide evidence-based recommendations to practicing clinicians on management of patients with stage III non–small-cell lung cancer (NSCLC).

METHODS An Expert Panel of medical oncology, thoracic surgery, radiation oncology, pulmonary oncology, community oncology, research methodology, and advocacy experts was convened to conduct a literature search, which included systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Outcomes of interest included survival, disease-free or recurrence-free survival, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 127 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations were developed to address evaluation and staging workup of patients with suspected stage III NSCLC, surgical management, neoadjuvant and adjuvant approaches, and management of patients with unresectable stage III NSCLC.

Additional information is available at www.asco.org/thoracic-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The purpose of this guideline is to help clinicians involved in the diagnosis and treatment of lung cancer accurately confirm the presence of stage III non–small-cell lung cancer (NSCLC) and offer the most appropriate treatments. We review clinical and radiographic characteristics and other medical factors that influence treatment decision-making (including but not limited to performance status and the presence or absence of comorbid illnesses). Stage III NSCLC represents one of the most heterogenous subgroups of lung cancer. Consequently, it is also the subgroup in which the choice of multimodality treatment and sequence of multimodality treatment varies significantly among clinicians, with variations being observed across institutes and within an institute. This guideline reviews the published evidence addressing diagnosis and management of stage III NSCLC and provides evidence-based guidance on the common clinical dilemmas that clinicians may have while evaluating a patient with suspected or known stage III NSCLC.

GUIDELINE QUESTIONS

This clinical practice guideline addresses five overarching clinical questions: (1) What is the appropriate evaluation and staging workup for patients with suspected stage III NSCLC? (2) Which patients with stage III NSCLC may be considered for surgical resection? (3) Which patients with potentially resectable stage III NSCLC should be considered for neoadjuvant therapy? (4) Which patients with resected stage III NSCLC should be considered for adjuvant therapy? (5) What is the appropriate management for patients with unresectable stage III NSCLC?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel included representatives from the American College of

THE BOTTOM LINE

Management of Stage III Non–Small-Cell Lung Cancer: ASCO Guideline

Guideline Questions

1. What is the appropriate evaluation and staging workup for patients with suspected stage III non–small-cell lung cancer (NSCLC)?
2. Which patients with stage III NSCLC may be considered for surgical resection?
3. Which patients with potentially resectable stage III NSCLC should be considered for neoadjuvant therapy?
4. Which patients with resected stage III NSCLC should be considered for adjuvant therapy?
5. What is the appropriate management for patients with unresectable stage III NSCLC?

Target Population

Patients with stage III NSCLC.

Target Audience

Medical oncologists, radiation oncologists, thoracic surgeons, pulmonologists, pathologists, radiologists, primary care physicians, nurse practitioners, physician assistants, pharmacists, nurses, and other providers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

Evaluation and staging.

Recommendation 1.1. For patients with suspected stage III NSCLC, an evaluation to exclude metastatic disease should include, at a minimum: history and physical exam and computed tomography (CT) scan of chest and upper abdomen (with contrast, unless contraindicated) (Type: Informal consensus; benefit outweighs harm; Evidence quality: low; Strength of recommendation: strong).

Clinical interpretation. Any suspected metastatic site identified on CT should be confirmed pathologically with biopsy. In general, biopsy sites should be selected to confirm highest possible disease stage and to maximize tissue yield.

Recommendation 1.2. Following evaluation with CT scan as per Recommendation 1.1, fluorodeoxyglucose positron emission tomography with CT scan and brain imaging should be performed (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.3. For patients with suspected stage III NSCLC, who are candidates for curative-intent treatment, mediastinal lymph node status should be confirmed by pathologic assessment (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 1.4. For patients who require pathologic assessment of lymph node status, endoscopic techniques should be offered as the initial staging modality (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 1.5. For patients who require pathologic assessment of lymph node status but for whom endoscopic staging is either unavailable or inconclusive, surgical confirmation of mediastinal stage should be performed (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 1.6. For patients who have suspected or confirmed stage III NSCLC, multidisciplinary discussion should occur prior to the initiation of any treatment plan (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Good practice point. Biopsy should generally be performed from the site that would establish the highest stage when feasible. Potential tissue yield for pathologic analysis and molecular sequencing should also be considered.

Surgery.

Recommendation 2.1. For patients with stage IIIA (N2) NSCLC, induction therapy followed by surgery (with or without adjuvant therapy) may be offered if all of the following conditions are met: (1) A complete resection (R0) of the primary tumor and involved lymph nodes is deemed possible; (2) N3 lymph nodes are deemed to be not involved by multidisciplinary consensus; (3) Perioperative (90-day) mortality is expected to be low ($\leq$ 5%) (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak).

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Recommendation 2.2. For selected patients with T4N0 disease (by size or extension), surgical resection may be offered if medically and surgically feasible following multidisciplinary review (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: weak).

Good practice points.

- Patients with stage III NSCLC generally should not be excluded from consideration for surgery by nonsurgical physicians.
- Presence of oncogenic driver alterations, available therapies, and patient characteristics should be taken into account.
- Patients and providers should consider enrollment on clinical trials when appropriate.

Neoadjuvant therapy.

Recommendation 3.1. Patients who are planned for a multimodality approach incorporating surgery as defined in Recommendation 2.1 should receive systemic neoadjuvant therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 3.2. Patients with N2 disease who are planned for surgical resection should receive neoadjuvant chemotherapy or neoadjuvant concurrent chemoradiation (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.3. For patients with resectable superior sulcus disease, neoadjuvant concurrent chemoradiation should be administered (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Adjuvant therapy.

Recommendation 4.1. Patients with resected stage III NSCLC who did not receive neoadjuvant systemic therapy should be offered adjuvant platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.2. Patients with resected stage III NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 4.3. For patients with completely resected NSCLC with mediastinal N2 involvement without extracapsular extension who have received neoadjuvant or adjuvant platinum-based chemotherapy, postoperative radiation therapy should not be routinely offered (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak).

Unresectable disease.

Recommendation 5.1. Patients with stage III NSCLC who are medically or surgically inoperable and with good performance status should be offered concurrent instead of sequential chemotherapy and radiation therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.2. Concurrent chemotherapy delivered with radiation therapy for definitive treatment of stage III NSCLC should include a platinum-based doublet, preferably cisplatin plus etoposide, carboplatin plus paclitaxel, cisplatin plus pemetrexed (non-squamous only), or cisplatin plus vinorelbine (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statement: Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin.

Recommendation 5.3. Patients with stage III NSCLC who are not candidates for concurrent chemoradiation but are candidates for chemotherapy should be offered sequential chemotherapy and radiation therapy over radiation alone (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.4. Patients with stage III NSCLC receiving concurrent chemoradiation should be treated to 60 Gy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.5. Doses higher than 60 Gy and up to 70 Gy may be considered for selected patients, with careful attention to doses to heart, lungs, and esophagus (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Recommendation 5.6. Patients with stage III NSCLC receiving definitive radiation without chemotherapy in standard fractionation may be considered for radiation dose escalation and for modest hypofractionation from 2.15 to 4 Gy per fraction (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: weak).

Recommendation 5.7. Patients with stage III NSCLC receiving concurrent chemoradiation without disease progression during the initial therapy should be offered consolidation durvalumab for up to 12 months (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statement: There is insufficient evidence to alter the recommendation for consolidation durvalumab following concurrent chemoradiation for molecularly defined subgroups (namely, patients with an oncogenic driver alteration or those with low or no expression of programmed death-ligand 1).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Chest Physicians and the American Society for Radiation Oncology. The Panel met via webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of two weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, and the guideline was submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC) before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review (SR) of evidence identified through online searches of PubMed (January 1990-August 2021) and Cochrane Library (January 2010-August 2021) of SRs and phase II and III randomized clinical trials (RCTs). Articles were selected for inclusion in the SR on the basis of the following criteria:

- Population: patients with stage III non–small-cell lung cancer (NSCLC)
- Interventions of interest: imaging studies {chest computed tomography (CT), fluorodeoxyglucose (FDG) positron emission tomography (PET)–CT, brain magnetic resonance imaging (MRI), head CT, and endoscopic staging (endobronchial ultrasound [EBUS] or esophageal ultrasound [EUS])}, mediastinoscopy, surgical interventions (eg, lobectomy and pneumonectomy), systemic therapy, radiotherapy, and multimodality treatment.
- Study designs: SRs, meta-analyses (MAs), phase III RCTs, and phase II RCTs for some specific research questions.

Articles were excluded from the SR if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; (3) published in a non-English language; (4) studies on small-cell lung cancer; and (5) studies that include patients with metastatic disease. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support methodology and accompanying BRIDGE-Wiz software.[1] In addition, a guideline implementability review was conducted. On the basis of the review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for type, strength of the recommendation, and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[2,3] GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the

guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 1,638 articles were identified in the literature search. After applying the eligibility criteria, 127 remained, forming the evidentiary basis for the guideline recommendations. These include 23 SRs and MAs,[4-26] two pooled analyses,[27,28] 91 RCTs (six studies with multiple publications),[29-50,51-75,76-95,96-127] and 4 phase II studies.[128-131]

The identified trials were published between January 1990 and August 2021. The studies included topics on imaging for evaluation and staging workup for patients, radiation therapy, surgery, and systemic therapies. The primary outcome of these studies includes overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), detection of stage IV disease or N3 disease, downstaging, upstaging, detection of brain metastasis, and perioperative morbidity or mortality. Characteristics of the studies' participants and study outcomes are given in the Data Supplement (online only). The SR flow diagram is shown in Figure 1.

Study Quality Assessment

Study quality was formally assessed for the RCTs identified. Design aspects related to the individual study quality were assessed by the research methodologist, with factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources, generally indicating an unclear (58%) to high (35%) overall risk of bias assessment for most of the identified evidence. Details of the assessment can be found in Figure 2 and in the Data Supplement. Refer to the Methodology Manual for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

Clinical Question 1

What is the appropriate evaluation and staging workup for patients with suspected stage III NSCLC?

