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

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ABSTRACT

Introduction: The treatment of locally advanced non-small cell lung cancer (LA-NSCLC) has been informed by over five 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. The American Radium Society (ARS) Appropriate Use Criteria (AUC) Thoracic Committee has developed case-referenced consensus and evidence-based guidelines to inform clinical practice in unresectable LA-NSCLC.

Methods: The ARS AUC 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. Treatment appropriateness of a variety of LA-NSCLC variant scenarios were assessed by a consensus-based modified Delphi approach using a caliper of three points out of a range of nine points to denote consensus agreement. Committee recommendations were vetted by the ARS AUC Executive Committee and a two-week public comment period prior to official approval and adoption.

Results: Standard of care management of good prognosis locally advanced non-small cell lung cancer consists of combined concurrent radical (60-70Gy) chemoradiation followed by adjuvant immunotherapy irrespective of PDL1 status. Planning and delivery of locally advanced lung cancer radiotherapy usually should be performed using IMRT 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 multi-disciplinary input and shared decision making with the patient.

Conclusions: Evidence-based guidance on the management of various unresectable LA-NSCLC scenarios are provided by the ARS AUC in order to optimize multidisciplinary patient care for this challenging patient population.

Keywords: Lung cancer; Non-small cell, Locally-advanced, Non-metastatic, Appropriate Use

INTRODUCTION

Lung cancer remains the second most frequently diagnosed cancer in both males and females, with a total estimated annual incidence of over 235,000 cases in the United States. Lung cancer lethality 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 (SCLC) subtypes based on morphological and immunohistochemical parameters of biopsy and/or surgical samples obtained in the diagnosis and treatment of lung cancer [2]. Additionally, modern molecular pathological gene alteration analyses of NSCLC pathological samples have provided the opportunity to employ novel therapeutics beyond those of systemic therapy with traditional chemotherapeutic agents [3,4]. Notable actionable gene mutations include epidermal growth factor receptor (EGFR) gene mutations, anaplastic lymphoma kinase (ALK) gene rearrangements, mesenchymal-epithelial transition (MET) exon 14 skipping variants, and programmed death ligand 1 (PD-L1) molecule among others currently actionable and non-actionable gene mutations.

Approximately 20-30% of all NSCLC patients present with locally-advanced disease. Locally advanced non-small cell lung cancer (LA-NSCLC) is a heterogeneous group of patients that generally is considered to have advanced local (T4N0M0) and/or regional nodal (T3-4N1M0 or T1-4N2-3MO) disease without evidence of metastatic disease by modern staging approaches [5,6].

Patients with unresectable LA-NSCLC are not considered appropriate candidates for surgical resection either alone or in combination with neoadjuvant or adjuvant 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 pre- and post-resection and other pre-existing co-morbidities. 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 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 (ACR) in 2010 [8] 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- and consensus-based guidance for this patient population is from the National Comprehensive Cancer Network (NCCN) practice guidelines in oncology for NSCLC [10]. This document is regularly updated online (www.nccn.org) 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 (ASTRO) [11], European Society of Medical

Oncology [12] and the American Society of Clinical Oncology [13].

Since the last appropriate use criteria publication in 2014 [9], important clinical studies in radiation 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 have significantly informed systemic therapy options for many patients with NSCLC and their integration into LA-NSCLC pathways needs to be clarified. Given these significant 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.

MATERIALS AND METHODS

The ARS Appropriate Use Criteria (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 of the PubMed database from 1/1966 to 12/2022 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 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 in relation to time from exposure, and methods of assessments in accordance with ARS criteria (Supplementary Appendix).

Clinical variants were then developed through consensus conference calls to address key practice paradigms and controversies in management. A well-established methodology (modified Delphi) was used by the expert panel to rate the appropriate use of procedures pertaining to the clinical variants through three rounds of anonymous voting with monthly conference calls to discuss rationale to reach consensus. Majority attendance was required for 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 for 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 methodology and other supporting documents are available at http://www.americanradiumsociety.org/page/aucmethodology.

