Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung Cancer

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American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

www.asco.org/endorsements/NSCLCradiotherapy

Introduction

Individuals with locally advanced non–small-cell lung cancer (LA NSCLC) comprise a significant and growing proportion of patients diagnosed with NSCLC each year in the US and elsewhere.

The American Society for Radiation Oncology (ASTRO) produced an evidence-based guideline on external-beam radiotherapy (EBRT) for patients with LA-NSCLC addressing curative-intent EBRT, plus or minus chemotherapy, and the use of neoadjuvant or adjuvant radiotherapy.

ASCO Endorsement Process

The ASCO Clinical Practice Guidelines Committee (CPGC) endorsement review process includes:

- a methodological review by ASCO guidelines staff
- a content review by an ad hoc expert panel
- final endorsement approval by ASCO CPGC.

The full ASCO Endorsement methodology supplement can be found at:
www.asco.org/endorsements/NSCLCradiotherapy

The full original ASTRO Guideline and Methodology can be found at:
www.practicalradonc.org

ASTRO Clinical Questions

(1) What is the ideal external-beam dose-fractionation for the curative-intent treatment of LA-NSCLC with radiation therapy alone?

(2) What is the ideal external-beam dose-fractionation for the curative-intent treatment of LA-NSCLC with chemoradiotherapy?

(3) What is the ideal timing of external-beam radiation therapy in relation to systemic chemotherapy for the curative-intent treatment of LA-NSCLC?

(4) What are the indications for adjuvant post-operative radiotherapy for the curative-intent treatment of LA-NSCLC?

(5) When is neoadjuvant radiotherapy prior to surgery indicated for the curative-intent treatment of LA-NSCLC?

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Target Population and Audience

- Patients with stage II to III NSCLC who cannot undergo a definitive resection (either because of surgical resectability and/or medical operability factors [see Definition of Terms in Data Supplement]) and patients with stage II to III NSCLC who can undergo a definitive resection after assessment

- Oncology clinicians and patients

Summary of Recommendations

The Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA-NSCLC (ASTRO)

- 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 (high-quality evidence [HQE],"Strong")

- 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, "Strong").

- 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, "Strong").

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Summary of Recommendations

The Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA-NSCLC (ASTRO)

- 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 (moderate quality evidence [MQE], “Strong”).

- 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 (low quality evidence [LQE], “Strong”).

- 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, “Strong”).

Summary of Recommendations

The Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA-NSCLC

ASCO agrees and has summarized these statements as follows:

For curative-intent treatment of LA-NSCLC, concurrent chemoradiation is recommended because it improves local control and overall survival compared with sequential chemotherapy followed by radiation or therapy alone. For patients who cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by radical (definitive) radiation is recommended because it improves overall survival compared with radiotherapy alone. Radiotherapy alone may be used for patients who are ineligible for combined modality treatment; it may offer better tolerability but poorer survival.

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Summary of Recommendations

The Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA-NSCLC

ASCO comments:

There is no role for the routine use of induction chemotherapy before chemoradiotherapy. Current data fail to support routine use of consolidation chemotherapy after chemoradiotherapy; however, this treatment remains an option for patients who did not receive full systemic chemotherapy doses during radiotherapy. The ideal concurrent chemotherapy regimen has not been determined. The two most common regimens are cisplatin/etoposide and carboplatin/paclitaxel.

Summary of Recommendations

Appropriate Dose of Radiotherapy for Patients With Unresectable LA-NSCLC (ASTRO)

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

- 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, “Strong”).

- Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be associated with any clinical benefits including overall survival (MQE, “Strong”).

Summary of Recommendations

Appropriate Dose of Radiotherapy for Patients With Unresectable LA-NSCLC

ASCO agrees and has summarized these statements as follows:

The standard dose-fractionation of radiation with concurrent chemotherapy is 60 Gy given in fractions of 2 Gy once per day over 6 weeks. Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be of benefit.

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Summary of Recommendations

Role of Postoperative Radiotherapy in Resected LA-NSCLC (ASTRO)

- Phase III studies and meta-analyses of postoperative radiotherapy (PORT) in completed 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, “Strong”).

- 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 recommended (MQE, “Strong”)

Summary of Recommendations

Relevant ASTRO Statements Concerning the Role of Postoperative Radiotherapy in Resected LA-NSCLC

ASCO agrees and has summarized these statements as follows:

Postoperative radiotherapy may be recommended for patients with complete resection of N2 disease to improve local control, but should be delivered sequentially after adjuvant chemotherapy.