Recommendation 1.1. For patients with suspected stage III NSCLC, an evaluation to exclude metastatic disease should include, at a minimum: history and physical exam and CT scan of chest and upper abdomen (with contrast, unless contraindicated) (Type: Informal consensus; benefit

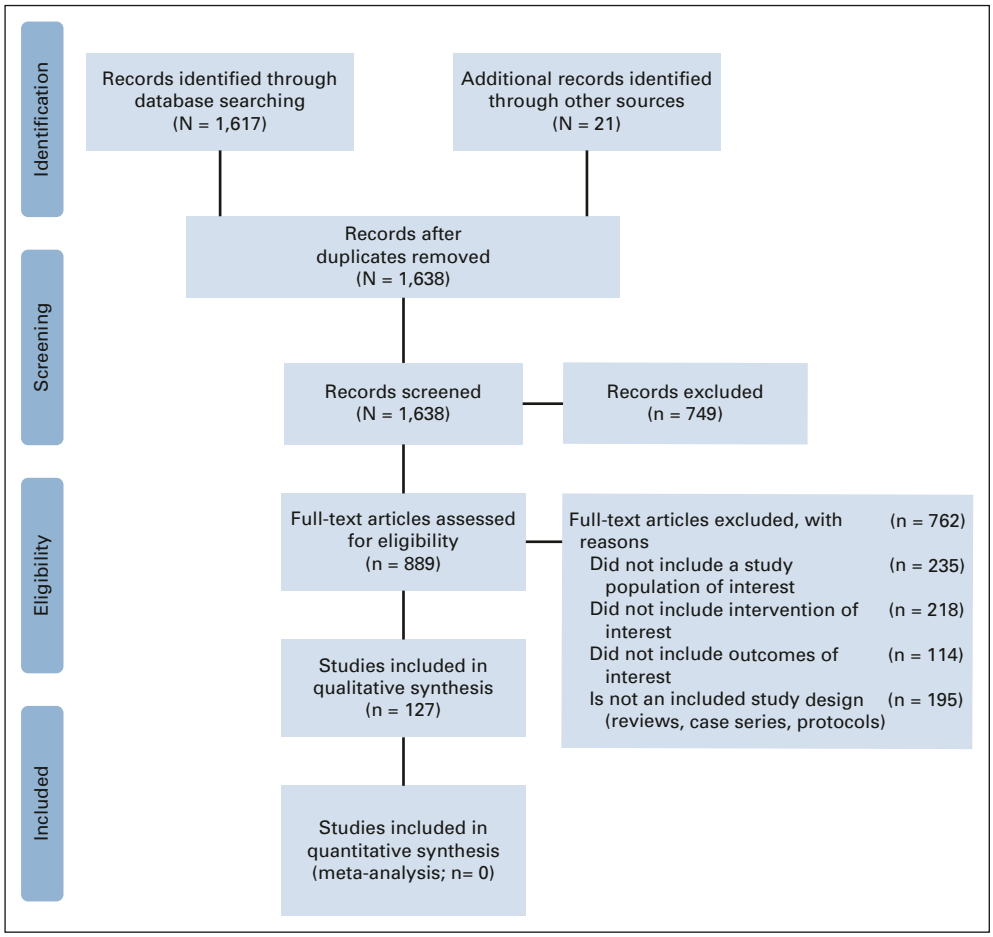

FIG 1. PRISMA flow diagram.

outweighs harm; Evidence quality: low; Strength of recommendation: strong).

Clinical interpretation. Any suspected metastatic site identified on CT should be confirmed pathologically with biopsy. In general, biopsy sites should be selected to confirm highest possible disease stage and to maximize tissue yield.

Literature review and clinical interpretation. Although there are no randomized controlled trials directly supporting this recommendation, the authors emphasize the importance of accurate staging when considering a treatment plan for patients with suspected stage III lung cancer. Evidence of metastasis, if present on history, physical examination, routine cross-sectional imaging (CT scan of the chest and upper abdomen), or FDG PET-CT scan, should prompt efforts to unequivocally confirm the stage with tissue biopsy if technically feasible, especially for suspected oligometastatic disease.

Studies examining the detection of occult metastases demonstrate that patients with clinical stage III disease and a negative clinical examination (defined here as history, physical examination, and CT imaging) have a clinically meaningful rate of detection of metastases on PET or PET-CT scan. For example, studies have demonstrated that 17%-24% of patients with clinical stage III lung cancer had unexpected stage IV disease detected by FDG-PET scan.[132]

Recommendation 1.2. Following evaluation with CT as per Recommendation 1.1, FDG PET–CT scan and brain imaging should be performed (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. A MA of 56 studies including 8,699 patients demonstrated improved detection of occult metastasis with the use of integrated PET-CT scan compared with clinical staging without PET scan.[133] PET-CT scan, however, is not adequate to exclude CNS metastases, given the high obligate utilization of glucose by the brain. Studies of CNS imaging in asymptomatic patients with stage III lung cancer find a wide range (2%-21%) of patients with clinically occult CNS metastases.[134-136] Dedicated brain imaging, preferably with contrast-enhanced MRI scan (a contrast-enhanced head CT scan may be substituted if MRI is contraindicated) is, therefore, necessary to exclude clinically silent CNS metastases in patients with clinical stage III lung cancer.

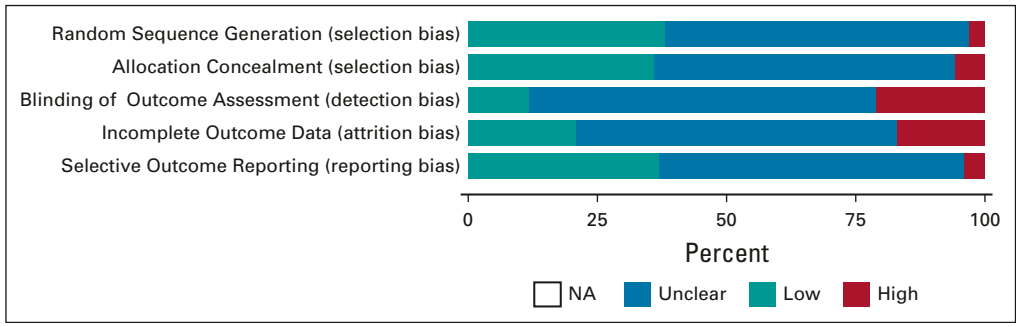

FIG 2. Risk of bias bar graph. NA, not available.

Recommendation 1.3. For patients with suspected stage III NSCLC, who are candidates for curative-intent treatment, mediastinal lymph node status should be confirmed by pathologic assessment (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. The accuracy of imaging alone (CT or integrated PET-CT scan) is inadequate for confidently staging the mediastinum for most situations. A 2003 MA of 39 studies by Gould et al[7] demonstrated point estimates from a pooled sensitivity of 0.61 (95% CI, 0.50 to 0.71) and a specificity of 0.79 (95% CI, 0.66 to 0.89) for CT scan alone. The same authors examined metabolic imaging with PET-CT scan and found a sensitivity of 0.85 (95% CI, 0.67 to 0.91) and a specificity of 0.90 (95% CI, 0.82 to 0.96).[7] A 2014 Cochrane Review of the evidence for PET-CT–based staging of mediastinal nodes included 45 studies using different criteria to define a positive scan. The analysis showed point estimates of sensitivity and specificity of 81.3% (95% CI, 70.2 to 88.9) and 79.4% (95% CI, 70 to 86.5), respectively, using maximum standardized uptake values ≥ 2.5 on PET-CT as the criterion. The same Cochrane review found that studies defining a positive node on PET-CT scan as standardized uptake value greater than mediastinal background had similar sensitivity (77.4%; 95% CI, 65.3 to 86.1) and slightly higher specificity (90.1%; 95% CI, 85.3 to 93.5), but still too low to substitute for pathologic confirmation. This study also found very high between-study heterogeneity and wide 95% CIs around point estimates of sensitivity and specificity.[137] This inaccuracy dictates that mediastinal node metastasis, even for nodes with increased FDG activity on imaging, must be confirmed pathologically whenever feasible and that this is particularly important when the pretest probability of N2 nodal involvement is intermediate.

Recommendation 1.4. For patients who require pathologic assessment of lymph node status, endoscopic techniques should be offered as the initial staging modality (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 1.5. For patients who require pathologic assessment of lymph node status but for whom endoscopic staging is either unavailable or inconclusive, surgical confirmation of mediastinal stage should be performed (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. When pathologic confirmation of mediastinal stage is indicated, the choice of invasive staging should be based on the accuracy of the technique used, the availability of timely access to accurate staging, the cost(s), safety, and availability of experienced clinicians to perform the procedure. Pooled point estimates of the sensitivity of EBUS (0.81; 95% CI, 0.75 to 0.86) compared with mediastinoscopy (0.81; 95% CI, 0.75 to 0.86) for diagnosing mediastinal lymph node involvement in patients with potentially operable NSCLC suggest that the two approaches are equivalent. The specificity of both methods is similar.[4] A 2019 MA found that patients with clinical N0 or N1 disease by imaging have a prevalence of N2 nodal disease of 0.15 (95% CI, 0.06 to 0.24) and that the mean negative predictive value for EBUS in these patients is 91% (95% CI, 82 to 100).[5] This and other studies conclude that the rate of detection of N2 or N3 disease may be meaningfully increased when EUS is added to EBUS, such that the number of patients needed to undergo endoscopic staging to detect occult N2 or N3 involvement is 14 (95% CI, 10.8 to 16.3) when performing EBUS alone and decreases to approximately seven when also performing EUS.[5,6] A small prospective randomized trial did not find any additive value of performing EUS in patients who first underwent EBUS.[29] Randomized trials[30,138] and aggregate data from these MAs demonstrate that endoscopic-based staging is at least equivalent to mediastinoscopy and is more cost-effective,[139,140] at least when used as the first staging modality. A 2017 decision analysis suggests that the cost-effectiveness of EBUS-based mediastinal staging varies by the pretest probability of N2 disease with mediastinal staging not cost-effective in clinical N0 patients if the probability of N2 involvement is very low (< 2.5%). In patients with a probability of mediastinal metastasis from 2.5% to 57%, EBUS-transbronchial fine needle aspiration was considered cost-effective (using

the threshold of $80,000 US dollars per quality adjusted life year) as the only staging modality. The same study suggested that confirmatory mediastinoscopy is cost-effective when the risk of N2 metastases was > 57% after a negative or nondiagnostic EBUS-transbronchial fine needle aspiration.[141] A useful model (Help with Oncologic Mediastinal Evaluation for Radiation; HOMER) has been published online for predicting the probability of nodal metastasis.[142,143]

Recommendation 1.6. For patients who have suspected or confirmed stage III NSCLC, multidisciplinary discussion should occur prior to the initiation of any treatment plan (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. Direct comparisons of treatment outcomes for patients with stage III NSCLC with and without multidisciplinary team care have not been performed. However, a study using propensity score matching of patients taken from a national (Taiwan) cancer registry suggests the advantage of treatment in the context of a multidisciplinary team. Outcomes in patients with stage III and IV NSCLC treated with multidisciplinary care were significantly better than those in patients treated outside the context of a multidisciplinary team (adjusted hazard ratio [HR] for mortality = 0.87; 95% CI, 0.84 to 0.90).[144] A study from a single center found that adherence to multidisciplinary recommendations was associated with improved overall and PFS compared with patients for whom care deviated from those recommendations.[145] Given the complexity, and heterogeneity of patients with stage III lung cancer, and the varying impact of comorbidities on suitability for systemic chemotherapy, thoracic radiation, and lung resection, the authors of this guideline emphasize the importance of the input of a multidisciplinary team, consisting of at least a medical oncologist, a radiation oncologist, and a thoracic surgeon, all of whom devote a significant portion of their clinical care to thoracic oncology. Outside of emergent, life-threatening situations, this discussion should take place before initiating any plan of treatment to allow for the coordination and proper timing of multimodality treatment.