RESULTS

Literature Review

Role of radiotherapy versus observation in unresectable LA-NSCLC

The primary evidence for the utilization of radiotherapy as a backbone of treatment in unresectable LA-NSCLC was generated over 50 years ago by the Veterans Administration Lung Group (VALG) [14]. This randomized three-arm study investigated 40-50Gy of radiotherapy (primarily orthovoltage RT with a minor proportion of patients receiving cobalt-60) vs. non-specified chemotherapy vs. placebo. Median overall survival (OS) was not different in any of the protocol arms; however, one-year survival of 18% was reported to be superior in the radiation therapy treatment arm compared to the other arms of the trial. No other confirmation trials were done in this space; however, a SEER-Medicare analysis of elderly LA-NSCLC patients (>65 years) demonstrates a reduction in the hazard of death (HR 0.76) in patients who are treated with radiotherapy versus other strategies such as observation or chemotherapy alone [15]. This improvement in outcome was primarily in patients receiving modern forms of radiotherapy planning and delivery. Ultimately, these investigations have identified radiotherapy as a cornerstone of clinical trials investigating both radical and palliative therapies for unresectable LA-NSCLC.

Early clinical trials of radiotherapy alone in unresectable LA-NSCLC

Early trials of conventionally fractionated radiotherapy alone for unresectable LA-NSCLC focused on questions regarding total dose and the role of continuous versus split course treatment. This question has been investigated by Routh et al. [16] and in the Radiation Therapy Oncology Group (RTOG) 7311 [17]. Routh et al. investigated split course radiotherapy (63Gy in 35 fractions with a 10-14 day break midway through treatment) versus 59.4Gy in 1.8Gy/day fractions in a randomized controlled trial of 273 patients. This trial did not find any differences in OS or in morbidity as measured by standardized scales and physician assessments. RTOG 7311 was a randomized controlled trial assessing four levels of conventionally fractionated radiotherapy (40Gy/20 fractions split course with a 2-week break, 40Gy/20 fractions continuous, 50Gy/25 fractions continuous, and 60Gy/30 fractions continuous). Overall survival was not found to be statistically different between the arms of this trial; however, a combined analysis of two RTOG trials confirmed that a dose-response relationship exists between radiotherapy total dose, local control and long-term OS (notably after 3 years follow-up) [18].

As a result of these early randomized trials, prior to the advent of sequential and concurrent chemotherapy and radiotherapy, 60Gy in 30 fractions (as well as similar 1.8Gy/day fractionations) became a common standard of care for unresectable LA-NSCLC. Subsequently, a prospective phase I/II investigation into the use of dose-escalated conventional fractionation radiotherapy alone for unresectable LA-NSCLC beyond 60Gy were published by the RTOG [19]. However, this approach of

conventional dose escalation did not further change standard of care treatment since randomized controlled trials integrating chemotherapy began to report results.

Parallel to the development of conventionally fractionated radiotherapy, several investigations into the use of altered fractionation schedules were also initiated. These investigations included various radiotherapy approaches, including hypofractionation (30-32Gy in 5-6 fractions with two fractions per week, and 45Gy in 15 fractions over three weeks) [20-21], hyperfractionation (69.6Gy 1.2Gy BID) [22-23], and accelerated hyperfractionation (CHART 54Gy in 1.5Gy fractions TID over 12 consecutive days, CHARTWEL 60Gy in 40 fractions 1.5Gy BID over 18 weekend-less days, and the Australian fractionation of 60Gy in 30 fractions BID over 3 weeks) [24-26]. In general, these altered fractionation approaches either did not demonstrate significant survival advantages in favor of altered fractionation or were associated with excess toxicity that made this form of treatment difficult to routinely deliver to this patient population.

Given the extensive literature and controversies associated with altered fractionation, the Meta-analysis of Radiotherapy in Lung Cancer Collaborative Group conducted an individual patient meta-analysis to clarify both treatment outcomes and toxicities for this patient population [27]. This investigation assessed various approaches including very accelerated radiotherapy (n=6 trials), moderately accelerated radiotherapy (n=1 trial), and hyperfractionated radiotherapy with (n=1) or without (n=2) increases in total dose. Comparisons were made to treatment with conventional fractionation schemes. This meta-analysis demonstrated that some improvement in survival was noted with the use of altered fractionation compared to conventional fractionation (4% and 2% absolute benefit at 3 and 5 years, respectively); however, this came at the cost of a significant increase in treatment-related esophagitis (absolute risk was 10% greater). Given this suboptimal therapeutic ratio and the development of sequential and concurrent chemotherapeutic approaches, altered fractionation did not become a worldwide standard of care treatment for unresectable LA-NSCLC.