Other ASTRO recommendations addressing the postoperative setting had LQE, which the ASTRO panel rated as "Strong" recommendations. ASCO endorses and summarizes them as follows:

Postoperative radiotherapy is recommended for patients with incomplete resection (microscopic or gross positive margin, or gross residual disease), to be given either concurrently or sequentially with chemotherapy.

Summary of Recommendations

Role of Radiotherapy in the Context of Trimodality Treatment of LA-NSCLC (ASTRO)

- 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, “Strong”).

- 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 North American Intergroup study INT 0139 analysis (MQE, “Strong”).

- 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, “Strong”).

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Summary of Recommendations

Role of Radiotherapy in the Context of Trimodality Treatment of LA-NSCLC

ASCO agrees and has summarized these statements as follows:

Patients with resectable stage III NSCLC should be managed by a multidisciplinary team that uses best surgical judgment. The best candidates for preoperative chemoradiotherapy have preoperatively planned lobectomy (as opposed to pneumonectomy), no weight loss, female sex, and only one involved nodal station.

Discussion Summary Points

Lack of a standard definition of what constitutes "locally advanced" and how to define "unresectable" :

- The ASTRO statement: ***"…resectable LA NSCLC is practically defined as consisting of stage II-III patients that can undergo a definitive resection after assessment to ensure appropriate surgical resectability, adequate pulmonary reserve, and acceptable medical operability risk…"*** refers to patients who can undergo definitive resection as their primary cancer treatment (with possible adjuvant therapy), but could also be (mis)interpreted as referring to patients undergoing surgery after (re)assessment following induction therapy.

How to manage patients with potentially resectable tumors who are candidates for surgery and who have preoperative evidence of mediastinal nodal disease:

- Given the lack of high-quality evidence and the heterogeneity of patients, the ASCO panel concluded that *"patients with resectable stage III NSCLC should be managed by a multidisciplinary team that incorporates best surgical judgment,"* but believes that it is not defined at this point which patients would be considered as having resectable disease.

Discussion Summary Points

Limitations

- Small trial populations (typically hundreds of patients, as compared with breast and prostate clinical trials, which may include more than 1,000 patients) with a heterogeneous trial group with different histologic subtypes

- Many trials were conducted before the routine use of positron emission tomography staging, and thus may have included patients with occult stage IV disease. Any conclusions about evidence or lack of evidence need to be tempered by these and other caveats listed here.

- Prospective comparative trials are lacking in the comparison of different types of external-beam radiotherapy, such as three-dimensional conformal, intensity-modulated radiotherapy, and image-guided radiotherapy and there are no high-quality data currently available on hyper- or hypofractionated radiotherapy.

Discussion Summary Points

Limitations (con't)

- Controversy regarding which dose of radiotherapy to consider standard. The ASTRO guideline has two statements:
  - "a minimum dose of 60 Gy is recommended… " (that refers to radiotherapy alone, without concurrent chemotherapy)

  and

  - "the standard… dose-fractionation is 60 Gy given in 2 Gy once daily fractions over 6 weeks (which refers to concurrent chemoradiotherapy).

- Some studies suggest that higher doses provide better local control, but phase III studies have not demonstrated the superiority of any doses higher than 60 Gy over 30 fractions.
  - The ASCO panel believed that it could state that 60 Gy is optimal, but could state that 60 Gy is standard.

Role of consolidation chemotherapy after concurrent chemotherapy

- Supported by early trials that has become standard in many centers, but which current interpretation of data does not support. Notably, the ASTRO guideline on this issue reflected low-quality evidence, and the ASCO panel emphasized lack of phase III evidence of the benefit.

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Endorsement of Definitive and adjuvant radiotherapy in locally advanced non-small cell lung cancer: An American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline (by Rodrigues G, Choy H, Bradley J, et al) by permission of the American Society for Radiation Oncology.

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Endorsement Recommendation

ASCO endorses "Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer: An American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline," summarized by Rodrigues et al[1,2] in 2015 in *Practical Radiation Oncology*, with minor qualifying statements. The full ASTRO guideline can be accessed in the supplementary materials of the executive summaries by Rodrigues et al.

1. Rodrigues G, Choy H, Bradley J, et al: Definitive radiotherapy 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 [epub ahead of print on May 5, 2015]
2. Rodrigues G, Choy H, Bradley J, et al: Adjuvant radiotherapy 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 [epub ahead of print on May 5, 2015]

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Additional Resources

More information, including a Data Supplement with a reprint of all ASTRO recommendations, a Methodology Supplement, slide sets, and clinical tools and resources, is available at:

www.asco.org/endorsements/NSCLCradiotherapy

All original ASTRO recommendations can be found at:

www.practicalradonc.org

Patient information is available at www.cancer.net

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