



Published in final edited form as:

JAMA Oncol. 2024 June 01; 10(6): 799–806. doi:10.1001/jamaoncol.2024.0294.

American Radium Society Appropriate Use Criteria for Unresectable Locally Advanced Non–Small Cell Lung Cancer

George Rodrigues, MD, PhD,

Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada

Kristin A. Higgins, MD,

Winship Cancer Institute, Emory University, Atlanta, Georgia

Andreas Rimner, MD,

Memorial Sloan Kettering Cancer Center, New York, New York

Arya Amini, MD,

City of Hope National Medical Center, Duarte, California

Joe Y. Chang, MD, PhD,

The University of Texas, MD Anderson Cancer Center, Houston

Stephen G. Chun, MD,

The University of Texas, MD Anderson Cancer Center, Houston

Jessica Donington, MD,

University of Chicago, Chicago, Illinois

Martin J. Edelman, MD,

Fox Chase Comprehensive Cancer Center, Philadelphia, Pennsylvania

Matthew A. Gubens, MD,

Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco

Puneeth Iyengar, MD, PhD,

The University of Texas at Southwestern Medical Center, Dallas

Benjamin Movsas, MD,

Henry Ford Cancer Institute, Detroit, Michigan

Matthew S. Ning, MD,

Corresponding Author: George Rodrigues, MD, PhD, Department of Radiation Oncology, London Health Sciences Centre, London, ON N6A 4L6, Canada (george.rodrigues@lhsc.on.ca).

Author Contributions: Dr Rodrigues had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Rodrigues, Higgins, Amini, Chang, Chun, Edelman, Movsas, Simone.

Acquisition, analysis, or interpretation of data: Rodrigues, Higgins, Rimner, Chang, Chun, Donington, Edelman, Gubens, Iyengar, Ning, Park, Wolf, Simone.

Drafting of the manuscript: Rodrigues, Higgins, Edelman, Iyengar, Simone.

Critical review of the manuscript for important intellectual content: Rodrigues, Higgins, Rimner, Amini, Chang, Chun, Donington, Edelman, Gubens, Iyengar, Movsas, Ning, Park, Wolf.

Administrative, technical, or material support: Higgins, Simone.

Supervision: Rodrigues, Donington, Iyengar, Simone.

Additional Contributions: The panel acknowledges Ms Andrea Taylor and the ARS Appropriate Use Criteria Steering Committee for their assistance in the generation and completion of this document.

The University of Texas, MD Anderson Cancer Center, Houston

Henry S. Park, MD, MPH,

Yale School of Medicine, New Haven, Connecticut

Andrea Wolf, MD,

Mount Sinai Health System, New York, New York

Charles B. Simone II, MD

New York Proton Center, New York, New York

Abstract

IMPORTANCE—The treatment of locally advanced non–small cell lung cancer (LA-NSCLC) has been informed by more than 5 decades of clinical trials and other relevant literature. However, controversies remain regarding the application of various radiation and systemic therapies in commonly encountered clinical scenarios.

OBJECTIVE—To develop case-referenced consensus and evidence-based guidelines to inform clinical practice in unresectable LA-NSCLC.

EVIDENCE REVIEW—The American Radium Society (ARS) Appropriate Use Criteria (AUC) Thoracic Committee guideline is an evidence-based consensus document assessing various clinical scenarios associated with LA-NSCLC. A systematic review of the literature with evidence ratings was conducted to inform the appropriateness of treatment recommendations by the ARS AUC Thoracic Committee for the management of unresectable LA-NSCLC.

FINDINGS—Treatment appropriateness of a variety of LA-NSCLC scenarios was assessed by a consensus-based modified Delphi approach using a range of 3 points to 9 points to denote consensus agreement. Committee recommendations were vetted by the ARS AUC Executive Committee and a 2-week public comment period before official approval and adoption. Standard of care management of good prognosis LA-NSCLC consists of combined concurrent radical (60-70 Gy) platinum-based chemoradiation followed by consolidation durvalumab immunotherapy (for patients without progression). Planning and delivery of locally advanced lung cancer radiotherapy usually should be performed using intensity-modulated radiotherapy techniques. A variety of palliative and radical fractionation schedules are available to treat patients with poor performance and/or pulmonary status. The salvage therapy for a local recurrence after successful primary management is complex and likely requires both multidisciplinary input and shared decision-making with the patient.

CONCLUSIONS AND RELEVANCE—Evidence-based guidance on the management of various unresectable LA-NSCLC scenarios is provided by the ARS AUC to optimize multidisciplinary patient care for this challenging patient population.

Lung cancer remains the second most frequently diagnosed cancer in both men and women, with a total estimated annual incidence of more than 235 000 cases in the US. The lethality of lung cancer remains the leading cause of cancer mortality, with an estimated 130 180 deaths expected to occur in 2022.¹ Lung cancer continues to be categorized into both non–small cell lung cancer (NSCLC) and small cell lung cancer subtypes based on structural and immunohistochemical parameters of biopsy and/or surgical samples obtained in the

diagnosis and treatment of patients with lung cancer.² Additionally, modern molecular pathological gene alteration analyses of NSCLC pathological samples have provided the opportunity to use novel therapeutics beyond those of systemic therapy with traditional chemotherapeutic agents.^{3,4} Notable actionable gene sequence variations include *EGFR* gene variations, *ALK* gene rearrangements, *MET* skipping variants, and PD-L1 molecule among others currently actionable and nonactionable gene variations.