Good practice point. Biopsy should generally be performed from the site that would establish the highest stage when feasible. Potential tissue yield for pathologic analysis and molecular sequencing should also be considered.

Clinical Question 2

Which patients with stage III NSCLC may be considered for surgical resection?

Recommendation 2.1. For patients with stage IIIA (N2) NSCLC, induction therapy followed by surgery (with or without adjuvant therapy) may be offered if all of the following conditions are met: (1) A complete resection (R0) of the primary tumor and involved lymph nodes is deemed possible; (2) N3 lymph nodes are deemed to be not involved by multidisciplinary consensus; (3) Perioperative (90-day) mortality is expected to be low (≤ 5%) (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak).

Literature review and clinical interpretation. Curative-intent treatment involves multimodal treatment; surgery, radiation, or systemic therapy alone is not optimal. Both chemoradiotherapy without surgery and chemotherapy (with or without radiation) with surgery are treatment options. RCTs comparing multimodal treatment with or without surgery have demonstrated equivalent OS (ie, for overlapping CI, see evidence in Table 1).[31,33,35,147] This result has been consistent among the RCTs although the trials involved differences in treatment regimens and inclusion criteria (Table 2). Three of these trials accrued patients primarily from 1990 to 2000, whereas the other two primarily accrued from 2000 to 2010.[31,147] Surgical multimodality treatment was compared against definitive concurrent chemoradiotherapy in two trials and against sequential chemotherapy and then radiotherapy in the other three trials. Some trials permitted patients with bulky mediastinal involvement or unresectable disease; some trials randomly assigned patients only after assessment of response to induction therapy.

Although avoiding surgery if not proven to be beneficial is a reasonable recommendation, there are factors that justify consideration of surgery in a multimodality approach. Currently, surgery for NSCLC, even with stage III disease, in most experienced centers primarily involves minimally invasive approaches. Although not significant, the HR for OS generally favors the surgery arms in the RCTs (with one exception)[33] and one of the five RCTs demonstrated a statistically significantly better PFS.[32] Patient preferences are also an important consideration.

Given the evidence, it is reasonable to ask whether there are specific patient or tumor characteristics that would favor definitive chemoradiotherapy or a multimodality approach including surgery. It is important to note that there are no data from RCTs that clearly establish the superiority of one or the other approach in any specific subgroup. Thus, selection of the approach is based on extrapolation of data and expert consensus.

As a first step, evaluate for factors that argue against surgery. This includes the inability to achieve a complete resection, as an incomplete resection does not improve outcomes relative to no resection at all. This also includes the presence of N3 node involvement, as surgery generally does not include removal of contralateral or supraclavicular nodes, resulting in an incomplete resection. Finally, this may include extensive mediastinal involvement (ie, that obscures identification of discrete nodes and American College of Chest Physicians type D N2,3 involvement).[148]

A high perioperative mortality can offset any potential long-term survival advantage to a surgical multimodality

TABLE 1. Evidence Table Regarding Multimodality Treatment With or Without Surgery for Stage III NSCLC

Patient or population: Patients with stage III NSCLC
Setting: Outpatient
Intervention: Induction/Concurrent CRT + Surgery
Comparison: Definitive RT or CRT

	Anticipated Absolute Effects[a] (95% CI)					
Outcomes	Risk With Definitive RT or CRT	Risk With Induction CRT + Surgery	Relative Effect (95% CI)	No. of Participants (studies)	Certainty of the Evidence (GRADE)	Comments
OS	320 per 1,000	298 per 1,000 (271 to 330)	HR 0.92 (0.82 to 1.04)	1,322 (six RCTs) Meta-analysis	Low[b,c,d]	Meta-analysis did not find a significant difference in OS in patients with locally advanced NSCLC after induction treatment and surgery compared with definitive CRT[8]
OS follow up: mean 22.5 months	325 per 1,000	289 per 1,000 (240 to 351)	HR 0.87 (0.70 to 1.10)	396 (one RCT)	Low[b,e]	There was no significant survival advantage to surgery after CRT despite improved PFS[32]
OS follow-up: median 78 months	175 per 1,000	144 per 1,000 (97 to 214)	HR 0.81 (0.53 to 1.25)	161 (one RCT)	Low[b,f]	The evidence suggests that induction CRT + surgery results in little to no difference in OS[31]
OS follow-up: median 6 years	303 per 1,000	318 per 1,000 (264 to 377)	HR 1.06 (0.85 to 1.31)	332 (one RCT)	Low[b,g]	Surgery did not improve OS or PFS compared with radiotherapy[33]
OS	344 per 1,000	289 per 1,000 (57 to 856)	HR 0.81 (0.14 to 4.60)	61 (one RCT)	Low[h]	The evidence suggests that induction CRT + surgery results in little to no difference in OS[35]
OS	392 per 1,000	351 per 1,000 (290 to 418)	HR 0.87 (0.69 to 1.09)	341 (one RCT)	Low[h,i]	Induction CRT + surgery may result in little to no difference in OS[146]

NOTE. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CRT, chemoradiotherapy; CT, computed tomography; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; HR, hazard ratio; NSCLC, non–small-cell lung cancer; OS, overall survival; PET, positron emission tomography; PFS; progression-free survival; RCT, randomized clinical trial; RT, radiotherapy.

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Study stopped early because of slow accrual of study participants, and hence, the study was underpowered.

[c]These studies cover treatment periods through two decades (1990s until 2012) and reflect the differences of diagnostic investigations (CT, PET, and PET-CT) and treatment over time with a variety of combinations of first-, second- and third-generation drugs and the change from older radiation techniques toward three-dimensional conformal radiation therapy.

[d]Broad heterogeneity of patient groups.

[e]High risk of bias because allocation to the two arms was unconcealed and fewer patients in the surgical group received consolidation chemotherapy. Blinding procedures were not reported.

[f]Blinding procedures were not reported.

[g]Patient selection might have been affected by changing standards for tumor staging during trial accrual. Outcome might have been affected by changing treatment standards during the trial.

[h]Trial was stopped early because of evolving evidence for superiority of concurrent CRT.

[i]Results are from a published abstract, and hence, random assignment methodology could not be adequately assessed.

approach. This was demonstrated in a retrospective matching analysis of the Intergroup 0139 study, which compared neoadjuvant chemoradiation followed by surgery versus definitive chemoradiation.[32] This study had high perioperative mortality after pneumonectomy (26%) compared with lobectomy (1%). Matching features of patients in the nonsurgical arm to those in the surgical arm (ie, those who underwent pneumonectomy or lobectomy) demonstrated that the high perioperative mortality in the pneumonectomy arm resulted in persistently worse long-term OS in the surgical arm, whereas those patients who underwent lobectomy had better long-term OS in the surgical arm. It should be noted that perioperative mortality involves many factors besides the extent of resection (eg, open *v* video-assisted thoracoscopic surgery approach, pulmonary reserve, and comorbidities). Many series report

TABLE 2. Characteristics of Randomized Clinical Trials Involving Multimodality Treatment With or Without Surgery for Stage III Non–Small-Cell Lung Cancer

First Author	Accrual Years	No.	% With N2	Mediastinal Tumor Burden	% Pneumonectomy	% Perioperative mortality	Induction Chemotherapy	Control Arm[a]	5-Year PFS (%)			5-Year OS (%)		
									Ind → S	ChRT	*P*	Ind → S	ChRT	*P*
Albain	94-01	396	100	24% multistation[b]	36	10	EP-RT	ChRT	22	11	.017	27	20	NS
Eberhardt	04-12	161[c]	67	33% T4N0,1 and 33% N3/T4N2	33	2	PVn-RT[d]	ChRT[d]	32	35	NS	44	40	NS
Van Meerbeeck	94-02	342[c]	100	All unresectable	59	4	P-based	Ch → RT	12	12	NS	16	14	NS
Johnstone	90-94	45	100	54% bulky	—	4	MVP	Ch → RT	—	—	—	22[e]	22[e]	NS
Sorensen	98-09	341	100	—	—	—	CbTx	Ch → RT	—	—	—	20	16	NS

Abbreviations: CbTx, carboplatin pacitaxel; Ch → RT, sequential chemo- and radiotherapy; ChRT, concurrent chemo- and radiotherapy; EP etoposide plus cisplatin; MVP, mitomycin C, vincristine, and cisplatin; NS, not significant; OS, overall survival (point estimate); P-based, cisplatin doublet; PFS, progression-free survival (point estimate); PVn, Cisplatin vinorelbine; RT, radiotherapy.

[a]Same chemotherapy regimen as in the surgical arm.

[b]Documentation of the status of a single node station was sufficient for enrollment; the true number with multistation involvement is likely higher.

[c]Only responders randomly assigned.

[d]Concurrent hyperfractionated (45 Gy induction, 60 Gy) in the definitive arm.

[e]4-year survival.

low perioperative mortality after neoadjuvant treatment and pneumonectomy (average 7% in a MA),[149] suggesting that pneumonectomy alone is not an adequate marker of a perioperative risk that overshadows any potential long-term benefit. Although arbitrary, we suggest that perioperative mortality above 5% would argue against a surgical multimodality treatment approach.

It is important to note that favorable prognostic factors (better outcomes regardless of treatment approach) should not be misinterpreted as predictive that the inclusion of surgery in the treatment approach is beneficial. Such prognostic factors include a low disease burden (primary tumor or extent of N2 involvement or both), young age, few comorbidities, and low PET activity. Similarly, treatment response to neoadjuvant therapy (tumor shrinkage, mediastinal downstaging, and decreased PET activity) is prognostic, but has not been demonstrated as predictive for improved outcomes with surgery.

The decision whether to include or exclude surgery as part of a multimodal treatment approach for patients with discrete N2 involvement should be made during a multidisciplinary discussion that includes a surgeon. This consensus reflects that the ability to achieve complete resection and the degree of perioperative risk are key factors; assessment of these requires surgical input. Tumors with overt mediastinal infiltration or clear N3 involvement may be reasonably excluded from surgery without surgical input.

Recommendation 2.2. For selected patients with T4N0 disease (by size or extension), surgical resection may be offered if medically and surgically feasible following multidisciplinary review (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: weak).

Literature review and clinical interpretation. T4N0 disease alone should not be viewed as a contraindication to the consideration of surgery.[150] Surgical feasibility and extent of resection must be considered when offering surgical resection. These decisions should be made by surgical physicians, rather than nonsurgical physicians. A review of surgical resection (with or without other modalities) demonstrates 5-year OS rates of approximately 30%.[151] Limited data suggest possible benefit for preoperative chemo- or chemoradiotherapy[152-154] On the other hand, in database studies of T4N0M0 tumors on the basis of size alone, the use of preoperative therapy was not associated with significantly better survival.[155] The best results for large T4N1M0 tumors appears to be resection and adjuvant chemotherapy.[156]

Good practice points.

