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Special Article

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

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Abstract

Purpose: To provide guidance to physicians and patients with regard to the use of definitive external beam radiation therapy (RT) in locally advanced non-small cell lung cancer (LA NSCLC) based on available medical evidence complemented by consensus-based expert opinion.

Methods and materials: A panel authorized by the American Society for Radiation Oncology (ASTRO) Board of Directors and Guidelines Subcommittee conducted 3 systematic reviews on the following topics: (1) ideal radical RT dose fractionation for RT alone; (2) ideal radical RT dose fractionation for chemoradiation; and (3) ideal timing of radical radiation therapy with systemic chemotherapy. Practice guideline recommendations were approved using an a priori–defined consensus-building methodology supported by ASTRO and approved tools for the grading of evidence quality and the strength of guideline recommendations.

Results: For patients managed by RT alone, a minimum dose of 60 Gy of RT is recommended. Dose escalation beyond 60 Gy in the context of combined modality concurrent chemoradiation has not been found to be associated with any clinical benefits. In the context of combined modality therapy, chemotherapy and radiation should ideally be given concurrently to maximize survival, local control, and disease response rate.

Conclusions: A consensus and evidence-based clinical practice guideline for the definitive radiotherapeutic management of LA NSCLC has been created that addresses 3 important questions.

Introduction

External beam radiation therapy is routinely used for the definitive treatment of unresectable locally advanced (LA) non-small cell lung cancer (NSCLC) either as therapy given concurrently or sequentially with systemic therapy or as primary curative therapy without any other surgical or drug therapy (for patients that cannot tolerate these additional treatments).[1] Given the central importance of radiation therapy in the management of unresectable LA NSCLC combined with an impressive track record of completed phase 3 randomized clinical trials informing the management of this challenging patient population over the past 35 years; a radiation therapy-focused practice guideline for unresectable LA NSCLC is timely.[2] Because of the length of the guideline, the document was split into 2 parts. This document focusses on definitive radiation therapy; the second is on adjuvant radiation therapy. The purpose of this executive summary is to provide guidance to physicians and patients with regard to the use of definitive external beam radiation therapy for unresectable LA NSCLC, based on available medical evidence complemented by expert opinion. This document is an executive summary of 3 key questions addressing definitive radiation therapy for unresectable NSCLC; the full guideline document is available as supplementary material online only at www.practicalradonc.org. Other free supplementary materials include evidence tables for each key question, the search strategy, and processes for grading evidence and recommendations.

Methods and materials

Process and literature review

Please see the full-text version of the practice guideline (available as supplementary material online only at www.practicalradonc.org) for details of the panel selection and review process. An analytic framework, based on the identified population, interventions, comparators, and outcomes was used to refine the systematic review search (for articles between January 1966 and March 2013; searches were done on March 11, 2013). Inclusion criteria keywords used to construct strategies for literature review included: human, adult, locally advanced non-small cell lung cancer, and radiation therapy. Exclusion criteria keywords included: small cell lung cancer, metastatic disease, noncurative or palliative intent, preclinical data, pediatric populations, and carcinoid/mesothelioma or thymic tumors. Initially, 570 abstracts were identified. A total of 74 articles were fully abstracted to provide supporting evidence for the clinical guideline recommendations. The 3 key questions (KQs) and guideline statements related to definitive radiation therapy management are shown in Table 1.

Grading of evidence, recommendations, and consensus methodology

Where available, a high quality of evidence (HQE) formed the basis of the recommendation statements in accordance with the Institute of Medicine standards and was categorized by the American College of Physicians' Strength of Evidence Rating.[3] A modified Delphi approach was used to grade the strength of the recommendation (strong or weak). Panelists rated the agreement with each recommendation pertaining to the KQs on a 5-point Likert scale, ranging from strongly disagree to strongly agree. In determining the strength of the recommendation, the balance of risks and benefits was assessed. A strong recommendation was defined as "the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus." A weak recommendation was defined as "the benefit of the intervention equals the risk, or vice versa, and the panel

has reached uniform or nonuniform consensus." An a priori threshold of ≥75% of raters was determined to indicate when consensus was achieved.[4] The process for grading evidence and recommendations can be found in the supplementary materials (available online only at www.practicalradonc.org).

