Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

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Data Supplement 1: Summary of ASTRO Guideline Statements:¹

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

A. Radiotherapy 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, recommendation rated as “Strong”).

B. Radiotherapy alone may be used as definitive radical treatment for patients with LA NSCLC who are ineligible for combined modality therapy (i.e. 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”).

C. In the context of conventionally fractionated radiotherapy, a minimum dose of 60Gy is recommended to optimize important clinical outcomes such as local control (HQE, recommendation rated as “Strong”).

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 two), 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 45Gy/15 fractions (hypofractionation), 69.6Gy/58 fractions BID (hyperfractionation), 54Gy/36 fractions TID over 12 consecutive days (CHART, accelerated hyperfractionation), and 60Gy/40 fractions TID over 18 days (CHARTWEL, accelerated hyperfractionation). (No evidence rating, recommendation rated as “Strong”).

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

Guideline Statements
A. The standard thoracic radiotherapy 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 overall survival (MQE, recommendation rated as “Strong”).

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

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

E. Although the impact of increasing the predicted biologic equivalent dose via accelerated radiotherapy 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, radiotherapy planning, and treatment delivery. (No evidence rating, recommendation rated as “Strong”).

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

A. There is phase III 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”).

B. There is no proven role for the routine use of induction chemotherapy prior to chemoradiotherapy; 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”).

C. There are no phase III data specifically supporting the role for consolidation chemotherapy after chemoradiotherapy 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 radiotherapy (LQE, recommendation rated as “Strong”).

D. For patients that cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by radical radiation has been shown to be associated with an overall survival benefit when compared to radiotherapy alone (HQE, recommendation rated as “Strong”).

E. The ideal concurrent chemotherapy regimen has not been determined; however, the two most common regimens (cisplatin/etoposide and carboplatin/paclitaxel) are the subject of a completed phase III clinical trial (NCT01494558). (No evidence rating, recommendation rated as “Strong”).

KQ4: What are the indications for adjuvant post-operative radiotherapy for the curative-intent treatment of locally advanced non-small cell lung cancer?

Guideline Statements

A. Phase III studies and meta-analyses of postoperative radiotherapy (PORT) in completely resected (R0) LA NSCLC with N2 disease suggest that its addition to surgery does not improve overall survival but may improve local control when compared to observation strategies (MQE, recommendation rated as “Strong”).

B. Phase III studies and meta-analyses of PORT in completely resected (R0) LA NSCLC with N0-1 disease demonstrate inferior survival when compared to observation strategies; therefore, PORT therapy for this patient population is not routinely recommended. (MQE, recommendation rated as “Strong”).

C. Since level 1 evidence supports the administration of adjuvant chemotherapy for completely resected (R0) LA NSCLC based on improvements in overall survival compared to patients on
observation, any PORT therapy should be delivered sequentially after chemotherapy in order not to interfere with standard of care chemotherapy (LQE, recommendation rated as “Strong”).

D. For patients receiving adjuvant PORT for R0 disease, conventionally fractionated doses in the range of 50 Gy to 54 Gy (in 1.8-2.0 Gy/day) should be utilized (LQE, recommendation rated as “Strong”).

E. Patients with microscopic residual (R1) primary disease (i.e., positive margin) and/or microscopic (i.e., extra-capsular extension) nodal disease may be appropriate candidates for PORT (given either concurrently or sequentially with chemotherapy) with conventionally fractionated doses in the range of 54 Gy to 60 Gy (in 1.8-2.0 Gy/day fraction size) in order to improve local control (LQE, recommendation rated as “Strong”).

F. Patients with gross residual primary and/or macroscopic nodal (R2) disease of LA NSCLC may be appropriate candidates for PORT (given either concurrently or sequentially with chemotherapy) with conventionally fractionated doses of at least 60 Gy (in 1.8-2.0 Gy/day fraction size) in order to improve local control (LQE, recommendation rated as “Strong”).

KQ5: When is neoadjuvant radiotherapy prior to surgery indicated for the curative-intent treatment of locally advanced non-small cell lung cancer?