- Patients with stage III NSCLC generally should not be excluded from consideration for surgery by nonsurgical physicians.
- Presence of oncogenic driver alterations, available therapies, and patient characteristics should be taken into account.
- Patients and providers should consider enrollment on clinical trials when appropriate.

Clinical Question 3

Which patients with potentially resectable stage III NSCLC should be considered for neoadjuvant therapy?

Recommendation 3.1. Patients who are planned for a multimodality approach incorporating surgery as defined in Recommendation 2.1 should receive systemic neoadjuvant therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. A MA in patients with resectable stage IB-IIIA NSCLC involving 15 randomized controlled trials demonstrated significantly improved OS, time to distant recurrence, and recurrence-free survival when preoperative chemotherapy was used compared with surgery alone.[157] This analysis included 2,385 patients and demonstrated a 13% reduction in the relative risk of death with the use of preoperative chemotherapy. There is no published randomized phase III trial in patients with stage III NSCLC comparing neoadjuvant versus adjuvant chemotherapy. The NATCH trial was conducted in earlier-stage disease (stages IA $>$ 2 cm to II) and demonstrated identical disease survival rates for neoadjuvant versus adjuvant chemotherapy.[158] Possible downsides of a neoadjuvant versus adjuvant chemotherapy approach are a delay in surgical resection because of early progression or toxicity. Benefits of neoadjuvant chemotherapy include a high compliance to systemic platinum-based treatment (90% *v* 61% in the NATCH trial[158]), reduction in tumor size with increased operability, early eradication or prevention of micrometastasis, and the opportunity to assess the efficacy of the neoadjuvant treatment. Multiple trials have demonstrated improved survival to be associated with nodal downstaging and pathologic complete response (CR) rates and R0 resection.[27,41]

Recommendation 3.2. Patients with N2 disease who are planned for surgical resection should receive neoadjuvant chemotherapy or neoadjuvant concurrent chemoradiation (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. A MA of three randomized controlled trials in stage IIIA N2 NSCLC indicated higher rates of mediastinal downstaging, pathologic CR of mediastinal lymph nodes, and higher rates of R0 resections with the addition of radiotherapy to neoadjuvant chemotherapy. However, induction chemoradiation did not improve overall or PFS rates as compared with chemotherapy alone.[11] In addition, a large randomized controlled trial, which included a considerable proportion of patients with stage IIIB

NSCLC (> 60%), did not also demonstrate improved survival with neoadjuvant chemoradiotherapy as compared with neoadjuvant chemotherapy despite improved pathologic response rates and mediastinal downstaging.[37,42]

Intergroup 0139 compared neoadjuvant chemoradiation with definitive chemoradiation in patients with operable stage IIIA N2 NSCLC and identified a benefit in PFS with surgery but no OS benefit. However, in an unplanned subgroup analysis, an OS benefit was observed in the subgroup of patients treated with lobectomy, suggesting that neoadjuvant chemoradiation followed by surgery may represent a possible treatment option for well-selected patients who could undergo a lobectomy. However, as no individual phase III trial has demonstrated a significant survival benefit using neoadjuvant chemoradiotherapy compared with neoadjuvant chemotherapy alone, neoadjuvant chemotherapy alone is the preferred treatment approach.[11]

Recommendation 3.3. For patients with resectable superior sulcus disease, neoadjuvant concurrent chemoradiation should be administered (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. Although local control in patients with locally advanced NSCLC has consistently been shown to correlate with OS,[18,159] local control is particularly important for superior sulcus tumors. Like for other patients with NSCLC, those with superior sulcus tumors who achieve local control have better survival than those who do not.[160] In addition, patients with superior sulcus tumors can uniquely present with brachial plexus invasion and Horner's syndrome, in addition to generalized edema, chest wall invasion, and shortness of breath,[161] making local control critically important. However, control of locoregional disease is the major challenge when treating superior sulcus lung cancers,[162] yet it remains challenging since these tumors have a predilection for early invasion into bone, vascular, and nervous structures at the apex of the chest.[163]

An attractive option for optimizing local control in the lung apex is the use of concurrent chemoradiation followed by surgery. Induction therapy for patients with superior sulcus tumors may have an effect on micrometastatic disease and can reduce tumor bulk and increase resectability, and the combination of two local modalities with radiotherapy and surgery can help to maximize local control.[164] This trimodality approach with chemoradiation followed by surgery has been demonstrated to achieve excellent local control and prolonged OS in this patient population.[165,166]

Intergroup 0160-SWOG 9416 assessed the use of two cycles of cisplatin and etoposide concurrently with radiation therapy (45 Gy in 1.8 Gy daily fractions) among 110 patients with T3-4, N0-1 superior sulcus NSCLC. Those with stable or responsive disease underwent resection, followed by two additional cycles of chemotherapy. In total, 88 patients underwent this trimodality approach, 83 of whom achieved a complete resection. Pathologic CR or minimal microscopic disease was achieved in 61 patients, with pathologic CR associated with improved OS ($P = .02$). The 5-year OS in patients who underwent this trimodality treatment was 54% after complete resection versus 44% for the whole cohort, and the median survival was 33 months for all eligible patients versus 94 months for patients who had an R0 resection.[153]

In SWOG S0220, 44 eligible patients with T3-4, N0-1 superior sulcus NSCLC underwent induction therapy with cisplatin-etoposide concurrently with thoracic radiotherapy to 45 Gy, followed by surgical resection in nonprogressing patients and then consolidation docetaxel for three cycles. Twenty-nine patients underwent surgery, with all but one undergoing an R0 resection and 21 achieving a pathologic CR or near CR to neoadjuvant chemoradiation. This trimodality regimen achieved excellent local control, with the isolated site of first recurrence local in only two patients, and the 3-year OS was 61%.[167]

Clinical Question 4

Which patients with resected stage III NSCLC should be considered for adjuvant therapy?

Recommendation 4.1. Patients with resected stage III NSCLC who did not receive neoadjuvant systemic therapy should be offered adjuvant platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. There have been multiple randomized controlled trials to evaluate the benefit of adjuvant chemotherapy after surgical resection; some compared different chemotherapy regimens or chemotherapy versus best supportive care. Most of these studies included stage I-III NSCLC, and inclusion criteria were based on older versions of the American Joint Committee on Cancer staging system. Therefore, data must be extrapolated to focus on stage III patients. Overall, the results have been mixed, with several studies showing a benefit to adjuvant chemotherapy,[56,57,59,61] whereas others show little or mixed survival benefit.[44,48,58,60] The ANITA study presented by Douillard et al[57] is one of the largest and most recent RCTs conducted in this setting in which adjuvant cisplatin-based chemotherapy was compared with best supportive care in patients with completely resected IB-IIIA NSCLC. This study showed a 5-year OS benefit of 8.6% with adjuvant chemotherapy. Another frequently cited RCT, the International Adjuvant Lung Cancer Trial (IALT) also showed a 5-year OS benefit with cisplatin-based adjuvant chemotherapy although the effect was more muted at 4%.[59] However, the Adjuvant Lung Project Italy (ALPI) study, a RCT conducted in Italy,[45] did not demonstrate an OS benefit with adjuvant chemotherapy (HR, 0.96; 95% CI, 0.81 to 1.13; $P = .589$). This difference may be explained by the toxicity of the chemotherapy regimen

used in ALPI (mitomycin, cisplatin, and vindesine) compared with what was used in ANITA (cisplatin and vinorelbine) and IALT (cisplatin doublets with etoposide, vinorelbine, vinblastine, or vindesine). Toxicity (both from the chemotherapy itself and the lack of optimal supportive care medications) likely played an important role in the negative results seen in other earlier trials.[58] A MA by the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group, which pooled and analyzed data from the five largest trials testing adjuvant cisplatin versus observation in surgically resected NSCLC, demonstrated a 5.4% 5-year improvement in OS, and this benefit was most pronounced in stage III patients (HR, 0.83; 95% CI, 0.72 to 0.94).[168]

Cisplatin also has significant toxicities including ototoxicity, nephrotoxicity, and neurotoxicity, which may limit its use, especially in older patients. Carboplatin-based adjuvant chemotherapy has also been evaluated. Notably, Ou et al[56] randomly assigned surgical patients with resected stage III NSCLC to adjuvant carboplatin-based chemotherapy or observation and found a statistically significant improvement in OS with adjuvant chemotherapy (33 months *v* 24 months, $P = .037$). Therefore, although the bulk of adjuvant studies used cisplatin-based chemotherapy, carboplatin-based chemotherapy is a reasonable alternative for patients with contraindications to cisplatin. Although direct comparisons have not been made, it is reasonable to infer that there is no benefit from triplet chemotherapy. Therefore, for patients with completely resected stage III NSCLC who did not receive neoadjuvant treatment, adjuvant platinum-doublet chemotherapy should be offered.

Recommendation 4.2. Patients with resected stage III NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy (Type: Evidence based; benefit outweighs harm; Evidence quality: moderate; Strength of recommendation: strong).

Literature review and clinical interpretation. The ADAURA trial evaluated 3 years of adjuvant osimertinib versus placebo in resected stage IB-IIIA NSCLC.[49] The primary end point of the study was DFS in patients with stage II-IIIA disease (unlike the OS end point in the adjuvant chemotherapy regimens discussed), which was shown to be significantly prolonged with the use of osimertinib, HR 0.17 ($P < .001$), with median DFS not reached in the osimertinib arm and 19.6 months in the placebo arm. In a subgroup analysis of patients with stage IIIA NSCLC, the DFS HR was 0.12 (95% CI, 0.07 to 0.20). OS data are still immature at the time of this guideline, and neither cure rate nor outcomes upon progression are yet known, but this approach is now approved by the US Food and Drug Administration (FDA) and should be discussed with eligible patients.

Although adjuvant chemotherapy was allowed on the ADAURA trial, it was not required before osimertinib initiation. Given the known OS benefit of chemotherapy in this population, the panel recommends adjuvant platinum chemotherapy for patients with chemotherapy eligible resected NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutations before consideration of osimertinib.

Recommendation 4.3. For patients with completely resected NSCLC with mediastinal N2 involvement without extracapsular extension who have received neoadjuvant or adjuvant platinum-based chemotherapy, postoperative radiation therapy should not be routinely offered (Type: Evidence based; balance of benefit and harm; Evidence quality: moderate; Strength of recommendation: weak).