Results

KQ1: What is the ideal external beam dose fractionation for the curative-intent treatment of locally advanced non-small cell lung cancer with radiation therapy alone?

Guideline statements and evidence summary

A. Radiation therapy alone has been shown to be superior to observation strategies or chemotherapy alone for LA NSCLC in terms of overall survival, but at the cost of treatment-related side effects such as esophagitis and pneumonitis **(a moderate quality of evidence [MQE], recommendation rated as "strong")**.

There has been a paucity of randomized control trials (RCTs) evaluating the role of radiation therapy versus observation or chemotherapy alone in LA NSCLC; however, 1 early RCT randomized 800 patients to radiation therapy (40-50 Gy), chemotherapy, and placebo.[5] The trial demonstrated an improvement in overall survival (OS) in the radiation therapy arm (18% one-year survival vs. 14% in the control group). This finding was confirmed by a recent Surveillance, Epidemiology, and End Results registry analysis.[6] The study found that radiation therapy was associated with improved OS (hazard ratio, 0.76) at the cost of increased risk of hospitalization for pneumonitis (odds ratio, 89), and esophagitis (odds ratio, 8).

B. Radiation therapy alone may be used as definitive radical treatment for patients with LA NSCLC who are ineligible for combined modality therapy (ie, due to poor performance status, medical comorbidity, extensive weight loss, and/or patient preferences) but with a tradeoff of survival for improved treatment tolerability **(HQE, recommendation rated as "strong")**.

Until the 1980s, radiation therapy alone had been the standard of care for LA NSCLC despite dismal survival data associated with this approach.[5,7,8] Subsequent results of RCTs shifted the standard first toward sequential chemotherapy followed by radiation therapy and then immediate concurrent chemoradiation therapy to treat both locoregional and micrometastatic disease in patients with LA NSCLC.[9-14] The net result of these studies demonstrated that OS improved with treatment intensity; however, treatment-related toxicity (including radiation pneumonitis and esophagitis) also increased. For patients that cannot tolerate chemotherapy, treatment with radical-intent radiation alone can still provide some OS benefits and improved treatment tolerability.

C. In the context of conventionally fractionated radiation therapy, a minimum dose of 60 Gy is recommended to optimize important clinical outcomes such as local control **(HQE, recommendation rated as "strong")**.

Radiation Therapy Oncology Group (RTOG) 7301 investigated conventionally fractionated (CF, 2 Gy) radiation therapy comparing 40 Gy (continuous or split course), 50 Gy continuous, and 60 Gy continuous for LA NSCLC.[15] Although the OS was not improved with the increased radiation therapy dose in this study, further review of 2 RTOG trials concluded that a dose-response relationship existed for local control and OS.[16] As a result of these studies, a minimum dose of 60 Gy in 2-Gy fractions defined a standard of care for LA NSCLC. Subsequent phase 1 dose escalation trials have not translated into RCTs to further define the ideal CF schedule for radiation alone treatment.

D. Altered fractionation schedules that have been explored in the medical literature include hyperfractionation (lower dose per fraction over the standard treatment duration), accelerated fractionation (conventional fraction size and same total dose, given in a shorter period), accelerated hyperfractionation (combination of these 2), and hypofractionation (higher dose per fraction and fewer fractions) **(no evidence rating, recommendation rated as "strong")**.

E. Specific altered fractionation schemes that have been investigated in various comparative effectiveness research investigations (including randomized controlled trials) include 45 Gy/15 fractions (hypofractionation), 69.6 Gy/58 fractions twice daily (BID) (hyperfractionation), 54 Gy/36 fractions TID over 12 consecutive days (continuous hyperfractionated accelerated radiation therapy [CHART], accelerated hyperfractionation), and 60 Gy/40 fractions TID over 18 days (continuous hyperfractionated accelerated radiation therapy weekend-less [CHARTWEL], accelerated hyperfractionation) **(no evidence rating, recommendation rated as "strong")**.

A retrospective report evaluated hypofractionated radiation therapy (45 Gy in 15 fractions over 3 weeks) as compared with CF (≥60 Gy) radiation therapy.[17] There were no local control or OS differences between the radiation therapy groups. The investigators contend that hypofractionated regimens may be a reasonable alternative to CF and should be prospectively studied.