Role of concurrent chemoradiotherapy in unresectable LA-NSCLC

Initially, radiation alone was both the standard of care and primary focus of investigations attempting to optimize the therapeutic ratio for the treatment of unresectable LA-NSCLC. Based upon preclinical and feasibility studies, it was hypothesized that chemotherapy could improve outcomes when added to radiotherapy. Initially, sequential chemotherapy followed by radical radiation therapy was investigated to reduce potential overlapping toxicity profiles of both approaches, but concurrent chemoradiation was subsequently investigated as evidence regarding the safety of this approach became more widely available and acceptable.

The landmark study investigating the role of sequential chemotherapy followed by radiotherapy alone was conducted by the Cancer and Leukemia Group B (CALGB) and reported by Dillman et al. [28]. This randomized controlled trial assessed radical conventional radiotherapy with 60Gy in 30 fractions in both study arms; with the addition of two cycles of cisplatin/vinblastine neoadjuvant chemotherapy in the experimental

arm. Chemotherapy followed by radiotherapy demonstrated superior OS (median OS of 13.7 vs. 9.6 months; 5-year survival of 17% vs 6%). This finding was replicated in a three-arm Intergroup study assessing hyperfractionated radiotherapy and sequential chemotherapy followed by conventional radiotherapy versus the control arm of 60Gy in 30 fractions of radiation therapy alone [23]. This study confirmed that sequential chemotherapy followed by conventionally fractionated radiotherapy versus radiotherapy alone was the superior approach in terms of both median OS and 2-year OS. Two systematic reviews were conducted, and both affirmed the benefits of a sequential chemotherapy and radiotherapy approach to this patient population [29-30].

In follow-up to the successful integration of chemotherapy in the management of unresectable LA-NSCLC, the role of concurrent chemoradiotherapy was investigated to determine whether or not this approach could be utilized safely to further improve patient outcomes. The West Japan Lung Cancer Group investigated this approach with a randomized controlled trial assessing two cycles of concurrent versus sequential cisplatin, mitomycin, and vindesine-based chemotherapy with 56Gy in 28 fractions of split course (28Gy in 14 fractions x 2 split by 10 days) radiation therapy [31]. This trial demonstrated a benefit favoring the concurrent arm in terms of response rate, median OS and 5-year OS; however, it failed to fully shift the standard of care approach in unresectable LA-NSCLC given the split course nature of the radiotherapy in this trial. There was community uncertainty regarding whether a true benefit existed for concurrent therapy, as it was hypothesized that the benefits seen in this trial may not be replicated if conventionally fractionated non-split course radiotherapy was utilized instead.

The RTOG 9410 randomized trial was a three-arm study initiated to tackle two research questions (concurrent vs. sequential chemotherapy and conventional versus altered fractionation with hyperfractionation) [32]. The arms of the study included 1) sequential chemotherapy followed by 63Gy in 30 fractions, 2) concurrent chemoradiotherapy with 63Gy in 30 fractions, and 3) concurrent chemoradiotherapy with 69.6Gy BID with 1.2Gy/fraction. The concurrent arms of the study confirmed that this approach was superior to the sequential approach in terms of median OS (17.0 vs. 14.6 months) and 5-year OS (16% vs. 10%). However, this was at the cost of additional acute grade 3 or higher non-hematological toxicity (absolute additional risk of 18%, largely driven by esophagitis). No additional late toxicities were observed on this trial. This study shifted practice patterns increasingly towards the use of concurrent chemoradiotherapy for patients who are fit and can tolerate such therapy. This approach has been also affirmed by additional randomized trials and by systematic reviews on the topic of concurrent versus sequential chemotherapy integrated with radiation therapy [33-34].

The ideal concurrent chemotherapy regimen to be used has been the subject of many retrospective and prospective reports; however, a randomized controlled trial comparing the two most dominant regimens have been reported in the medical literature [35]. Liang J et al. conducted a 200-patient randomized controlled trial in China comparing two cycles of etoposide and cisplatin (EP) versus weekly paclitaxel and