Approximately 20% to 30% of all patients with NSCLC present with locally advanced disease. Locally advanced NSCLC (LA-NSCLC) is a heterogeneous group of patients that generally is considered to have advanced local (T4N0M0) and/or regional nodal (T3-4N1M0 or T1-4N2-3M0) disease without evidence of meta-static disease by modern staging approaches.^{5,6}

Patients with unresectable LA-NSCLC are not considered candidates for surgical resection either alone or in combination with neoadjuvant or adjuvant/consolidation chemotherapeutic and/or radiotherapeutic modalities. This population of patients tends to be either surgically inoperable due to local and/or regional tumor burden making complete resection of disease unlikely, or medically inoperable due to suboptimal cardiopulmonary reserve preresection and postresection and other preexisting comorbidities. Ideally, surgical management of LA-NSCLC should be considered within the context of a multidisciplinary group setting.⁷ At this time, there are no uniform published guidelines for determining resectable vs unresectable scenarios.

Various publications currently exist to provide clinicians with evidence-based guidance in the management of LA-NSCLC. Previous guidance on the appropriate management of unresectable LA-NSCLC was published by the American College of Radiology in 2010⁸ and updated in 2014.⁹ These documents rated available evidence for this patient population and provided consensus-based guidance for commonly occurring clinical presentations of LA-NSCLC. Another source of evidence-based and consensus-based guidance for this patient population is from the National Comprehensive Cancer Network practice guidelines in oncology for NSCLC.¹⁰ This document is regularly updated online¹¹ and provides detailed evidence-based care maps for all stages of NSCLC based on a multidisciplinary consensus-based approach. Other organizational guidelines on unresectable LA-NSCLC also exist from the American Society of Radiation Oncology,¹² European Society of Medical Oncology¹³, and the American Society of Clinical Oncology.¹⁴

Since the last appropriate use criteria (AUC) publication in 2014,⁹ important clinical studies in radiation therapy technique and dosing, as well as systemic therapy selection, have been published in the medical literature. Information regarding the treatment of recurrent disease either locally or with oligometastatic disease after primary treatment for LA-NSCLC is increasingly available and should be integrated into modern clinical decision-making. Additionally, the use of molecular markers such as *EGFR*, *ALK*, and *PD-L1* has significantly informed systemic therapy options for many patients with NSCLC, and their integration into LA-NSCLC treatment pathways needs to be clarified. Given these substantial developments, the American Radium Society (ARS) has undertaken a review of the literature and assessment of treatment appropriateness in unresectable LA-NSCLC to

provide clinicians with updated tools and information to manage this challenging patient population.

Methods

The ARS AUC Executive Steering Committee selected 15 members for this ARS Thoracic AUC multidisciplinary expert panel composed of radiation, medical, and surgical oncologists with subject matter expertise. An analysis of the medical literature from peer-reviewed journals in the PubMed database from January 1966 to December 2022 was conducted to retrieve a comprehensive set of relevant articles. The search strategy was developed on the basis of the National Library of Medicine Medical Subject Headings with the addition of relevant subject-specific keywords. Owing to the broad scope of medical literature on unresectable LA-NSCLC, the Thoracic AUC expert panel reviewed pertinent studies and excluded those that were not relevant or determined to be of lower impact or quality. The literature was reviewed and rated by the multidisciplinary panel for quality of study design, cohort size, selection bias, evaluation of participants compared with time from exposure, and methods of assessments per ARS criteria (eTable 1 in the Supplement).

Clinical scenarios were then developed through consensus conference calls to address key practice paradigms and controversies in management. A well-established method (modified Delphi) was used by the expert panel to rate the appropriate use of procedures on the clinical scenarios through 3 rounds of anonymous voting with monthly conference calls to discuss the rationale to reach a consensus. Majority attendance was required for a conference call quorum to rate the evidence and review anonymous voting. Using panel consensus findings, an evidence-based AUC consensus document was generated and approved by the expert panel. Panel agreement/consensus was defined as ratings falling less than or equal to 3 points from the group median, whereas disagreement was defined as any group ratings falling greater than 3 points from the group median. The document was then vetted by the ARS AUC Executive Steering Committee and returned to the panel with reviewer comments for modification. The AUC document was then subject to a 2-week public comment period before finalization. Full details on the ARS AUC methodologic approach and other supporting documents are available online.¹⁵

Results

Literature Review

The entire literature review for this project is available within the full guideline in eTable 1 in the Supplement. This full literature review includes a discussion of clinical trials and other evidence related to the role of radiotherapy compared with observation alone in unresectable LA-NSCLC and other early clinical trials assessing radiotherapy alone. The literature review presented within this communication is focused on modern issues of combined chemoradiation therapy, dose escalation, consolidation systemic therapy, and palliative radiotherapy.

Scenarios

Scenario 1: Treatment of a Patient With Unresectable LA-NSCLC and Good

Performance Status—The first scenario in this AUC report for LA-NSCLC was designed to describe a typical case that radiation oncologists would manage routinely in their practice. This patient with unresectable *PD-L1*-positive stage III cancer and good prognostic baseline performance status (Eastern Cooperative Oncology Group [ECOG] score of 0 or 1 [scale ranges from 0 to 5 with lower numbers indicating better performance status]), low weight loss (<5%), and no contraindications to any forms of radiation and/or systemic therapies were designed both to investigate this scenario and to serve as a base case for the additional scenarios described in this report (Table 1).