Based on the phase 1/2 RTOG 8311 study,[18] RTOG/SWOG/Eastern Cooperative Oncology Group launched a 3-arm RCT evaluating CF radiation therapy to 60 Gy, hyperfractionated (HF) 69.6 Gy (BID, 4-6 hours apart), and induction chemotherapy followed by standard radiation therapy.[9] Although the median survival with HF radiation therapy was intermediate to those receiving combined therapy and standard radiation therapy arms, this finding failed to reach statistical significance.

The Medical Research Council of Britain completed a study of CHART.[18] It consisted of thrice-daily (TID)

Table 1 Grading of evidence, recommendations and consensus methodology

Guideline statement	Strength of evidence	Strength of recommendation	Percent agreement
Key Question #1: What is the ideal external beam dose fractionation for the curative-intent treatment of locally advanced non-small cell lung cancer with radiation therapy alone?			
Statement A. Radiation therapy alone has been shown to be superior to observation strategies or chemotherapy alone for LA NSCLC in terms of overall survival but at the cost of treatment-related side effects such as esophagitis and pneumonitis.	MQE	Strong	86
Statement B. Radiation therapy alone may be used as definitive radical treatment for patients with LA NSCLC who are ineligible for combined modality therapy (ie, due to poor performance status, medical comorbidity, extensive weight loss, and/or patient preferences) but with a tradeoff of survival for improved treatment tolerability.	HQE	Strong	100
Statement C. In the context of conventionally fractionated radiation therapy, a minimum dose of 60 Gy is recommended to optimize important clinical outcomes such as local control.	HQE	Strong	100
Statement D. Altered fractionation schedules that have been explored in the medical literature include hyperfractionation (lower dose per fraction over the standard treatment duration), accelerated fractionation (conventional fraction size and same total dose, given in a shorter period of time), accelerated hyperfractionation (combination of these 2), and hypofractionation (higher dose per fraction and fewer fractions).	n/a	Strong	100
Statement E. Specific altered fractionation schemes that have been investigated in various comparative effectiveness research investigations (including randomized controlled trials) include 45 Gy/15 fractions (hypofractionation), 69.6 Gy/58 fractions BID (hyperfractionation), 54 Gy/36 fractions TID over 12 consecutive days (CHART, accelerated hyperfractionation), and 60 Gy/40 fractions TID (CHARTWEL, accelerated hyperfractionation).	n/a	Strong	100
Key Question #2: What is the ideal external beam dose fractionation for the curative-intent treatment of locally advanced non-small cell lung cancer with chemotherapy?			
Statement A. The standard thoracic radiation therapy dose fractionation for patients treated with concurrent chemotherapy is 60 Gy given in 2 Gy once daily fractions over 6 weeks.	MQE	Strong	93
Statement B. Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be associated with any clinical benefits including overall survival.	MQE	Strong	86
Statement C. Hyperfractionated radiation therapy regimens that do not result in acceleration of the treatment course, even though the total nominal radiation therapy dose may be modestly increased, do not appear to improve outcomes compared with conventionally fractionated therapy.	MQE	Strong	93
Statement D. The optimal thoracic radiation therapy regimen for patients receiving sequential chemotherapy and radiation therapy is not known; however, results from the CHARTWEL and HART phase 3 studies suggest that increasing the biologic equivalent dose by using accelerated hyperfractionated radiation therapy may be of benefit following induction chemotherapy in locally advanced non-small cell lung cancer.	MQE	Strong	86
Statement E. Although the impact of increasing the predicted biologic equivalent dose via accelerated radiation therapy regimens is not clear, further study of accelerated hypofractionated regimens is of interest to optimize the therapeutic ratio of treatment, particularly in the context of advanced imaging, radiation therapy planning, and treatment delivery.	n/a	Strong	100
Key Question #3: What is the ideal timing of external beam radiation therapy in relation to systemic chemotherapy for the curative-intent treatment of locally advanced non-small cell lung cancer?			
Statement A. There is phase 3 evidence demonstrating improved overall survival, local control, and response rate associated with concurrent chemoradiation when compared against sequential chemotherapy followed by radiation.	HQE	Strong	100
Statement B. There is no proven role for the routine use of induction chemotherapy prior to chemoradiation therapy, although this treatment paradigm can be considered for the management of bulky tumors to allow for radical planning after chemotherapy response.	MQE	Strong	93
Statement C. There are no phase 3 data specifically supporting the role for consolidation chemotherapy after chemoradiation therapy for the improvement of overall survival; however, this treatment is still routinely given to manage potential micrometastatic disease particularly if full systemic chemotherapy doses were not delivered during radiation therapy.	LQE	Strong	93
Statement D. For patients that cannot tolerate concurrent chemoradiation therapy, sequential chemotherapy followed by radical radiation has been shown to be associated with an overall survival benefit when compared to radiation therapy alone.	HQE	Strong	86