carboplatin (PC) with concurrent 60-66Gy of conventionally fractionated radiotherapy. There was a statistically significant improvement in three-year OS in favor of the EP arm with a non-significant improvement in median OS as well. EP was associated with more grade 3 or greater esophagitis, whereas PC was associated with worse grade 2 or greater radiation pneumonitis. It should be noted that the OS seen in the carboplatin/paclitaxel arm was substantially less effective than that seen in the contemporaneous RTOG 0617 study (20.7 months vs. 28.7 months). Analysis of data from the Veterans Administration and a systemic review of the two regimens have indicated comparable efficacy with increased toxicity for cisplatin/etoposide [36-37]. Both regimens are currently utilized internationally by clinicians and are listed as options on various guideline statements [10-12]. Additionally, the PROCLAIM study evaluated a concurrent pemetrexed/cisplatin regimen compared to concurrent etoposide/cisplatin in a randomized phase 3 setting [38]. The enrollment on this trial was terminated early due to futility, as the pemetrexed/cisplatin arm was found not to be superior to the standard arm in terms of OS (hazard ratio 0.98 95% CI 0.79-1.20, p=0.831).

The role of induction chemotherapy followed by chemoradiotherapy has been investigated by the CALGB in a phase III randomized setting [39]. In CALGB 39081, the experimental arm of the trial was two cycles of carboplatin with paclitaxel chemotherapy followed by concurrent chemoradiotherapy that was compared to the same concurrent chemoradiotherapy regimen alone. This trial failed to detect any differences in median or 2-year OS. Phase III evidence for the use of either targeted agents or immunotherapy prior to chemoradiotherapy is currently lacking. However, a randomized phase II study assessing erlotinib versus gemcitabine/cisplatin as neoadjuvant treatment for EGFR mutant stage III NSCLC with N2 disease has been reported [40]. This trial did not demonstrate a statistically significant difference in the primary endpoint of objective response rate but did report an improvement in progression-free survival (PFS) in the erlotinib arm. Although, these trials did not confirm a routine role for neoadjuvant systemic therapy prior to concurrent chemoradiotherapy for unresectable LA-NSCLC, induction therapy can be considered to potentially downsize the bulk of cancer prior to definitive treatment, if necessary, to reduce the risk of significant acute and late toxicities.

Role of radiation dose intensification in concurrent chemoradiotherapy in unresectable LA-NSCLC

Contemporaneous with the development of the concurrent chemoradiation approach, significant advancements in imaging and radiotherapy techniques occurred to provide additional opportunities for further dose intensification. Increasing use of fluorodeoxyglucose-positron emission tomography (FDG-PET) and/or mediastinal staging combined with systemic therapies have led to the evidence-based recommendation that elective mediastinal nodal radiotherapy should not be routinely employed [41]. A randomized controlled trial has demonstrated that this recommendation may lead to the ability to further escalate total dose as the volume treated is reduced [42]. Additional, recent advances in treatment delivery such as intensity-modulated radiation therapy (IMRT), proton therapy, image-guided radiation

therapy, treatment gating, and four-dimensional CT simulation have all further improved the ability to potentially dose intensify radiation treatment [43].

In response to a series of previous reviewed retrospective and prospective phase I/II trials, the RTOG/NRG Oncology conducted a four arm (2x2 factorial design) study to assess the impact of dose intensification (74Gy in 37 fractions versus 60Gy in 30 fractions) as well as the role of consolidation cetuximab on OS in unresectable LA-NSCLC (RTOG 0617) [44-45]. A longer-term update of this clinical trial was recently published reporting a median of five years of follow-up [44]. This update demonstrated that the higher-dose arm of the study was associated with worse median OS (20.3 vs. 28.7 months, p=0.0072) and PFS (p=0.055). Treatment with higher dose was also associated with worse acute esophagitis and more treatment-related death (9 vs 3 cases). Interestingly, the control arm of the study demonstrated excellent survival characteristics when compared to other previously published clinical trial reports likely due to stage migration and improvements in supportive care and treatment delivery. Subsequent secondary analyses from this trial reported that patients treated with IMRT had lower pneumonitis risk, lower cardiac doses, and higher compliance with consolidative chemotherapy [46], as well as better preservation of quality-of-life [47].

Therefore, RTOG 0617 affirmed 60Gy in 30 fractions as the standard of care dose fractionation in concurrent chemoradiation; however, other intermediate dose fractionations (63-70Gy) have been employed as the control and/or superior arms on cooperative group trials are commonly used by clinicians [48]. Other altered fractionation schedules in concert with concurrent chemoradiotherapy have also been investigated in randomized trials, including the RTOG hyperfractionation regimen of 69.6Gy given in 1.2Gy per fraction BID [32] as well as the CHART [24], CHARTWEL [25], HART [49] and Australian [26] accelerated fractionation regimens. No trials have shown clear superiority to conventionally fractionated approaches to shift commonly accepted and reported international standards of care. Hypofractionated radiotherapy with 55Gy in 20 fractions was found to be tolerable in a phase II trial setting when given concurrently with chemotherapy; however, this approach has not been directly compared to conventional chemoradiotherapy in a randomized phase III trial [50].