Consensus was reached that dosages of 60 Gy to 63 Gy in 1.8 Gy/d to 2.0 Gy/d were appropriate, given the results of the RTOG 9410 and 0617 studies.¹⁶⁻¹⁸ Modest escalation of dose up to 70 Gy was considered to be appropriate by the committee, although prospective evidence for this approach is lacking.¹⁹ Dose escalation to high levels exceeding 70 Gy, including 74 Gy as investigated in the 0617 trial, was considered to be usually not appropriate given the poor outcomes reported to date with this approach.^{17,18}

Various techniques including 3-dimensional conformal radiotherapy (3DCRT) and intensity-modulated proton therapy (IMPT) may be appropriate depending on the planning complexity and treatment planning and delivery system available; however, intensity-modulated radiotherapy (IMRT) was assessed to be a usually appropriate approach for the treatment of LA-NSCLC given its conformal delivery and general widespread availability in the radiation oncology community.²⁰ A subgroup analysis of the RTOG0617 trial demonstrated that the use of IMRT instead of 3DCRT was associated with improvements in health-related quality of life.¹⁹

The committee found that the systemic management that is usually appropriate was that of platinum-based chemotherapy given concurrently with radiation followed by consolidation durvalumab immunotherapy, as was administered in the PACIFIC trial.²¹⁻²³ This is primarily based on the advantages in overall survival and progression-free survival without notable compromise in health-related quality of life observed in this trial. Although durvalumab immunotherapy is currently approved for consolidation treatment in all patients with unresectable LA-NSCLC whose disease has not progressed after platinum-based chemoradiation therapy, subgroup analysis suggests that patients with a PD-L1 expression of less than 1% may not appreciably benefit from such treatment.²⁴ However, the accurate determination of the population with PD-L1 expression of less than 1% can be challenging given the uncertainties with fine-needle aspiration sampling and tumor heterogeneity. Additional prospective research is encouraged to provide evidence to better select patients for consolidation durvalumab immunotherapy. Such information may improve consensus among thoracic oncologists regarding indications for the use of consolidation durvalumab immunotherapy in unresectable LA-NSCLC.

Other approaches, including sequential therapy or the omission of consolidation durvalumab immunotherapy, were considered to usually not be appropriate for patients who qualify

and accept standard-of-care treatment with concurrent chemoradiation therapy followed by consolidation durvalumab.

Scenario 2: Treatment of a Patient With Unresectable LA-NSCLC and Good Performance Status and Bulky Disease—This scenario is similar to the base case (scenario 1) in terms of baseline factors except this situation deals with the scenario of bulky disease where radical radiotherapy cannot be safely planned and delivered at the initiation of primary treatment. In this scenario, the patient has both a bulky primary tumor and bilateral mediastinal nodes leading to unacceptable dose-volume histogram lung parameters for up-front treatment (Table 2).

The use of sequential chemotherapy followed by radiotherapy was considered to be usually appropriate for scenario 2 as it is both RCT evidence-based^{25,26} and still allows for radical radiation therapy to be used for chemotherapy responders. The use of delayed radical radiotherapy is still desirable compared with other approaches including palliative chemotherapy or palliative radiation therapy in terms of potential survival outcomes. Other approaches including sequential immunotherapy or chemotherapy/immunotherapy followed by radiotherapy are currently investigational and have not been confirmed in prospective trials in unresectable disease.

The committee found that the use of IMRT in these challenging bulky locally advanced lung cancer cases is usually appropriate given the conformal advantages of this approach over 3DCRT. IMPT may be appropriate in these patients given the conformal delivery associated with this approach.

Scenario 3: Treatment of a Patient With *EGFR*-Positive Unresectable LA-NSCLC and Good Performance Status—Scenario 3 changes the base case (scenario 1) primarily by presenting an LA-NSCLC with an *EGFR* variation instead of PD-L1 expression to investigate whether or not the biological signature of this particular form of lung cancer should change the recommended systemic management. Refer to the base case (scenario 1) for the consensus that was reached regarding both radiation dose and treatment delivery (Table 3).

The committee considered 12 different systemic therapy approaches, including various combinations of radiation therapy with or without various forms of systemic therapy (chemotherapy, immunotherapy, and targeted therapy). The timing of systemic therapy was also investigated in terms of neoadjuvant, concurrent, and adjuvant/consolidation approaches. Platinum-based concurrent chemoradiation remains a standard of care in this patient population. Although the US Food and Drug Administration has approved consolidation durvalumab across all patients with inoperable stage III NSCLC, including those with actionable *EGFR* variations, data that have been reported since the initial publication of the PACIFIC trial suggest a lack of benefit in this patient population.²⁷⁻²⁹ As such, the committee recommended concurrent platinum-based chemoradiotherapy with consolidation immunotherapy to be usually inappropriate in an *EGFR*-positive patient.

Additionally, the use of tyrosine kinase inhibitors as an alternative consolidation approach to immunotherapy is considered to be potentially appropriate in this *EGFR* variation-positive patient population. Randomized evidence supporting this approach in unresectable disease is currently lacking but may be considered in patients with contraindications to durvalumab immunotherapy, that is until prospective data clarify the role of this approach in the consolidation setting.³⁰ Although outside the scope of this unresectable guideline, results of the recently published ADAURA osimertinib trial,³¹ which demonstrated a survival benefit in the adjuvant postoperative setting, may assist clinicians in the selection of a tyrosine kinase inhibitor-agent in this scenario.