Literature review and clinical interpretation. The use of postoperative radiotherapy (PORT) after resection of NSCLC has been controversial for several decades. Before the routine use of adjuvant platinum-based systemic therapy, PORT was evaluated as a means to reduce high rates of regional and distant failure after primary resection of NSCLC. Nine randomized trials conducted from 1966 to 1995 examined the utility of PORT compared with surgery alone and have been summarized in the PORT Meta-Analysis (930, 929, and 599). Overall, PORT was found to reduce local regional relapse (HR, 1.16; $P = .005$); however, OS was also *reduced* (5-year OS 58% *v* 53%, $P = .001$), driven by an increase in noncancer death in the PORT arm (18% *v* 11%) felt to stem from cardiopulmonary toxicity. This detriment seemed to be confined primarily to N0 and N1 disease, with a potential benefit for N2 disease. Notable criticisms of these trials relate to the time period that they were run, the use of outdated radiotherapy equipment and techniques, and larger doses and larger treatment volumes that are known to increase the risk of toxicity compared with modern radiotherapy. However, a subgroup analysis of a randomized trial and multiple population-based analyses in more modern eras have suggested that PORT may be associated with a survival benefit for patients with pN2 disease.[62,169,170]

To address the criticisms of the PORT Meta-Analysis and the conflicting more modern literature, the Lung ART study was initiated to explore the impact of modern PORT specifically in patients with completely resected N2 NSCLC receiving standard-of-care neoadjuvant or adjuvant cytotoxic chemotherapy and was recently reported at ESMO 2020.[171(abstr)] A total of 501 patients treated primarily in France (85%) and the United Kingdom (10%) were randomly assigned 1:1 to PORT (54 Gy over 5 weeks) or no PORT, stratified by center, administration of chemotherapy, histology, extent of mediastinal nodal involvement, and use of PET-CT. R0 resection and absence of nodal extracapsular extension were required for eligibility. Central review was used for radiotherapy, and most patients (89%) received three-dimensional conformal radiation therapy (3DCRT; *v* 11% intensity-modulated radiation therapy [IMRT]). The primary end point was DFS. PORT was found

to reduce mediastinal relapse (46.1% *v* 25%), but not DFS (47.1% *v* 43.8%, $P = .16$), driven in large part by an increase in death (14.6% *v* 5.3%). Further investigation into causes of death revealed numerical reductions in progression or recurrence (69.4% *v* 86.1%) with PORT, at the cost of increased cardiopulmonary toxicity (16.2% *v* 2.0%). OS was likewise not improved with PORT (66.5% *v* 68.5%, $P =$ not significant).

There is much yet to learn from the Lung ART trial in terms of which subgroups, if any (such as high % lymph node–positive, high number of positive nodal stations, close margins, etc), might benefit from PORT and whether additional technological innovations such as IMRT and/or proton therapy could improve the therapeutic ratio in light of the clear reductions in relapse with PORT. Similarly, since patients with positive margins and extracapsular extension were excluded, findings from this study do not directly apply to these patients, and it is reasonable to consider PORT in these cases. However, given the overall lack of clear benefit from older trials, coupled with new data from Lung ART, there are currently no data to support the routine use of PORT for patients with completely resected N2 who have received neoadjuvant and/or adjuvant platinum-based chemotherapy.

Clinical Question 5

What is the appropriate management for patients with unresectable stage III NSCLC?

Recommendation 5.1. Patients with stage III NSCLC who are medically or surgically inoperable and with good performance status should be offered concurrent instead of sequential chemotherapy and radiation therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. There have been prospective randomized trials comparing concurrent chemotherapy and radiation with sequential chemotherapy and radiation (ie, chemotherapy before or after radiation). In a SR of 2,043 patients from 11 randomized control trials (six phase III and five phase II) spanning from 1992 to 2005, concurrent chemoradiation resulted in a statistically significant increase in median survival time, response rate, and tumor relapse control.[15] Of the 10 trials included in the survival analysis, three individual trials showed a statistically significantly improved survival with concurrent chemoradiation, whereas the majority of the remaining trials showed a trend favoring the concurrent strategy. With a median follow-up of 3.3 years, the pooled analysis demonstrated a median survival of 16.3 months with concurrent chemoradiation versus 13.9 months with sequential chemoradiation (median ratio 1.17; 95% CI, 1.09 to 1.26), which remained significant when excluding trials that did not have survival as the primary end point. The greatest impact of the concurrent strategy was in decreasing locoregional relapses (odds ratio, 0.68; 95% CI, 0.52 to 0.87). Although the details of the platinum regimens and toxicity data were reported variably among the trials, an increase in toxicity with the concurrent strategy was noted, including both hematologic such as neutropenia and thrombocytopenia and nonhematologic such as nausea and/or vomiting, stomatitis, and esophagitis. In an individual-patient MA, with a subset of trials from the SR examined, six trials (1,205 patients) with a median follow-up of 6 years noted significant survival benefit of concurrent chemoradiation over sequential chemoradiation (HR, 0.84; 95% CI, 0.74 to 0.95; $P = .004$).[18] This translated into absolute survival benefits of 5.7% at 3 years and 4.5% at 5 years. The greatest impact of chemoradiation was again observed in decreasing locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; $P = .01$). In this MA, there was no difference in results whether sequential chemotherapy was given as induction or consolidation although only one of the six trials used a consolidation approach. There was also an increased relative risk of grade 3-4 esophageal toxicity noted. In a pooled study of five completed RTOG trials (461 patients), combined sequential and concurrent chemoradiation resulted in similar severe acute nonhematologic toxicities as the sequential approach; however, there were more severe late nonhematologic toxicities (26% *v* 14%; $P = .046$) observed, including severe late lung toxicity.[28] One of the largest trials included in the aforementioned SR and individual patient MA was RTOG 9410, a phase III study in 610 patients with stage II-IIIB NSCLC randomly assigned to three arms: sequential chemoradiation, concurrent chemoradiation with standard fractionation, and concurrent chemoradiation with hyperfractionation. The median survival and 5-year survival rate were higher in patients treated with concurrent chemoradiation with standard fractionation compared with sequential treatment (concurrent median 17.0 months, 5-year OS 16% and sequential median 14.6 months, 5-year OS 10%; $P = .046$).[69] Patients with a good performance status should receive concurrent chemoradiation over sequential chemoradiation,[76] especially as the previously conducted trials demonstrating increased toxicity compared with the concurrent approach that used older radiation techniques such as two-dimensional and 3D conformal and/or more antiquated chemotherapy regimens. However, before initiation of concurrent therapy, multidisplinary tumor board review is recommended to assess patient fitness and risk of morbidities with concurrent as opposed to sequential therapy.

Recommendation 5.2. Concurrent chemotherapy delivered with radiation therapy for definitive treatment of stage III NSCLC should include a platinum-based doublet, preferably cisplatin plus etoposide, carboplatin plus paclitaxel, cisplatin plus pemetrexed (non-squamous only), or cisplatin plus vinorelbine (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statement: Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin.

Literature review and clinical interpretation. There has been much discussion regarding the most effective chemotherapy regimen among patients with locally advanced NSCLC who receive concurrent chemoradiation. The most widely accepted regimen and hence most studied involves platinum doublet.[16,73,74,172] Two randomized phase III controlled trials have evaluated patients on platinum doublets.[73,74] In the first, 200 patients were allocated to etoposide 50 mg/m^2 once daily on days 1-5 with cisplatin 50 mg/m^2 once daily on days 1 and 8 (EP) every 4 weeks for two cycles concurrent with radiation *v* paclitaxel 45 mg/m^2 and carboplatin (area under curve [AUC] 2; paclitaxel and carboplatin [PC]) once daily on day 1 weekly concurrent with radiation. Consolidation chemotherapy was given to 50.5% of patients in the EP arm and 35.4% in the PC arm ($P = .035$), and the most common regimen was PC. The median survival times were 23.3 months in the EP arm *v* 20.7 months in the PC arm (log-rank test $P = .095$; HR, 0.76; 95% CI, 0.55 to 1.05). Chemotherapy interruptions were more common in the PC arm compared with the EP arm during concurrent treatment (37.5% *v* 13.6%; $P < .001$). Two- and five-year OS rates in the EP arm were 48.4% and 28% and were 42.7% and 19.7% in the PC arm, respectively. A significant factor contributing to the improved PFS and OS in the EP arm after longer follow-up appeared to be a higher rate of completion of treatment compared with the PC arm.[74] This represents the largest phase III study to date to compare the two most historically common platinum regimens with the longest median follow-up of patients. The second notable phase III trial was the PROCLAIM study of 598 patients with nonsquamous NSCLC enrolled between 2008 and 2012 from 125 institutions in 21 countries comparing pemetrexed-cisplatin with etoposide-cisplatin. Patients received pemetrexed 500 mg/m^2 intravenously (IV) plus cisplatin 75 mg/m^2 IV once every 3 weeks for three cycles with concurrent radiation followed by consolidation pemetrexed 500 mg/m^2 IV once every 3 weeks for four cycles vs etoposide 50 mg/m^2 once daily on days 1-5 with cisplatin 50 mg/m^2 once daily on days 1 and 8 (EP) once every 4 weeks for two cycles concurrent with radiation followed by consolidation chemotherapy of two cycles of platinum doublet (EP, vinorelbine plus cisplatin, and PC). Median survival was not significantly longer for pemetrexed-cisplatin versus etoposide-cisplatin (median OS, 26.8 *v* 25 months), and 1-, 2-, and 3-year survival rates did not differ in each arm (76% *v* 77%, 52% *v* 52%, and 40% *v* 37%, respectively). Although PROCLAIM was not designed as a noninferiority trial, given numerically similar outcomes, pemetrexed-cisplatin has been adopted as an option for the treatment of patients with nonsquamous NSCLC.[74]

In a SR and network MA in 2019, 14 randomized controlled trials (12 two-arm studies and two three-arm studies) published before 2018 reviewed 12 categories of platinum doublets (EP, PC, pemetrexed plus cisplatin or carboplatin, S-1 plus cisplatin, uracil plus tegafur-cisplatin, vinorelbine plus cisplatin, gemcitabine plus cisplatin, docetaxel plus cisplatin, irinotecan plus carboplatin, mitomycin plus vindesine plus cisplatin, PC plus cetuximab, and pemetrexed plus cisplatin or carboplatin plus cetuximab) among 2,975 patients with the primary outcome of OS. Both the aforementioned phase three trials were included. EP and PC were the only regimens that could be compared directly favoring EP in OS. Other comparisons did not offer statistically significant differences regarding survival.[16] Although S1-cisplatin showed tolerability and prolonged survival, to date, it is not approved by the FDA. Attention to both tolerability and OS is key to treatment selection and is of significant importance among older patients.[173]