Role of consolidation systemic therapy in unresectable LA-NSCLC

The use of consolidation chemotherapy after concurrent chemoradiotherapy has been studied in multiple randomized phase III trials [51-52]. The Hoosier Oncology group trial assessed three cycles of docetaxel versus placebo after concurrent cisplatin/etoposide-based chemoradiotherapy [51]. This trial was prematurely stopped prior to completing accrual targets due to a futility stopping rule. When reported, there was no difference in median OS between the study arms (21.2 months for docetaxel and 23.3 months for placebo) but a difference in treatment-related death was observed (5.5% vs. 0% in favor of the placebo arm). An additional randomized trial assessing consolidation cisplatin/vinorelbine vs. observation was conducted and reported not to show any clinical benefits in terms of OS or PFS [52]. The regimen itself was well tolerated with limited additional side-effects. Unfortunately, no trial has addressed the

utility of consolidation full dose chemotherapy with carboplatin/paclitaxel following the use of weekly low dose carboplatin/paclitaxel in LA-NSCLC. This approach was employed in RTOG 0617 with the results as described above.

The Southwest Oncology Group (SWOG) conducted a placebo-controlled randomized trial assessing the use of an EGFR tyrosine-kinase inhibitor (gefitinib) after concurrent chemoradiation with three cycles of docetaxel consolidation for stage III NSCLC [53]. This use of gefitinib was associated with inferior median OS (23 vs. 35 months, p=0.013), with 2% of patients having treatment-related death with use of the tyrosine-kinase inhibitor. This trial was done in an unselected population (i.e. EGFR mutation status was not assessed). Additionally, RTOG 0617 investigated the role of cetuximab (EGFR receptor inhibitor) as consolidation therapy after definitive chemoradiation and three cycles of consolidation carboplatin/paclitaxel for stage III NSCLC [44-45]. The additional use of cetuximab was not shown to provide any additional clinical benefit to this patient population.

The role of immunotherapy has been clarified with publication of the PACIFIC trial assessing consolidation durvalumab in non-progressing unresectable LA-NSCLC patients after primary chemoradiotherapy [54-57]. In total, 713 patients were randomized in a 2:1 ratio to either intravenous weekly durvalumab or placebo for up to 12 months. An initial report demonstrated a statistically significant improvement in PFS (16.8 months vs. 5.6 months, p<0.001) with acceptable toxicity and treatment-related events [55]. A subsequent publication reported improved two-year OS associated with the experimental immunotherapy arm (66.3% vs. 55.6% p=0.005) with no additional safety issues arising in the interim [54]. An analysis of patient-reported outcomes (PROs) did not identify any compromise in relevant domains such as cough, chest pain fatigue, appetite, physical functioning or global quality-of-life [56]. The latest update to the PACIFIC trial reporting five-year OS demonstrates persistent benefits to the addition of consolidation durvalumab (42.9% vs. 33.4%) [56]. Consolidation durvalumab has become the standard of care for consolidation in unresectable non-progressing LA-NSCLC after concurrent chemoradiotherapy.

There is interest in the investigation of concurrent immunotherapy and targeted therapy with concurrent chemoradiation in the medical literature. The KEYNOTE-799 non-randomized phase II trial assessing concurrent pembrolizumab demonstrated objective response rates of over 70% for both squamous and non-squamous histologies with manageable toxicity profiles [58]. Ongoing follow-up phase III studies assessing concurrent immunotherapy with concurrent chemoradiotherapy include the MK-7339-012/KEYLYNK-012 concurrent pembrolizumab trial (NCT04380636) and the fully accrued PACIFIC-2 durvalumab trial (NCT03519971). Concurrent administration of EGFR targeted therapy with concurrent chemoradiation is being investigated with the ongoing LAURA trial [59].

Role of palliative radiotherapy in unresectable LA-NSCLC

The main focus of many clinical trials for unresectable LA-NSCLC has been in the

radical treatment with curative intent for this patient population. However, some patients with locally advanced non-metastatic disease are not appropriate for these treatment protocols due to a variety of factors including performance status, disease burden, and patient preferences. Despite not being appropriate for aggressive multi-modality radical therapy, many of these patients may still benefit from palliative radiotherapy for thoracic symptoms such as cough, shortness of breath, bronchial obstruction, and hemoptysis.