Scenario 4: Treatment of a Symptomatic Patient With Unresectable LA-NSCLC and Poor Performance Status

Scenario 4 details a case similar to the base case (scenario 1); however, the patient is symptomatic requiring palliation. Additionally, this patient has impaired performance status (ECOG score of 3) and weight loss of greater than 20%. Specifically, this scenario explores the appropriateness of both palliative and radical radiation fractionation regimens as well as treatment delivery for this class of patients. Systemic management was not considered in this scenario to isolate the discussion and consensus specifically to radiotherapy considerations. In this scenario, palliative fractionation schedules considered to be usually appropriate included 30 Gy in 10 fractions as well as 40 Gy to 45 Gy in 15 fractions (Table 4). This is consistent with previously published guidance for the management of palliative radiotherapy in lung cancer.³²⁻³⁵ The use of 20 Gy in 5 fractions or 1 to 2 fraction schemes was considered to be potentially appropriate, likely most optimally used in scenarios where fewer fractions are desirable by the patient.

Radical dosing that was considered to be usually appropriate consisted of dose fractionations such as 50 Gy to 55 Gy in 20 fractions and 60 Gy to 70 Gy in 1.8 Gy/d to 2.0 Gy/d. They have the benefit of potentially being combined with concurrent chemotherapy if deliverable. Other fractionation schemes, such as 60 Gy in 15 fractions and dose fractionations exceeding 70 Gy, were considered to be less desirable given the potential additional toxic effects either alone or with platinum-based concurrent chemotherapy. Similar to the other scenarios, these patients should be considered for IMRT treatment planning and delivery, although IMPT or 3DCRT may also be appropriate depending on the practice setting.

Individualization of treatment approach given this challenging patient population (scenarios 4 and 5) is recommended given the competing risk of death and morbidity from noncancer disease entities. A shared decision-making approach should be used with this patient population to coordinate treatment goals with patient expectations.

Scenario 5: Treatment of an Asymptomatic Patient With Unresectable LA-NSCLC Patient and Poor Performance Status

Scenario 5 explores the role of systemic therapy in an asymptomatic locally advanced *PD-L1*-positive lung cancer patient with poor pulmonary (forced expiratory volume < 0.7 L) and performance status (ECOG 3), otherwise with similar disease as the base case (scenario 1). No strong consensus was seen regarding a desirable approach that is usually appropriate; however, radiation therapy alone or radiation therapy in combination with either neoadjuvant or adjuvant/consolidation

systemic therapy were found to be potentially appropriate (eTable 2 in the Supplement). Concurrent chemoradiation therapy regimens were considered usually not appropriate in the setting of patients with compromised performance and pulmonary status.³⁶ Management of this scenario will likely benefit from both shared decision-making with the patient, as well as a multidisciplinary discussion at the tumor board.

Scenario 6: Treatment of a Patient With Unresectable LA-NSCLC and Local Recurrence—This final scenario explores the management of local progression after standard-of-care treatment for locally advanced lung cancer. In this case, the patient was found to have a *PET*-positive local recurrence 18 months after primary and maintenance therapy was completed. Both surgically resectable/operable and not surgically resectable/operable scenarios were investigated regarding the multimodality treatment of this complex entity.

In the surgically resectable and operable scenario, the use of neoadjuvant or adjuvant systemic therapy in combination with surgery to improve results was considered to be usually appropriate (eTable 3 in the Supplement).³⁷ Combinations of chemotherapy, immunotherapy, or both as primary treatments were all considered to be appropriate depending on patient preferences and tolerability. Observation was not considered to be generally appropriate unless selected by patient preference.

In the inoperable scenario, various forms of radiotherapy including palliative radiation therapy, radical alone or with neoadjuvant/concurrent systemic therapy, as well as SBRT alone, were all considered to be potentially appropriate, and the selection of therapy would depend on the characteristics of various patients, tumors, and treatment factors, which are potentially dependent on shared decision-making between clinician and patient (supported by a multidisciplinary tumor board). Combination chemotherapy and immunotherapy were preferred to be given over chemotherapy alone, immunotherapy alone, or observation for this patient population.

Discussion

Guideline Scope

The ARS AUC Thoracic Committee has developed consensus-based guidelines on the appropriate use of radiation and systemic therapies for the management of unresectable LA-NSCLC. This guideline has commented on the management of unresectable LA-NSCLC in terms of both radical and palliative-intent therapies, radiation dose, volume and technique, systemic therapy selection and timing, as well as the management of local and oligometastatic failure after primary radical therapy. This document also provides consensus-based recommendations for the management of various clinical presentations for this important and challenging patient population.

Summary of Evidence

In the creation of this document, a total of 69 references (between 1966 and 2021) were cited for the creation of the AUC guideline (eTable 1 in the Supplement). Of these, there were 30 well-designed studies (prospective randomized clinical trials), 9 moderately

well-designed studies, and 2 studies with design limitations. Additionally, there were 28 nonprimary data references (eg, meta-analyses or guidelines) or other documents (eg, commentaries). All references are summarized in eTable 1 in the Supplement.