(Continued)

Table 1 (*continued*)

Guideline statement	Strength of evidence	Strength of recommendation	Percent agreement
Statement E. The ideal concurrent chemotherapy regimen has not been determined; however, the 2 most common regimens (cisplatin/etoposide and carboplatin/paclitaxel) are the subject of a completed phase 3 clinical trial (NCT01494558).	n/a	Strong	100

HQE, high quality of evidence; LA, locally advanced; LQE, low quality of evidence; MQE, moderate quality of evidence; n/a, not applicable; NSCLC, non-small cell lung cancer.

radiation therapy to a dose of 54 Gy in 1.5 Gy per fraction (6-hour intervals over 12 consecutive days). This trial demonstrated a survival benefit of CHART over CF standard radiation therapy, predominantly in squamous cell carcinoma patients. The Medical Research Council investigated a CHARTWEL schedule of 60 Gy in 1.5 Gy TID over 18 days versus the CHART TID approach with weekends.[19] In a report focusing on toxicity comparisons, the CHARTWEL approach was associated with enhanced esophagitis and low-grade lung toxicity. More recently, the European cooperative RCT (ARO 97-1) investigated either 66 Gy in 2 Gy per fraction or a CHARTWEL schedule of 60 Gy in 40 fractions over 2.5 weeks.[20] OS did not differ significantly between these 2 regimens, and CHARTWEL was associated with higher rates of acute dysphagia and radiological pneumonitis.

KQ2: What is the ideal external beam dose fractionation for the curative-intent treatment of locally advanced non-small cell lung cancer with chemotherapy?

Guideline statements and evidence summary

A. The standard thoracic radiation therapy dose fractionation for patients treated with concurrent chemotherapy is 60 Gy given in 2 Gy once-daily fractions over 6 weeks **(MQE, recommendation rated as "strong")**.

B. Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be associated with any clinical benefits, including OS **(MQE, recommendation rated as "strong")**.

Based on various phase 1/2 investigations, RTOG 0617 was a 2 × 2 factorial RCT with 2 objectives: (1) to determine if chemoradiation using 74 Gy led to superior OS compared with 60 Gy and (2) to determine if the addition of postradiation therapy cetuximab improved OS. This trial demonstrated that 74 Gy is not superior to standard 60 Gy of radiation therapy and was associated with worse OS.[21] The median survival times and 18-month OS rates are 28.7 months and 66.9% versus 19.5 months and 53.9%, for the 60-Gy and 74-Gy arms, respectively ($P = .0007$, 1-sided). Additionally, there was an increased rate of severe esophagitis on the 74-Gy arm. The addition of cetuximab had no effect on OS compared with chemoradiation alone. Prospective evidence related to intermediate doses between the RTOG 0617 treatment arms of 60 Gy to 74 Gy is currently of paramount importance to help define clinical benefits and risks of the delivery of such treatment.

C. Hyperfractionated radiation therapy regimens that do not result in acceleration of the treatment course, even though the total nominal radiation therapy dose may be modestly increased, do not appear to improve outcomes compared with conventionally fractionated therapy **(MQE, recommendation rated as "strong")**.