This patient population has been the subject of an ASTRO practice guideline [60] with a recent update [61] and two systematic reviews [62-63]. Collectively, these investigations recommend shorter fractionation schedules (e.g 20Gy in 5 fractions or 16-17Gy in 2 fractions) for symptomatic patients with poor performance status or other negative prognostic factors. More protracted radiotherapy regimens (e.g. 30Gy in 10 fractions or 39-60Gy in 13-15 fractions) should be reserved for patients with good performance status. In this patient population there may be more acute side effects with such therapy; however, there may be improvement in total symptom score and a suggestion of modest survival benefits as well. Additionally, two randomized trials have demonstrated that the addition of chemotherapy to palliative radiotherapeutic regimens for unresectable LA-NSCLC are associated with significant improvements in one- and two-year survival outcomes [64-65]. These same trials did not find any benefit in patients with stage IV disease that were included in the same clinical trials.

Variant Scenarios

Variant 1: Treatment of a LA-NSCLC patient with good performance status

The first variant of this appropriate use criteria document for LA-NSCLC was designed to describe a typical case that radiation oncologists would manage routinely in their practice. This unresectable PDL1 positive stage III patient with good prognostic baseline performance status, low weight loss, and no contraindications to any forms of radiation and/or systemic therapies was designed both to investigate this scenario and to serve as a base case for the additional variants described in this report (Table 1).

There was consensus that doses of 60-63Gy in 1.8-2.0Gy/day was appropriate given the results of the RTOG 9410 and 0617 studies [32, 44-45]. Modest escalation of dose up to 70Gy was considered to be appropriate by the committee, although prospective evidence for this approach is lacking [47] and will be informed by the results of RTOG 1308 when completed [66]. Dose escalation to high levels over 70Gy, including 74Gy as investigated in the 0617 trial, was considered to be usually not appropriate given the poor outcomes reported to date with this approach [44-45].

Various techniques including three-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 radiation therapy (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 [42]. A subgroup analysis of the RTOG 0617 trial demonstrated that the use of IMRT instead of 3DCRT was associated with improvements in health-related quality-of-life [47].

The committee found that the systemic management that is usually appropriate was that of chemotherapy given concurrently with radiation followed by adjuvant immunotherapy, as was administered in the PACIFIC trial [54-57]. This is based on the advantages in overall survival and progression-free survival without significant compromise in health-related quality-of-life. Other approaches, including sequential therapy or the omission of adjuvant immunotherapies, were considered to be usually not appropriate for patient who qualify and accept standard of care treatment with concurrent chemoradiation followed by adjuvant immunotherapy.

Variant 2: Treatment of a LA-NSCLC patient with good performance status and bulky disease

This variant is similar to the variant 1 base case 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 variant, the patient has both a bulky primary tumor and bilateral mediastinal nodes leading to unacceptable dose-volume histogram lung parameters for upfront treatment (Table 2).

The use of sequential chemotherapy followed by radiotherapy was considered to be usually appropriate for variant 2 as it is both RCT evidence-based [23,28] and still allows for radical radiation therapy to be employed for chemotherapy responders. The use of delayed radical radiotherapy is still desirable compared to 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 cases given the conformal delivery associated with this approach.

Variant 3: Treatment of an EGFR-positive LA-NSCLC patient with good performance status

Variant 3 changes the variant 1 base case primarily by presenting a LA-NSCLC with an EGFR mutation instead of PDL1 expression to investigate whether or not the biological signature of this particular form of lung cancer should change recommended systemic management. Consensus regarding both radiation dose and treatment delivery were similar to base variant 1 and will not be further discussed here (Table 3).

The committee considered 12 different systemic therapy approaches, including

various combinations of radiation with or without various forms of systemic therapy (chemotherapy, immunotherapy, and targeted therapy). Timing of systemic therapy was also investigated in terms of neoadjuvant, concurrent, and adjuvant approaches. Concurrent chemoradiation remains a standard of care in this patient population. Although there is an FDA approval for consolidation durvalumab across all patients with inoperable stage III non-small cell lung cancer, including those with actionable EGFR mutations, data that have been reported since the initial publication of PACIFIC suggest lack of benefit in this patient population [67-69]. As such, the committee recommended concurrent chemoradiotherapy with consolidation immunotherapy to be usually inappropriate in an EGFR-positive patient.