Recommendation 5.3. Patients with stage III NSCLC who are not candidates for concurrent chemoradiation but are candidates for chemotherapy should be offered sequential chemotherapy and radiation therapy over radiation alone (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. There have been randomized control trials examining concomitant chemotherapy and radiation versus radiation alone in patients with locally advanced NSCLC.[19] In a recent MA and SR, which included a total of 13 randomized control trials (1,936 patients), patients receiving some form of chemotherapy with radiation had a higher OS (pooled HR, 0.72; 95% CI, 0.62 to 0.84; $P < .001$) and a higher PFS (pooled HR, 0.73; 95% CI, 0.60 to 0.89; $P = .002$) compared with patients receiving radiation alone. This MA and SR examined heterogeneous treatment regimens. However, there are randomized trials that specifically examined sequential chemotherapy followed by radiation versus radiation alone. Dasgupta et al[70] reported on 103 patients randomly assigned to three treatments, including radiation alone (65 Gy in 30 fractions) versus neoadjuvant cisplatin-etoposide chemotherapy for three cycles followed by radiation (60 Gy in 30 fractions) and three more cycles of chemotherapy. In the chemotherapy-containing radiation arm, there were a statistically significant improvement in survival and a decrease in distant metastases (48.6% *v* 62.5%). Kim et al[85] reported a phase III randomized trial examining induction platinum-based chemotherapy for three cycles followed by radiation versus radiation alone (60-65 Gy in 1.8-2 Gy fractions) in 101 patients. A trend for improved OS with the incorporation of chemotherapy was observed (median 13.8 v 8.5 months, respectively), with significance found in a subgroup of patients with nonsquamous NSCLC and stage IIIB disease. When only examining this subgroup (stage IIIB nonsquamous), the median survival was 11.6 months with sequential chemoradiotherapy versus 8 months with radiotherapy alone ($P = .046$). In a study by Komaki et al,[82] 490 patients with

NSCLC were randomly assigned to three arms: radiation alone (60 Gy in 30 fractions), weekly cisplatin-vinblastine chemotherapy followed by radiation (60 Gy in 30 fractions), and hyperfractionated radiation. There were significant differences in median OS observed, with longest survival noted in the sequential chemoradiation arm: 11.4, 13.6, and 12.3 months, respectively. Despite no differences in local tumor control rates, there were fewer distant metastases observed in the sequential chemoradiation arm. In the CALGB8433 trial, 78 patients were assigned to cisplatin-vinblastine weekly for 5 weeks followed by radiation on day 50 (60 Gy in 30 fractions) versus radiation alone (60 Gy over 6-7 weeks).[80] After a 7-year follow-up, the median survival was greater in the sequential chemoradiation arm compared with the radiation-alone arm (13.7 months *v* 9.6 months, $P = .012$; 3-year OS, 24% *v* 10%, respectively). Finally, there were 66 patients randomly assigned to cisplatin-based chemotherapy for three cycles followed by radiotherapy versus radiotherapy alone, with a higher response rate (53% *v* 32%, respectively) and a trend for higher median survival noted (52 weeks *v* 30 weeks, respectively).[95] Because of the improved survival observed in prospective randomized studies of sequential chemoradiation versus radiation alone, patients not fit to undergo concurrent chemotherapy radiation with locally advanced NSCLC should be offered a sequential chemoradiation approach.

Recommendation 5.4. Patients with stage III NSCLC receiving concurrent chemoradiation should be treated to 60 Gy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. In one of the earliest cooperative group radiation dose-escalation randomized trials, RTOG 7301 established 60 Gy as the early standard-of-care dose for radiotherapy in patients with locally advanced NSCLC by showing that 60 Gy led to longer 3-year OS rates than 50 Gy, 40 Gy, or 40 Gy delivered as a split course with a 2-week break after 20 Gy (15% *v* 10% vs. 6% *v* 6%) and fewer infield recurrences (35% *v* 49% *v* 58% *v* 53%).[174,175] The delivery of 60 Gy in 30 fractions was subsequently similarly found to improve outcomes of hyperfractionated radiotherapy in a phase III North Central Cancer Treatment Group and Mayo Clinic trial.[102] On the basis of these early data from the RTOG 7301 study, the investigators concluded that higher doses of radiation are necessary to improve intrathoracic tumor control.[174]

Given the high rates of local and regional failures after concurrent chemotherapy when radiation therapy is delivered to 60 Gy in 30 fractions,[100] as well as the known association between local control and OS in patients with locally advanced NSCLC,[18,159] many groups have investigated further radiation dose escalation beyond the 60 Gy RTOG 7301 standard. Such dose-escalation strategies have been trialed in many forms, such as increasing the absolute dose of radiotherapy while maintaining 2 Gy daily fractions,[100] increasing the absolute dose of radiotherapy with mild hypofractionation (increasing the dose per fraction),[176] delivering higher total doses of radiotherapy by delivering boosts to a smaller target volume,[104,177] maintaining the same absolute radiotherapy dose while increasing the biologically effective dose through more appreciable hypofractionation (larger doses per fraction),[127,178] delivering an isotoxic integrated boost (increased dose per fraction to a limited portion of the target volume, typically gross tumor, limited by predicted risk of toxicity),[179] boosting high-uptake areas of PET avidity within the primary tumor,[180] or increasing the absolute dose using hyperfractionated (small fractions delivered more than once daily) radiotherapy.[108]

Although many of these earlier phase trials showed promising results, a definitive phase III trial of dose escalation was needed to assess if the standard-of-care dose should change from 60 Gy in 2 Gy fractions. RTOG 0617 was a randomized phase III trial with a two-by-two factorial design testing both the addition of cetuximab to concurrent chemoradiation and the use of 74 Gy compared with 60 Gy thoracic radiation in 2 Gy daily fractions. Concurrent chemotherapy was paclitaxel 45 mg/m^2 and carboplatin AUC 2 once a week, followed by two cycles of consolidation chemotherapy with paclitaxel 200 mg/m^2 and carboplatin AUC 6 once a week. Radiation therapy was delivered with either IMRT or 3DCRT. The median OS was 28.7 months for patients treated to 60 Gy versus 20.3 months for patients treated to 74 Gy ($P = .0072$). Although there were no statistical differences in all grade ≥ 3 toxic effects between radiotherapy arms, grade ≥ 3 dysphagia (12.1% *v* 3.2%; $P = .0005$) and esophagitis (17.4% *v* 5.0%, $P < .0001$) occurred more commonly among patients receiving 74 Gy, and there were more treatment-related deaths in the 74-Gy arm (9 *v* 3).[100,181]

Despite expectations for an improvement in OS with dose escalation above 60 Gy, RTOG 0617 showed that 74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not better than 60 Gy, was associated with inferior outcomes, and was potentially harmful.[100,181] Patients receiving 74 Gy were also found to have a greater decline in quality-of-life scores at 3 months (45% *v* 30%; $P = .02$).[182] A long-term report of this trial showed that 5-year OS (32.1% *v* 23.0%; $P = .007$) and PFS (18.3% *v* 13.0%; $P = .055$) were better with the standard dose arm, and this further established 60 Gy as the standard-of-care radiation dose to be delivered with concurrent chemotherapy, with the OS rate being among the highest reported in the literature for stage III NSCLC.[181]

Recommendation 5.5. Doses higher than 60 Gy and up to 70 Gy may be considered for selected patients, with careful attention to doses to heart, lungs, and esophagus (Type:

Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: strong).

Literature review and clinical interpretation. Although RTOG 0617 used 60 Gy as the standard dose arm that was compared with the dose escalation of 74 Gy, numerous previous cooperative group and other large studies have used radiation doses of > 60 Gy as their standard dose arm. As an example, 64 Gy in 2 Gy daily fractions was used in the control arm of the phase III ECOG 2597 trial assessing induction chemotherapy followed by standard versus hyperfractionated radiotherapy.[101] Recent SRs and MAs of randomized trials assessing radiation doses have been reported and demonstrate that common doses delivered for locally advanced NSCLC include 64 Gy and 66 Gy in 2 Gy fractions, with 1.8 Gy daily fractions to total 64.8 Gy or 66.6 Gy also used.[23,24] Furthermore, the ongoing phase III NRG Oncology RTOG 1308 trial uses 70 Gy in 2 Gy daily fractions as its standard dose.[183]

Comparisons of 60 Gy in 2 Gy fractions with doses above 60 Gy but < 74 Gy specifically delivered in once-daily radiotherapy using 1.8-2.0 Gy fractions are lacking to date. With well-established once-daily dose fractionation regimens from 60 to 70 Gy used in previous cooperative group studies and no direct comparisons between such doses, it remains to be defined what is the optimal radiation total dose. As such, higher doses above 60 Gy and up to 70 Gy can be considered for well-selected patients. Results of RTOG 1308, in which patients are being treated to 70 Gy with more strict normal tissue dose constraints than have previously been used in cooperative group studies, may in the future question the choice of 60 Gy as the standard dose of radiotherapy delivered concurrent with chemotherapy for locally advanced NSCLC. Doses above 70 Gy, however, should not be delivered concurrently with chemotherapy outside the context of a clinical trial.

In cases where doses above 60 Gy are being delivered, careful attention to irradiation doses to the heart, lungs, and esophagus is required to avoid excessive morbidity and even mortality from treatment. Dose volume parameters that should be carefully assessed in patients considered for doses up to 70 Gy include the mean lung dose and lung V20, cardiac mean and volumetric dose, esophageal mean dose, and spinal cord maximum dose, among others. Advanced radiation modalities may better spare these critical organs at risk and help to facilitate dose escalation more safely. In RTOG 0617, although patients treated with IMRT had more advanced stage grouping ($P = .056$) and larger planning target volumes ($P = .005$) than those treated with 3DCRT, IMRT was associated with lower lung irradiation doses ($P = .08$), lower heart doses ($P < .05$), fewer grade ≥ 3 pneumonitis events ($P = .0653$), and higher compliance with full-dose consolidative chemotherapy, with no difference in OS despite larger and less favorable tumors treated with IMRT.[184] The use of IMRT in population-based analyses has been reported to be associated with a survival benefit relative to 3DCRT in locally advanced NSCLC.[185] Similarly, proton therapy in a population-based analysis has been reported to be associated with a survival benefit relative to photon radiotherapy in locally advanced NSCLC[186] and may improve outcomes by more safely allowing for dose escalation, reducing toxicities, and reducing radiation-induced lymphopenia.[187]

Recommendation 5.6. Patients with stage III NSCLC receiving definitive radiation without chemotherapy in standard fractionation may be considered for radiation dose escalation and for modest hypofractionation from 2.15 to 4 Gy per fraction (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: weak).

Literature review and clinical interpretation. In less common situations where patients have locally advanced NSCLC and either are not candidates for (eg, comorbidities or pulmonary function) or refuse chemotherapy, radiation alone is typically used. This recommendation pertains to the radiation dose and fractionation that is used in these circumstances. There are prospective studies to support radiation dose and fractionation in this setting. Some are older and were largely carried out before the refinement of concurrent chemoradiation therapy, 3DCRT, IMRT, and/or proton therapy techniques. More recently, a phase III randomized trial was published that addresses this specific question.