Summary of Recommendations

The ARS AUC process and document provided the following summary recommendations for the treatment of LA-NSCLC:

1. Standard-of-care management of LA-NSCLC with good prognosis consists of combined concurrent radical (60 Gy to 70 Gy) platinum-based chemoradiation followed by appropriate consolidation therapy based on PD-L1/*EGFR* status.
2. Planning and delivery of locally advanced lung cancer radiotherapy usually should be performed using IMRT techniques, although 3DCRT and IMPT may be appropriate depending on tumor bulk and treatment availability.
3. A variety of palliative and radical fractionation schedules are available to treat patients with poor performance and/or pulmonary status. Concurrent regimens should be generally avoided in favor of either sequential therapy or radiation therapy alone in this compromised patient population to limit toxic effects while still deriving potential clinical benefits.

The salvage therapy for a local recurrence after successful primary management of locally advanced lung cancer is complex and likely requires both multidisciplinary input and shared decision-making with the patient. Various surgical, radiotherapeutic, and systemic options are available to manage this challenging patient population.

Conclusions

Evidence-based guidance on the management of various unresectable LA-NSCLC scenarios has been provided by the ARS AUC to optimize multidisciplinary patient care for this challenging patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest Disclosures:

Dr Higgins reported grants from Jazz Pharmaceuticals and other support from AstraZeneca, Janssen Pharmaceuticals, and RefleXion Medical during the conduct of the study. Dr Rimner reported grants from Varian Medical Systems, AstraZeneca, Merck, Boehringer Ingelheim, Pfizer, National Institutes of Health, personal fees from AstraZeneca, Merck, and MoreHealth outside the submitted work. Dr Chang reported grants from Bristol Myers Squibb (BMS), personal fees from the Varian Medical System, and IBA outside the submitted work. Dr Chun reported personal fees from AstraZeneca during the conduct of the study; personal fees from Norton Healthcare, Inc, Binaytara Foundation, ViewRay, Inc, Japanese Society for Radiation Oncology, Hong Kong Precision Oncology Society, National Cancer Institute (1R50CA275822), and personal fees from Curio Science, Inc outside the submitted work.

Dr Donington reported personal fees from Amgen, AstraZeneca, BMS, Merck, Roche/Genentech outside the submitted work. Dr Edelman reported personal fees from AstraZeneca, Takeda, Glaxo Smith Kline, Omega Therapeutics, personal fees from Novocure, InterVenn, WindMil, Seattle Genetics, Regeneron/Sanofi, Flame Consulting, Proventus Consulting, GE Healthcare Consulting, BioAlta Consulting, Replimmune Consulting,

Coherus Consulting, and AnHeart outside the submitted work. Dr Gubens reported personal fees from AnHeart, AstraZeneca, Atreca, BMS, Cardinal Health, Genzyme, Genentech/Roche, Gilead, Guardant, Invitae, iTeos, Merus, Sanofi, Summit, Surface, grants from Amgen, JNJ, Merck, OncoMed, and Trizell outside the submitted work. Dr Iyengar reported other support from Incyte and AstraZeneca outside the submitted work.

Dr Movsas reported grants from Varian Research, Philips Research, and ViewRay Research outside the submitted work. Dr Park reported personal fees from AstraZeneca, BMS, Daichi Sankyo, Inc, G1 Therapeutics, Galera Medical, and RefleXion Medical, and nonfinancial support from Merck Sharp & Dohme outside the submitted work. No other disclosures were reported.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33. doi:10.3322/caac.21708 [PubMed: 35020204]
2. Travis WD, Brambilla E, Nicholson AG, et al. ; WHO Panel. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10(9):1243–1260. doi:10.1097/JTO.0000000000000630 [PubMed: 26291008]
3. Vestergaard HH, Christensen MR, Lassen UN. A systematic review of targeted agents for non-small cell lung cancer. *Acta Oncol*. 2018;57(2):176–186. doi:10.1080/0284186X.2017.1404634 [PubMed: 29172833]
4. Guitoli G, Tiseo M, Di Maio M, Friboulet L, Facchinetti F. Immune checkpoint inhibitors in oncogene-addicted non-small cell lung cancer: a systematic review and meta-analysis. *Transl Lung Cancer Res*. 2021;10(6):2890–2916. doi:10.21037/tlcr-20-941 [PubMed: 34295687]
5. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer—major changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. *CA Cancer J Clin*. 2017;67(2):138–155. doi:10.3322/caac.21390 [PubMed: 28140453]
6. Detterbeck FC. The eighth edition TNM stage classification for lung cancer: what does it mean on main street. *J Thorac Cardiovasc Surg*. 2018;155(1):356–359. doi:10.1016/j.jtcvs.2017.08.138 [PubMed: 29061464]
7. Al Zaidi M, Wright GM. Locally advanced non-small cell lung cancer: the place of specialist thoracic surgery in the multidisciplinary team. *Transl Lung Cancer Res*. 2020;9(4):1680–1689. doi:10.21037/tlcr.2019.11.22 [PubMed: 32953541]
8. Gewanter RM, Rosenzweig KE, Chang JY, et al. ACR appropriateness criteria: nonsurgical treatment for non-small cell lung cancer: good performance status/definitive intent. *Curr Probl Cancer*. 2010;34(3):228–249. doi:10.1016/j.crrproblcancer.2010.04.001 [PubMed: 20541060]
9. Chang JY, Kestin LL, Barriger RB, et al. ACR Appropriateness criteria nonsurgical treatment for locally advanced non-small cell lung cancer: good performance status/definitive intent. *Oncology (Williston Park)*. 2014;28(8):706–710, 712, 714 passim. [PubMed: 25140629]
10. Ettinger DS, Wood DE, Aggarwal C, et al. ; OCN. NCCN guidelines insights: non-small cell lung cancer, version 1.2020. *J Natl Compr Canc Netw*. 2019;17(12):1464–1472. doi:10.6004/jnccn.2019.0059 [PubMed: 31805526]
11. National Comprehensive Care Network. Accessed March 8, 2024. <http://www.nccn.org>
12. Rodrigues G, Choy H, Bradley J, et al. Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. *Pract Radiat Oncol*. 2015;5(3):141–148. doi:10.1016/j.prr.2015.02.012 [PubMed: 25957184]
13. Postmus PE, Kerr KM, Oudkerk M, et al. ; ESMO Guidelines Committee. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv1–iv21. doi:10.1093/annonc/mdx222 [PubMed: 28881918]
14. Daly ME, Singh N, Ismaila N, et al. Management of stage III non-small cell lung cancer: ASCO guideline. *J Clin Oncol*. 2022;40(12):1356–1384. doi:10.1200/JCO.21.02528 [PubMed: 34936470]
15. American Radium Society appropriate use criteria methodology. Accessed March 8, 2024. <http://www.americanradiumsociety.org/page/aucmethodology>

16. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage III non–small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011;103(19):1452–1460. doi:10.1093/jnci/djr325 [PubMed: 21903745]
17. Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG Oncology RTOG 0617: standard-versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non–small cell lung cancer. *J Clin Oncol.* 2020;38(7):706–714. doi:10.1200/JCO.19.01162 [PubMed: 31841363]
18. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non–small cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol.* 2017;35(1):56–62. doi:10.1200/JCO.2016.69.1378 [PubMed: 28034064]
19. Movsas B, Hu C, Sloan J, et al. Quality of life analysis of a radiation dose-escalation study of patients with non–small cell lung cancer: a secondary analysis of the Radiation Therapy Oncology Group 0617 randomized clinical trial. *JAMA Oncol.* 2016;2(3):359–367. doi:10.1001/jamaoncol.2015.3969 [PubMed: 26606200]
20. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol.* 2007;30(3):239–244. doi:10.1097/01.coc.0000256691.27796.24 [PubMed: 17551299]
21. Antonia SJ, Villegas A, Daniel D, et al. ; PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379(24):2342–2350. doi:10.1056/NEJMoa1809697 [PubMed: 30280658]
22. Antonia SJ, Villegas A, Daniel D, et al. ; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non–small cell lung cancer. *N Engl J Med.* 2017;377(20):1919–1929. doi:10.1056/NEJMoa1709937 [PubMed: 28885881]
23. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small cell lung cancer. *J Clin Oncol.* 2022;40(12):1301–1311. doi:10.1200/JCO.21.01308 [PubMed: 35108059]
24. Paz-Ares L, Spira A, Raben D, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. *Ann Oncol.* 2020;31(6):798–806. doi:10.1016/j.annonc.2020.03.287 [PubMed: 32209338]
25. Sause W, Kolesar P, Taylor S IV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest.* 2000;117(2):358–364. doi:10.1378/chest.117.2.358 [PubMed: 10669675]
26. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. *J Natl Cancer Inst.* 1996;88(17):1210–1215. doi:10.1093/jnci/88.17.1210 [PubMed: 8780630]
27. Bauman J, Borghaei H. To give or not to give: consolidative durvalumab in EGFR-mutant NSCLC. *J Thorac Oncol.* 2021;16(6):894–896. doi:10.1016/j.jtho.2021.03.004 [PubMed: 34034885]
28. Liu Y, Zhang Z, Rinsurongkawong W, et al. Association of driver oncogene variations with outcomes in patients with locally advanced non–small cell lung cancer treated with chemoradiation and consolidative durvalumab. *JAMA Netw Open.* 2022;5(6):e2215589. doi:10.1001/jamanetworkopen.2022.15589 [PubMed: 35666500]
29. Negrao MV, Skoulidis F, Montesion M, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *J Immunother Cancer.* 2021;9(8):e002891. doi:10.1136/jitc-2021-002891 [PubMed: 34376553]
30. Lu S, Casarini I, Kato T, et al. Osimertinib maintenance after definitive chemoradiation in patients with unresectable egfr mutation positive stage III non–small cell lung cancer: LAURA trial in progress. *Clin Lung Cancer.* 2021;22(4):371–375. doi:10.1016/j.clc.2020.11.004 [PubMed: 33558193]
31. Herbst RS, Wu YL, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIa non–small cell lung cancer: updated results from the phase III randomized ADAURA trial. *J Clin Oncol.* 2023;41(10):1830–1840. doi:10.1200/JCO.22.02186 [PubMed: 36720083]

32. Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: an American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol.* 2011;1(2):60–71. doi:10.1016/j.pro.2011.01.005 [PubMed: 25740118]
33. Moeller B, Balagamwala EH, Chen A, et al. Palliative thoracic radiation therapy for non-small cell lung cancer: 2018 update of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol.* 2018; 8(4):245–250. doi:10.1016/j.pro.2018.02.009 [PubMed: 29625898]
34. Lester JF, Macbeth FR, Toy E, Coles B. Palliative radiotherapy regimens for non-small cell lung cancer. *Cochrane Database Syst Rev.* 2006;(4):CD002143. doi:10.1002/14651858.CD002143.pub2 [PubMed: 17054152]
35. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol.* 2008;26(24):4001–4011. doi:10.1200/JCO.2007.15.3312 [PubMed: 18711191]
36. Govindan R. Management of patients with non-small cell lung cancer and poor performance status. *Curr Treat Options Oncol.* 2003;4(1):55–59. doi:10.1007/s11864-003-0031-x [PubMed: 12525279]
37. Dickhoff C, Otten RHJ, Heymans MW, Dahele M. Salvage surgery for recurrent or persistent tumour after radical (chemo)radiotherapy for locally advanced non–small cell lung cancer: a systematic review. *Ther Adv Med Oncol.* 2018;10:1758835918804150. doi:10.1177/1758835918804150 [PubMed: 30305851]

Treatment of a Patient With Unresectable Locally Advanced Non–Small Cell Lung Cancer and Good Performance Status^a

Table 1.

Procedure	Final tabulations										Group median rating	Disagree ^b	Reference	SOE	SOR	
	Rating category															
		1	2	3	4	5	6	7	8	9						
Fractionation																
60-63 Gy (1.8-2.0 Gy/d)							1	1	11	9	NA	14-16	S		Str	
64-70 Gy (1.8-2.0 Gy/d)		1			1	3	8			7	X	15-17	EO		W	
>70 Gy (1.8-2.0 Gy/d)		5	5	5	1	1				3	NA	15	S		Str	
Technique																
3DCRT			1	1	11					5	NA	NA	EC		W	
IMRT						1	2	1	9	9	NA	17-18	M		Str	
IMPT				1	3	7	1	1	1	6	NA	NA	EC		W	
Systemic therapy																
Radiotherapy alone		6	4	2	1					2	NA	NA	EC		Str	
Sequential systemic therapy followed by radiotherapy		2	3	8						3	NA	NA	EC		Str	
Sequential radiotherapy followed by systemic therapy		1	7	5						2	NA	NA	EC		Str	
Concurrent chemoradiotherapy with no consolidation therapy		2	1	4	4	2				4	NA	NA	EC		W	
Concurrent chemoradiotherapy with consolidation chemotherapy		1	1	7	1	2				3	NA	NA	EC		W	
Concurrent chemoradiotherapy with consolidation immunotherapy									3	11	11	NA	19-21	S	Str	

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; EC, expert consensus; EO, expert opinion; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; M, medium; NA, not applicable; S, strong; SOE, strength of evidence; SOR, strength of recommendation; Str, strong recommendation; W, weak recommendation.

^aScenario 1: T3N2M0 (stage IIIB); 65-year-old man who was a current smoker (Eastern Cooperative Oncology Group performance status score of 0 or 1, weight loss <5%) with 6-cm left upper lobe adenocarcinoma (*ALK*-negative, *EGFR*-negative, and *PD-L1* expression of 70%) cancer and ipsilateral hilar and mediastinal nodes on computed tomography–positron emission tomography. No contraindications to chemotherapy or immunotherapy were present.

^bPer the University of California, Los Angeles/RAND Appropriateness Method, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation. The group median rating is set automatically to 5.

Table 2.
Treatment of a Patient With Unresectable Locally Advanced Non–Small Cell Lung Cancer, Good Performance Status, and Bulky Disease^a

Procedure	Technique	Rating category	Final tabulations									Group median rating	Disagree ^b	Reference	SOE	SOR	
			1	2	3	4	5	6	7	8	9						
3DCRT			2	2	7				1		3	NA	NA	EC	Str		
IMRT									2	3	8	9	NA	17-18	M	Str	
IMPT									4	6	2	1	6	NA	NA	EC	W
Systemic therapy																	
Radiotherapy alone (hypofractionated 40-45 Gy in 15 fractions)			1	1	11						3	NA	NA	EC	Str	Str	
Radiotherapy alone (conventional fractionation minimum 60 Gy)			1	3	9						3	NA	23-24	Str	Str	Str	
Sequential radiotherapy followed by systemic therapy				4	7	1	1				3	NA	NA	EC	W	W	
Sequential chemotherapy followed by radiotherapy						1			12		7	NA	23-24	Str	Str	Str	
Sequential Immunotherapy followed by radiotherapy			1			4	5	2			1	5	NA	EC	W	W	
Sequential chemoimmunotherapy followed by radiotherapy						2		8	3		6	NA	NA	EC	W	W	

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; EC, expert consensus; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; M, medium; NA, not applicable; SOE, strength of evidence; SOR, strength of recommendation; Str, strong recommendation; W, weak recommendation.

^aScenario 2: T4N3M0 (stage IIIC): a 60-year-old asymptomatic woman who was a current smoker (Eastern Cooperative Oncology Group performance status score of 0 or 1, weight loss <5%) with 10-cm right upper lobe adenocarcinoma (*ALK*-negative, *EGFR*-negative, and *PD-L1* expression of 70%) and ipsilateral hilar and bilateral mediastinal nodes on computed tomography–positron emission tomography. The patient was not currently a candidate for up-front concurrent chemoradiation due to unacceptable V20 and mean lung dose. No contraindications to chemotherapy or immunotherapy were present.

^bPer the University of California, Los Angeles/RAND Appropriateness Method, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation. The group median rating is set automatically to 5.

Table 3.