RTOG 9204 was a phase 2 RCT of standard dose (with CF, 63 Gy in 7 weeks) versus HF (69.6 Gy BID over 6 weeks, 1.2-Gy fractions) with concurrent chemotherapy for LA NSCLC.[22] The HF arm had a longer time to in-field progression (30% vs 49% at 4 years) with similar OS rates. In a follow-up RCT, RTOG 9410 used concurrent chemotherapy and HF to 69.6 Gy versus sequential and concurrent with once-daily radiation therapy.[11] The survival rates in the HF arm were found to be inferior to the concurrent chemoradiation arm. Acute grade 3-5 nonhematologic toxicity was greater in the HF arm.

D. The optimal thoracic radiation therapy regimen for patients receiving sequential chemotherapy and radiation therapy is not known; however, results from the CHARTWEL and hyperfractionated accelerated radiation therapy phase 3 studies suggest that increasing the biologic equivalent dose by using accelerated hyperfractionated radiation therapy may be of benefit following induction chemotherapy in locally advanced non-small cell lung cancer **(MQE, recommendation rated as "strong")**.

The CHARTWEL trial (see KQ1E) allowed neoadjuvant chemotherapy for 27% of the patients in the trial.[20] No OS benefit with HF accelerated radiation therapy was found, but improved local control after neoadjuvant chemotherapy was observed. Acute dysphagia and radiological pneumonitis was more common with accelerated radiation therapy. The hyperfractionated accelerated radiation therapy trial randomized 119 stage III NSCLC patients to HF accelerated radiation therapy, 57.6 Gy in 12 treatment days, or CF radiation therapy, 64 Gy in 2-Gy fractions both after 2 cycles of paclitaxel/carboplatin.[23] Median survival was not statistically different between HF accelerated (20.3 months) and standard radiation therapy (14.9 months). Acute esophagitis was increased with accelerated radiation therapy.

E. Although the impact of increasing the predicted biologic equivalent dose via accelerated radiation therapy regimens is not clear, further study of accelerated hypofractionated regimens is of interest to optimize the therapeutic ratio of treatment, particularly in the context of advanced imaging, radiation therapy planning, and treatment delivery **(no evidence rating, recommendation rated as "strong")**.

European Organization for Research and Treatment of Cancer study 08972-22973 randomized patients to receive 66 Gy in 2.75-Gy fractions with concurrent cisplatin or sequential to 2 cycles of cisplatin/gemcitabine.[24] Median survival was 16 months on both arms, with an improved 3-year survival for the concurrent arm. Acute esophageal toxicity was increased with concurrent therapy. The Cisplatin, Vinorelbine, and Radiation Therapy in Treating Patients With Stage III Non-Small Cell Lung Cancer That Cannot Be Removed By Surgery (SOCCAR) RCT employed hypofractionated radiation therapy at 55 Gy in 2.75-Gy fractions over 4 weeks, with either concurrent or sequential chemotherapy.[25] Median survival was 27.4 versus 18.6 months, favoring the concurrent arm. These trials suggest encouraging outcomes may be achieved with hypofractionated radiation therapy and concurrent chemotherapy, but randomized comparisons with CF radiation therapy have not been performed.

KQ3: What is the ideal timing of external beam radiation therapy in relation to systemic chemotherapy for the curative-intent treatment of locally advanced non-small cell lung cancer?

Guideline statements and evidence summary

A. There is phase 3 evidence demonstrating improved overall survival, local control, and response rate associated with concurrent chemoradiation when compared against sequential chemotherapy followed by radiation **(HQE, recommendation rated as "strong")**.

As discussed in KQ2C, RTOG 9410 was an RCT assessing sequential versus concurrent CF chemoradiation versus concurrent HF radiation.[11] Clinical outcomes were improved in the concurrent versus sequential arm (median survival, 17.0 vs 14.6 months). Acute grade 3 or higher nonhematologic toxicity was increased in the concurrent arm (53% vs 35%). These results were confirmed by the West Japan Lung Cancer Group (concurrent chemotherapy with CF 56 Gy in 2 courses separated by 10 days or sequential chemotherapy followed by 56 Gy in 28 fractions with no break).[14] Results favored the concurrent arm in regard to median survival (16.5 vs 13.3 months).

B. There is no proven role for the routine use of induction chemotherapy before chemoradiation therapy, although this treatment paradigm can be considered for the management of bulky tumors to allow for radical planning after chemotherapy response **(MQE, recommendation rated as "strong")**.