Older trials have also evaluated dose-escalated approaches when radiation is delivered as monotherapy. The most notable of the older trials was termed CHART (Continuous Hyperfractionated Accelerated Radiation Therapy). This phase III trial published by Saunders et al[188] in 1997 enrolled 563 patients across 13 centers in a 3:2 ratio to either CHART (1.5 Gy three times a day for 12 consecutive days) or 60 Gy in 30 fractions of 2 Gy each excluding weekends. Two-year OS favored CHART (29% *v* 20%; $P = .004$). A subsequent trial modified the CHART regimen to CHARTWEL (CHART WeekEnd Less) in an effort to make the regimen more widely accepted.[189,190] CHARTWEL randomly assigned 406 patients to either 60 Gy in 40 fractions over 2.5 weeks or 66 Gy in 33 fractions over 6.5 weeks. There were no differences in 2-, 3-, or 5-year OSs between regimens (31%, 22%, and 11% *v* 32%, 18%, and 7%, respectively; HR, 0.92; $P = .43$).

The first study to use 3DCRT was RTOG 9311, a phase I/II dose-escalation study, either alone or after two cycles of systemic chemotherapy.[176] Doses were 2.15 Gy/fraction to 70.9 Gy, 77.4 Gy, 83.8 Gy, or 90.3 Gy. The safe total radiation dose was determined to be 83.8 Gy in patients with a lung V20 < 25% and 77.4 Gy for lung V20 of 25%-36%.

None of these regimens are routinely used today, as CHART and CHARTWEL required three times daily

radiation therapy, and the RTOG 9311 trial safe dose of 83.8 Gy was administered over 39 total fractions. Most recent studies have investigated accelerating treatment with hypofractionation with larger radiation doses delivered once per day. Concerns about serious toxicity have been better addressed with the emergence of IMRT techniques and greater sparing of normal tissues. The preference has become hypofractionated radiation therapy using fraction sizes of 2.5-4 Gy. The studies supporting this preference consist of phase I prospective trials testing the use of more sophisticated techniques such as simultaneous integrated boosts where the gross tumor volume receives a higher daily fraction than the surrounding microscopic tumor volume and/or lymph nodes. Examples of these regimens include 60 Gy in 30 fractions to the larger planning target volume and administering up to 78 Gy simultaneously to the gross tumor volume.[191]

Gomez et al[192] published a prospective phase I dose-escalation trial using proton beam that escalated radiation dose in a 15-fraction course using 45 Gy (relative biologic effectiveness [RBE]), 52.5 Gy (RBE), and 60 Gy (RBE) in a 3 + 3 study design. With a median follow-up of 13 months (range 8-28 months), two of the 25 patients experienced dose-limiting toxicities. A similar, more recent multicenter prospective trial demonstrated that radiation doses in 15-24 fractions can be safely delivered with proton therapy concurrently with chemotherapy.[178] The authors of these trials determined that hypofractionation was well-tolerated and encouraged phase II and III trials. As protons are not available at most centers, a phase I dose-escalation study was later reported using photons at the University of Texas Southwestern in patients who were not chemotherapy candidates. The trial enrolled 55 patients among three doses, 50, 55, and 60 Gy, all delivered in 15 fractions. One patient developed grade 3 esophagitis, and two cases of grade 3 dyspnea were felt related to therapy. There was no association between fraction size and toxicity ($P = .24$), and the median OS was 6 months at all dose levels ($P = .59$).[193] The same investigator group subsequently conducted a randomized, multi-institution phase III comparison of 60 Gy in 15 versus 30 fractions of image-guided photon radiation therapy in patients ineligible for concurrent chemoradiation or with a Zubrod performance status of 2 or greater.[127] The primary end point was 1-year OS. The trial was closed to accrual when an interim analysis suggested futility at meeting the primary end point. With 103 randomly assigned patients, there was no significant difference in 1-year OS between groups (37.7% for the hypofractionated regimen and 44.6% for the conventional regimen [$P = .29$]), and no differences in grade 3 or higher adverse events were noted. Although the trial was not powered to test equivalence, these results do reassure that a regimen of 60 Gy in 15 fractions of radiation alone may yield similar results without additional toxicity, and the authors note that the convenience of the shorter treatment regimen may warrant its consideration for well-selected patients.[127]

Recommendation 5.7. Patients with stage III NSCLC receiving concurrent chemoradiation without disease progression during the initial therapy should be offered consolidation durvalumab for up to 12 months (Type: Evidence based; benefit outweighs harm; Evidence quality: high; benefit outweighs harm; Strength of recommendation: strong).

> Qualifying Statement: There is insufficient evidence to alter the recommendation for consolidation durvalumab following concurrent chemoradiation for molecularly defined subgroups (namely, patients with an oncogenic driver alteration or those with low or no expression of programmed death-ligand 1 [PD-L1]).

Literature review and clinical interpretation. The phase III randomized PACIFIC trial evaluated consolidation durvalumab for 1 year versus placebo in 713 patients with unresectable stage III NSCLC after definitive platinum-based chemoradiotherapy with at least two cycles.[122] Patients were enrolled irrespective of the PD-L1 status of their tumors, had no progression after definitive chemoradiotherapy, and had a good performance status (Eastern Cooperative Oncology Group 0 or 1), and were randomly assigned within 42 days of completing thoracic radiation. The primary end points of the trial included PFS and OS. The median PFS was 16.8 months (95% CI, 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo (HR, 0.52; 95% CI, 0.42 to 0.65; $P <$ .001). Grade 3 or 4 pneumonitis occurred in only 4.4% in the durvalumab arm and was the main higher-grade toxicity. An updated analysis with a median follow-up of 34.2 months continued to show a significant benefit in OS (HR, 0.72; 95% CI, 0.59 to 0.89) and PFS (HR, 0.55; 95% CI, 0.45 to 0.68). The median OS with durvalumab was 47.5 months versus 29.1 months in the placebo arm. The estimated 5-year OS rates were 42.9% versus 33.4% in favor of durvalumab, and 5-year PFS rates were 33.1% versus 19.0%, respectively.[126,194] Therefore, this trial provides level 1 evidence demonstrating a survival benefit from the administration of consolidation durvalumab. A post hoc analysis of the limited number of patients with available PD-L1 status (63% of the trial population) suggested a lack of benefit of durvalumab in PD-L1–negative tumors (20% of trial population; HR, 1.05; 95% CI, 0.69 to 1.62) and *EGFR*-mutated patients (6% of the study population, n = 43, HR, 0.97; 95% CI, 0.40 to 2.33). This analysis was performed in a small proportion of the study population and needs further evaluation before definitive conclusions can be made although certain authorities outside of the United States have restricted consolidation durvalumab to PD-L1–positive patients only.

Figures 3 and 4 provide visual interpretations of these recommendations in the management algorithm.

PATIENT AND CLINICIAN COMMUNICATION

Increasingly, cancer care continues to become more complex, and, as such, patient and clinician communication is critical. In our ever-changing world of growing digital health demands while facing challenges of high rates of limited health literacy among patients, evidence-based guidelines allow clinicians a data-driven foundation and an essential tool to have difficult discussions with patients about their cancer care management.[195] With a rapidly evolving treatment landscape for NSCLC, regular updates to care guidelines are paramount for ensuring optimal patient outcomes. Cotarla et al[196] describe deviations from treatment guidelines in a survey of 112 oncologists, reinforcing the importance of clear evidence-based, patient-centered guidelines for managing stage III NSCLC. These updated guidelines for managing stage III NSCLC include several aspects that are patient-centered to help achieve optimal care. For example, there is a consistent effort to prioritize the least invasive methods for evaluating and staging disease (Recommendations 1.3-1.5). Consistent with the published literature,[197] the recommendations also highlight the importance of multidisciplinary care and shared decision-making for maximizing patient outcomes (good practice points related to evaluating and staging disease and identifying candidates for surgical resection).

These guideline recommendations incorporate other elements that are patient-centered, including highlighting the growing importance of biomarker testing for both resectable and nonresectable disease (Recommendations 2.1 and 5.1). Recommendation 2.1 also emphasizes that patients and providers should consider clinical trials when appropriate. At the same time, these guidelines reflect some of the ongoing debate about the role of tyrosine kinase inhibitors (such as osimertinib for *EGFR*-mutated NSCLC) in earlier-stage disease (Recommendation 4.2). OS data with the use of osimertinib in the adjuvant setting are awaited.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[198]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation, gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[199] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor quality care than other Americans.[200-203] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. In addition, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[199]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision-making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan. For special populations, such as older adults, considerations should be made for geriatric assessment to assist in decision-making and how to optimally facilitate recommendations.[204]