Treatment of a Patient With *EGFR*-Positive Unresectable Locally Advanced Non–Small Cell Lung Cancer and Good Performance Status^a

Procedure	Rating category	Final tabulations									Group median rating	Disagree ^b	Reference	SOE	SOR
		1	2	3	4	5	6	7	8	9					
Fractionation															
60-63 Gy (1.8-2.0 Gy/d)					1			3	9	9	NA	14-16	S	Str	
64-70 Gy (1.8-2.0 Gy/d)	1				2	1	9			7	X	15-17	L	W	
>70 Gy (1.8-2.0 Gy/d)	4	6	1	1						3	NA	15	S	Str	
Technique															
3DCRT		1	1	10	1					5	NA	NA	EC	W	
IMRT					3	1	9			9	NA	17-18	M	Str	
IMPT	1			3	6	2	1			6	X	NA	EC	W	
Systemic therapy															
Radiotherapy alone															
Sequential chemotherapy followed by radiotherapy	6	4	2	1						2	NA	NA	EC	Str	
Sequential chemotherapy followed by chemotherapy	5	8								3	NA	NA	EC	W	
Sequential radiotherapy followed by chemotherapy	3	3	4	2	1					3	NA	NA	EC	W	
Sequential targeted therapy followed by radiotherapy		11	1	1						3	NA	NA	EC	Str	
Sequential radiotherapy followed by targeted therapy	1	3	7	2						3	NA	NA	EC	W	
Sequential targeted therapy followed by concurrent chemoradiotherapy		9	2	1	1					3	X	NA	EC	W	
Sequential targeted therapy followed by concurrent chemoradiotherapy followed by immunotherapy	2	5	6							2	NA	NA	EC	Str	
Sequential targeted therapy followed by concurrent chemoradiotherapy followed by targeted therapy		10	1	1	1					3	NA	NA	EC	W	
Concurrent chemoradiotherapy with no consolidation systemic therapy		2	1	4	4	1				5	NA	25-27	M	W	
Concurrent chemoradiotherapy with consolidation chemotherapy		3	9	1						4	NA	NA	EC	W	
Concurrent chemoradiotherapy with consolidation immunotherapy	2	7	1							3	NA	25-27	M	Str	
Concurrent chemoradiotherapy with consolidation targeted therapy			2	1	7	1	2			6	NA	28-29	L	W	

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; EC, expert consensus; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; L, limited; M, medium; NA, not applicable; S, strong; SOE, strength of evidence; SOR, strength of recommendation; Str, strong recommendation; W, weak recommendation.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Scenario 3: T4N2M0 (stage IIIB); a 55-year-old man who was a current smoker (Eastern Cooperative Oncology Group performance status score of 0 or 1, weight loss <5%) with 7-cm right lower lobe adenocarcinoma (*ALK*-negative, *EGFR*-positive, deletion 19, and *PD-L1*-negative) cancer and ipsilateral hilar and mediastinal nodes on computed tomography–positron emission tomography. No contraindications to chemotherapy, targeted therapy, or immunotherapy were present.

^bPer the University of California, Los Angeles/RAND Appropriateness Method, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation. The group median rating is set automatically to 5.

Treatment of a Patient With Symptomatic Unresectable Locally Advanced Non–Small Cell Lung Cancer and Poor Performance Status^a

Table 4.

Procedure	Rating category	Final tabulations									Group median rating	Disagree ^b	Reference	SOE	SOR
		1	2	3	4	5	6	7	8	9					
Palliative fractionation															
8 Gy in 1 fraction or 16-17 Gy in 2 fractions		1	1	5	2	2					4	NA	30-33	M	W
20 Gy in 5 fractions				3	1	4	3				6	NA	30-33	M	W
30 Gy in 10 fractions					1	2	7	1			7	NA	30-33	M	W
40-45 Gy in 15 fractions				1		1	8	1			7	NA	30-33	M	W
Radical fractionation															
60 Gy in 15 fractions		1		1	5	3	1				5	NA	NA	EC	W
50-55 Gy in 20 fractions					2		11				7	NA	NA	EC	W
60-70 Gy (1.8-2.0 Gy/d)				1	1	1	9	1			7	NA	NA	EC	W
>70 Gy (1.8-2.0 Gy/d)	5	4	1	2							3	NA	NA	EC	W
Technique															
3DCRT		1		1	3	3	2	1			5	NA	NA	EC	W
IMRT				1	1		3	3	5	8		NA	NA	EC	W
IMPT			1	1	3	5	2	1		6		X	NA	EO	W

Abbreviations: 3DCRT, 3-dimensional conformal radiotherapy; EC, expert consensus; EO, expert opinion; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; M, medium; NA, not applicable; S, strong; SOE, strength of evidence; SOR, strength of recommendation; W, weak recommendation.

^aScenario 4: T3N3M0 (stage IIIC): a 65-year-old symptomatic (partial collapse with shortness of breath and hemoptysis) woman who was a current smoker (Eastern Cooperative Oncology Group performance status score of 3, weight loss >20%) with 5-cm left upper lobe adenocarcinoma (*ALK*-negative, *EGFR*-negative, and *PD-L1*-negative) cancer and ipsilateral hilar and bilateral mediastinal nodes on computed tomography–positron emission tomography. For radiation therapy alone.

^bPer the University of California, Los Angeles/RAND Appropriateness Method, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation. The group median rating is set automatically to 5.