Additionally, the use of TKI as an alternative adjuvant approach to immunotherapy is considered to be potentially appropriate in this EGFR mutation positive patient population. There is a lack of randomized evidence supporting this approach in unresectable disease but may be considered in patients with contraindications to immunotherapy. Most of the reports of the use of TKI as an adjuvant therapy for lung cancer is in resectable (or potentially resectable) disease and is not within this scope of this report (and hence not further reviewed here).

Variant 4: Treatment of a symptomatic LA-NSCLC patient with poor performance status

Variant 4 details a case similar to the base case (Variant 1); however, the patient is symptomatic with symptoms requiring palliation. Additionally, this patient variant has impaired performance status and weight loss. Specifically, this variant is exploring the appropriateness of both palliative and radical radiation fractionation regimens as well as treatment delivery for this class of patient. Systemic management was not considered in this variant in order to isolate the discussion and consensus specifically to radiotherapy considerations.

In this scenario, palliative fractionation schedules considered to be usually appropriate included 30Gy in 10 fractions as well as 40-45Gy in 15 fractions. This is consistent with previously published guidance for the management of palliative radiotherapy in lung cancer [60-63]. The use of 20Gy in 5 fractions or 1-2 fraction schemes were considered to be potentially appropriate, likely most optimally employed for scenarios where fewer fractions are desirable by the patient.

Radical dosing that was considered to be usually appropriate consisted of dose fractionations such as 50-55Gy in 20 fractions and 60-70Gy in 1.8-2.0Gy/day. They have the benefit of potentially being combined with concurrent chemotherapy if deliverable. Other fractionation schemes, such as 60Gy in 15 fractions and dose fractionations over 70Gy, were considered to be less desirable given potential additional toxicity either alone or with concurrent chemotherapy. Similar to the other variants, these patients should be considered for IMRT treatment planning and delivery, although

IMPT or 3DCRT may also be appropriate depending on practice setting.

Variant 5: Treatment of an asymptomatic LA-NSCLC patient with poor performance status

Variant 5 explores the role of systemic therapy in an asymptomatic locally advanced PDL1 positive lung cancer patient with poor pulmonary and performance status otherwise with similar disease as the base case depicted in variant 1. No strong consensus was seen with regards to a desirable approach that usually is appropriate; however, radiation alone or radiation in combination with either neoadjuvant or adjuvant systemic therapy were found to be potentially appropriate. Concurrent chemoradiation regimens were felt to be usually not appropriate in the setting of patients with compromised performance and pulmonary status. Management of this scenario will likely benefit from both shared decision making with the patient as well as multi-disciplinary discussion at tumor board.

Variant 6: Treatment of a LA-NSCLC patient with local recurrence

This final variant 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 in order to improve results was considered to be usually appropriate. Combinations of chemotherapy, immunotherapy, or both as primary treatment 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, radical alone or with neoadjuvant/concurrent systemic therapy, and SBRT alone were all considered to be potentially appropriate, and selection of therapy would depend on various patient, tumor, and treatment factors that would be subject to shared decision making between clinician and patient (supported by multi-disciplinary tumor board). Combination chemotherapy and immunotherapy was preferred to be given over chemotherapy alone, immunotherapy alone, or observation for this patient population.

DISCUSSION

Guideline scope

The ARS AUC Thoracic Committee have 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. Of these, there were 30 well-designed studies (prospective randomized controlled trials), 9 moderately well-designed studies, and 2 studies with design limitations. Additionally, there 28 non-primary data references (such as meta-analyses or guidelines) or other documents (such as commentaries). All references are summarized in a supplementary appendix.

Summary of recommendations

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

1. Standard of care management of good prognosis locally advanced non-small cell lung cancer consists of combined concurrent radical (60-70Gy) chemoradiation followed by appropriate adjuvant therapy based on PDL1/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 alone in this compromised patient population in order to both limits toxicity while still deriving potential clinical benefits.

4. The salvage therapy for a local recurrence after successful primary management of locally advanced lung cancer is complex and likely requires both multi-

disciplinary input and shared decision making with the patient. Various surgical, radiotherapeutic and systemic options are available to manage this challenging patient population.

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DISCLOSURES

<ARS to provide disclosure text>

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