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

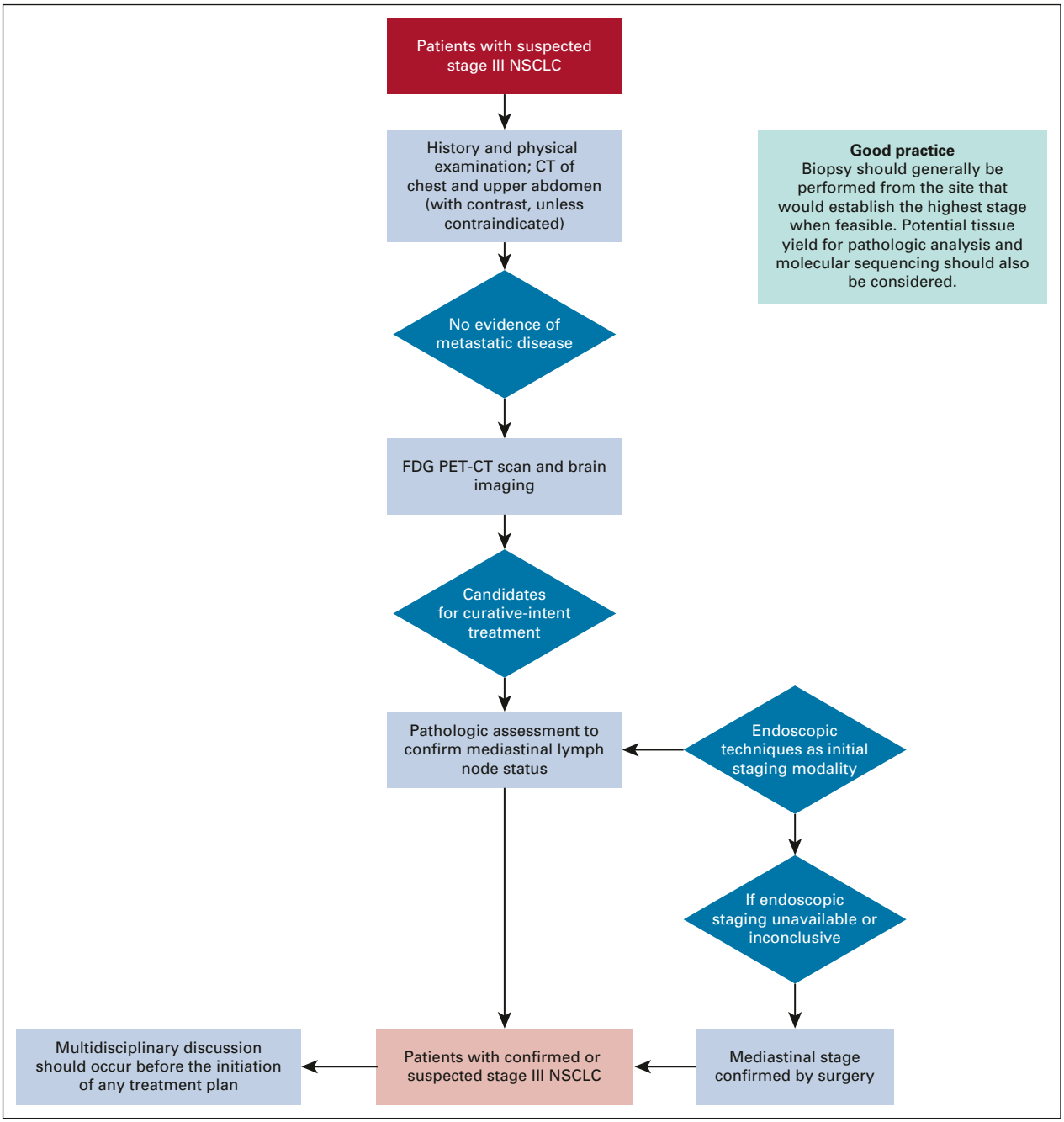

FIG 3. Algorithm for evaluation and staging in stage III NSCLC. CT, computed tomography; FDG, fluorodeoxyglucose; NSCLC, non–small-cell lung cancer; PET, positron emission tomography.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[205,206] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[207,208]

Discussion of cost can be an important part of shared decision-making.[209] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[209]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the

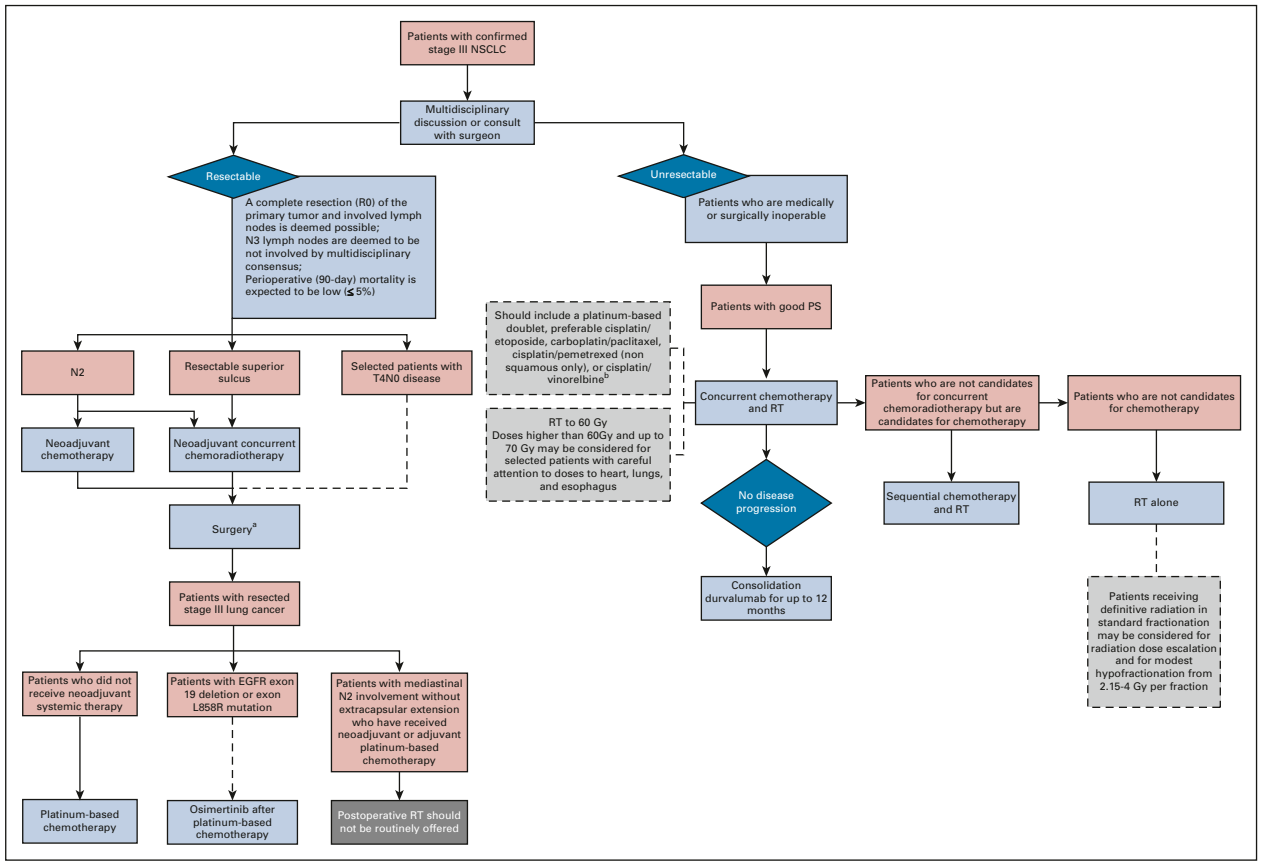

FIG 4. Management of stage III NSCLC algorithm. Arrows with dotted lines indicate that the level of obligation is a May (moderate) recommendation. [a]Patients with stage III NSCLC generally should not be excluded from consideration for surgery by nonsurgical physicians. [b]Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin. CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; PET, positron emission tomography; PS, performance status; RT, radiation therapy.

price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[209] In addition, patients should be fully aware of the treatment plan, including up to a year of immunotherapy, before the initiation of therapy.

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data, agents that are not currently available in either the United States or Canada, or are industry-sponsored. No cost-effectiveness analyses were identified to inform the topic.

OPEN COMMENT REVIEW

The draft recommendations were released to the public for open comment from May 18, 2021, through June 2, 2021. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with 62 written comments received. There were 14 respondents in total. There was representation from medical oncology (50%), radiation oncology (29%), thoracic surgery (14%), and industry (7%) A total of 80%-95% of the responses either agreed or agreed with slight modifications to the recommendations, whereas 5% of responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before EBMC review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative in the guideline panel is not only to assess the suitability of the recommendations to implementation

in the community setting but also to identify any other barrier to implementation that a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the Journal of Clinical Oncology.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

There are several gaps in our current understanding of the optimal treatment options for stage III NSCLC. As a deeply heterogenous disease, no single randomized trial can define treatment for the entire spectrum of stage III disease. Patient selection for surgical versus nonsurgical management is not well-defined by high-level evidence. Most trials comparing surgical versus nonsurgical treatments were conducted in an era without the availability of minimally invasive surgical techniques or advanced radiation technologies, and all were conducted before the PACIFIC trial demonstrated the survival benefit of consolidative immunotherapy for unresectable disease. The inconsistency of eligibility criteria used in these studies and the range of surgical and nonsurgical treatments, without a consistent standard-of-care arm, make intratrial comparisons deeply challenging. Currently, no randomized phase III trial has demonstrated a survival benefit to the inclusion of surgery. Well-designed studies to better define which patients with stage III NSCLC, if any, benefit from the inclusion of surgery in multidisciplinary management are needed. The role of immunotherapy in resectable stage III disease also remains under active investigation.

Ongoing studies in unresectable disease are evaluating whether there is a benefit to concurrent immunotherapy with chemoradiation or dual checkpoint blockade in the adjuvant setting. Patient selection for consolidative immunotherapy is also not fully defined. Although the PACIFIC trial included patients with PD-L1–negative disease and those with oncogenic driver mutations, subsequent analyses have called into question the use of immunotherapy for those patients. Future prospective studies are needed to better clarify patient selection for the incorporation of immunotherapy. Although RTOG 0617 found no benefit to radiation dose escalation for the unresectable stage III population as a whole, ongoing studies seek to identify any subgroup of patients who might benefit from higher radiation doses.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Adjuvant Chemotherapy and Adjuvant Radiation Therapy for Stage I-IIIA Resectable Non–Small-Cell Lung Cancer[210] (http://ascopubs.org/doi/10.1200/JCO.2017.72.4401)
- Molecular Testing for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors Guideline Endorsement[211] (http://ascopubs.org/doi/10.1200/JCO.2017.76.7293)
- Integration of Palliative Care into Standard Oncology Practice[212] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[198] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines.

EQUAL CONTRIBUTION

M.E.D. and N.S. were Expert Panel cochairs and cofirst authors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Stage III Non–Small-Cell Lung Cancer: ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Management of Stage III Non–Small-Cell Lung Cancer Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Megan Daly, MD (cochair)	University of California, Davis, CA	Radiation Oncology
Navneet Singh, MD (cochair)	Postgraduate Institute of Medical Education & Research, Chandigarh, India	Medical Oncology
Mara Antonoff, MD	MD Anderson Cancer Center, Houston, TX	Surgical Oncology
Douglas A. Arenberg, MD	University of Michigan, Ann Arbor, MI	Pulmonology; ACCP Representative
Jeffrey Bradley, MD	Emory University, Atlanta, GA	Radiation Oncology; ASTRO Representative
Elizabeth David, MD	University of Southern California, Los Angeles, CA	Surgical Oncology
Frank Detterbeck, MD	Yale Cancer Center, New Haven, CT	Surgical Oncology; ACCP Representative
Martin Fruh, MD, PhD	Department of Medical Oncology/Hematology, Cantonal Hospital of St Gallen, St Gallen, Switzerland; University of Bern, Bern, Switzerland	Medical Oncology
Matthew Gubens, MD, MS	University of California San Francisco, CA	Medical Oncology
Sukhmani K. Padda, MD	Department of Medicine, Division of Oncology, Cedars-Sinai Medical Center, Los Angeles, CA	Medical Oncology
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Tanyanika Phillips, MD, MPH	City of Hope, Lancaster, CA	Community Oncology
Amy Moore, PhD	LUNGevity Foundation, Chicago, IL	Patient Representative
Angel Qin, MD	University of Michigan, Ann Arbor, MI	Medical Oncology
Clifford Robinson, MD	Washington University, St Louis, MO	Radiation Oncology
Charles B. Simone, II, MD	New York Proton Center and Memorial Sloan Kettering Cancer Center, New York, NY	Radiation Oncology
Nofisat Ismaila, MD, MSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviations: ACCP, American College of Chest Physicians; ASTRO, American Society for Radiation Oncology.

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not