The use of induction chemotherapy before concurrent chemoradiation therapy was associated with increased toxicity, but no survival advantage, reduction in distant metastasis, or decrease in locoregional progression. These findings were observed in the Cancer and Leukemia Group B (CALGB) 39081 phase 3 study in which patients received 2 cycles of induction therapy with carboplatin and paclitaxel followed by chemoradiation therapy versus immediate concurrent chemoradiation therapy alone for LA NSCLC.[26] There was no statistically significant difference in the median survival (12 vs 14 months) or 2-year overall survival (29% and 31%).

C. There are no phase 3 data specifically supporting the role for consolidation chemotherapy after chemoradiation therapy for the improvement of overall survival; however, this treatment is still routinely given to manage potential micrometastatic disease particularly if full systemic chemotherapy doses were not delivered during radiation therapy **(low quality of evidence, recommendation rated as "strong")**.

Consolidation therapy following concurrent chemoradiation is routinely used in clinical practice to optimize the treatment of micrometastatic disease particularly when only 2 cycles of chemotherapy are used concurrently with radiation. When weekly radiosensitizing low-dose carboplatin and paclitaxel are administered concurrently with thoracic radiation therapy, consolidation therapy with full systemic doses is often given to address concern for systemic disease. Several studies have demonstrated improved survival outcomes for this approach.[27,28]

D. For patients that cannot tolerate concurrent chemoradiation therapy, sequential chemotherapy followed by radical radiation has been shown to be associated with an overall survival benefit when compared with radiation therapy alone **(HQE, recommendation rated as "strong")**.

The CALGB trial 8433, which randomized patients to conventional radiation therapy (60 Gy in 30 fractions) or 2 cycles of cisplatin and vinblastine followed by conventional radiation therapy, demonstrated an improvement in median survival to 13.7 months (compared with 9.6 months for conventional radiation therapy alone) and 5-year overall survival of 17% (compared to 6%).[10] These results were confirmed in an Intergroup trial, which randomized patients to conventional radiation therapy (60 Gy in 30 fractions), hyperfractionated radiation therapy (69.6 Gy in 58 fractions of 1.2 Gy BID), or chemotherapy (vinblastine and cisplatin) followed by conventional radiation therapy.[9]

E. The ideal concurrent chemotherapy regimen has not been determined; however, the 2 most common regimens (cisplatin/etoposide and carboplatin/paclitaxel) are the subject of a completed phase 3 clinical trial (NCT01494558) **(no evidence rating, recommendation rated as "strong")**.

The optimal chemotherapy regimen for use in conjunction with concurrent thoracic radiation therapy is not known. The 2 chemotherapy regimens that have been most commonly used are the combination of cisplatin and etoposide[29] and weekly carboplatin and paclitaxel[26]. In a recent Japanese study, concurrent carboplatin and

paclitaxel had the lowest rates of grade 3-4 neutropenia and equal outcomes (median survival, 22 months) compared with those receiving mitomycin, vindesine, and cisplatin or irinotecan and cisplatin.[30] Some argue, however, that cisplatin-based regimens may lead to improved outcomes over carboplatin-based regimens.[31] Results of a recently completed phase 3 study comparing these 2 regimens are eagerly anticipated (NCT01494558).

Conclusion

A consensus and evidence-based clinical practice guideline for the radiotherapeutic management of LA NSCLC has been created addressing 3 questions including: dose fractionation of radiation therapy alone, dose fractionation with concurrent chemoradiation, and timing of radiation therapy with chemotherapy. Specific guideline statements were graded in terms of evidence quality and were subjected to a consensus-building methodology requiring greater than 75% agreement to be adopted.

HQE was observed in several areas. In terms of radiation therapy management alone, a minimum dose of 60 Gy of conventionally fractionated radiation therapy is recommended. However, dose escalation beyond 60 Gy (conventionally fractionated) in the context of combined modality concurrent chemoradiation has not yet been shown to be associated with any improvement in clinical benefits. In the context of combined modality therapy, chemotherapy and radiation should ideally be given concurrently to maximize survival, local control, and disease response rate.

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