**Guideline Statements**

A. There is no level I evidence recommending the use of induction radiotherapy (or chemoradiotherapy) followed by surgery for patients with resectable stage III NSCLC (HQE, recommendation rated as “Strong”).

B. In those patients who are selected for trimodality approach, preoperatively planned lobectomy (as opposed to pneumonectomy), based on best surgical judgment is preferable since it was associated with survival benefit in the exploratory post-hoc INT 0139 analysis (MQE, recommendation rated as “Strong”).

C. No definitive statement can be made about best patient selection criteria for the trimodality therapy, although no weight loss, female gender, and one (vs. more) involved nodal stations were associated with improved outcome in INT 0139 (MQE, recommendation rated as “Strong”).
D. The ideal preoperative radiotherapy dose is currently not known; however, a minimum of 45 Gy should be delivered consistent with the INT 0139 trial (LQE, recommendation rated as “Strong”).

E. Preoperative conventionally fractionated doses up to 60 Gy (in 2Gy/day) may be associated with reasonable mediastinal clearance rates, although no significant correlation with improved overall survival has been demonstrated (LQE, recommendation rated as “Strong”).

Note: ASTRO guideline statements were developed based on the body of evidence categorized by the American College of Physicians (ACP) Strength of Evidence Rating (Qaseem A, Snow V, Owens DK, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med 2010;153:194-9.), consisting of high quality evidence (HQE), moderate quality evidence (MQE), and low quality evidence (LQE).

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Data Supplement 2: DEFINITION OF TERMS

Continuous hyperfractionated accelerated radiation therapy (CHART): Three times daily radiation treatments over 12 days without interruption with a minimum of 6-hour interval between treatments (fractions).

Definitive: Treatment is with curative intent. Surgery and radiation therapy are considered treatment modalities that can be used in the definitive setting with curative intent.

Dose-fractionation: relates to the radiation regimen and refers to the radiation dose and number of fractions (=treatments) that it is given as.

External Beam Radiation Therapy (EBRT): EBRT is delivered using a machine that generates high-energy x-rays that can be targeted at a tumor inside the body.

Gy: Gray

Hypofractionated radiotherapy: Fewer fractions with a higher dose per fraction than standard fractionation. Some hypofractionated regimens result in a higher biologically effective dose.

Intensity-Modulated Radiation Therapy (IMRT): This treatment better directs the radiation dose at the tumor than 3D-CRT by precisely modulating (varying) the intensity of the beam under strict computer guidance. (The positioning of the beam occurs during a specialized planning process.) Because of the modulation of the beam intensity and the special planning computers, IMRT protects healthy tissues from radiation better than 3D-CRT. (Source: cancer.net http://www.cancer.net/navigating-cancer-care/how-cancer-treated/radiation-therapy/what-radiation-therapy)

Locally advanced lung cancer: Patients with unresectable stage II-III disease and selected patients with stage II-III disease that are candidates for surgery as part of a multimodality treatment approach.

Medical operability factors: most common medical contraindications to surgery include cardiac and pulmonary function, but have to be checked in every patient and an individual determination of medical risks and benefits for or against surgery must be made. Examples of cardiac function issues can include, myocardial infarctions, coronary artery disease, and congestive heart failure. Pulmonary function issues can include severe emphysema, oxygen dependence, pulmonary fibrosis, and pulmonary hypertension.

N2: metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) (source: cancer.gov)

N3: metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) (source: cancer.gov)

3D-conformal Radiation Therapy: As part of this treatment, special computers create detailed three-dimensional pictures of the cancer. This allows the treatment team to aim the radiation more precisely, which means they can use higher doses of radiation while reducing the risk of damaging healthy tissue. (source: cancer.net http://www.cancer.net/navigating-cancer-care/how-cancer-treated/radiation-therapy/what-radiation-therapy)
Data Supplement 3: ASTRO Search terms

Please see http://www.practicalradonc.org/
REFERENCES


