Practical Radiation Oncology (2015) **5**, 149-155

practical radiation oncology
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www.practicalradonc.org

Special Article

Adjuvant 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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Received 5 December 2014; accepted 25 February 2015

Supplementary material for this article (http://dx.doi.org/10.1016/j.prro.2015.02.013) can be found online at www.practicalradonc.org.

Conflicts of interest: Before initiation of this guideline, all members of the Task Force were required to complete disclosure statements. These statements are maintained at the American Society for Radiation Oncology (ASTRO) Headquarters in Fairfax, VA, and pertinent disclosures are published within this report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, remedial measures to address any potential conflict are taken and will be noted in the disclosure statement. The guideline chairs (G.R. and G.V.) in concert with the ASTRO guidelines subcommittee reviewed these disclosures and determined that they have no substantive impact upon the content of the manuscript. George Rodrigues, MD, PhD, has received research funding from the Ontario Institute of Cancer Research. Jeffrey Bradley, MD, has received research funding from Calypso Medical Inc. Jeffrey Bogart, MD, has received travel expense funding from Alliance Clinical Trials Cooperative Group. Hak Choy, MD, is on the advisory board for EMD Serono and Bayer; in addition, he has received research funding from Celgene and has been a consultant for Eli Lilly. Walter J. Curran Jr, MD, has been a consultant for Bristol Meyers Squibb. Corey Langer, MD, has received honoraria, been a consultant to, or served on the advisory board of Bristol Meyers Squibb, Eli Lilly, Genentech, Synta, and Abbott. Mitchell Machtay, MD, served as a consultant to Bristol Meyers Squibb, Eli Lilly, and Imclone. Maria Werner-Wasik, MD, received travel expense funding from Elekta Oncology.

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http://dx.doi.org/10.1016/j.prro.2015.02.013

Abstract

Purpose: To provide guidance to physicians and patients with regard to the use of adjuvant 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 2 systematic reviews on the following topics: (1) indications for postoperative adjuvant RT and (2) indications for preoperative neoadjuvant RT. 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 who have undergone surgical resection, high-level evidence suggests that use of postoperative RT does not influence survival, but optimizes local control for patients with N2 involvement, and its use in the setting of positive margins or gross primary/nodal residual disease is recommended. No high-level evidence exists for the routine use of preoperative induction chemoradiation therapy; however, modern surgical series and a post-hoc Intergroup 0139 clinical trial analysis suggest that a survival benefit may exist if patients are properly selected and surgical techniques/postoperative care is optimized.

Conclusions: A consensus and evidence-based clinical practice guideline for the adjuvant radiotherapeutic management of LA NSCLC has been created addressing 2 important questions.

Introduction

Various randomized clinical trials and meta-analyses have investigated the additional role of preoperative (neoadjuvant) and postoperative (adjuvant) therapies (eg, radiation therapy and/or chemotherapy [CT]) in improving clinical outcomes such as overall survival, local control, and surgical resectability in the context of resectable locally advanced (LA) non-small cell lung cancer (NSCLC).[1] External beam radiation therapy can be considered for multimodality management of resectable LA NSCLC either as therapy given before or after surgical resection; however, the indications for employing such therapies are controversial.[2] Because of the length of the guideline, the document was split into 2 parts. This document focuses on neoadjuvant/adjuvant radiation therapy; the other is on definitive radiation therapy.

The purpose of this executive summary is to provide guidance to physicians and patients with regard to the use of neoadjuvant/adjuvant external beam radiation therapy for treatment of resectable LA NSCLC, based on available medical evidence complemented by expert opinion. This document is an executive summary of 2 questions addressing adjuvant radiation therapy in the context of resectable LA NSCLC with the full guideline document available as supplementary material online only at www.practicalradonc.org. Other free supplementary materials include evidence tables for each key question, 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.practicalradon.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 the strategy 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 related to all 5 key questions. A total of 74 articles were fully abstracted to provide supporting evidence for the clinical guideline recommendations (see supplementary materials available online only at www.practicalradonc.org). The 2 key questions (KQ) (KQ4 and KQ5, numbered sequentially after definitive radiation therapy KQ1-3; see supplementary materials for the full definitive and adjuvant guideline) and guideline statements related to adjuvant 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 assess the strength of the recommendation (strong or weak). Panelists rated the agreement with each recommendation pertaining to the

Table 1 Grading of evidence, recommendations, and consensus methodology.

Guideline statement	Strength of evidence	Strength of recommendation	Percent agreement
Key Question #4: What are the indications for adjuvant postoperative radiation therapy for the curative-intent treatment of locally advanced non-small cell lung cancer?			
Statement A. Phase 3 studies and meta-analyses of 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 with observation strategies.	MQE	Strong	93
Statement B. Phase 3 studies and meta-analyses of PORT in completely resected (R0) LA NSCLC with N0-1 disease demonstrate inferior survival when compared with observation strategies; therefore, PORT therapy for this patient population is not routinely recommended.	MQE	Strong	100
Statement C. Because level 1 evidence supports the administration of adjuvant chemotherapy for completely resected (R0) LA NSCLC based on improvements in overall survival compared with patients on observation, any PORT therapy should be delivered sequentially after chemotherapy in order not to interfere with standard of care chemotherapy.	LQE	Strong	93
Statement 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 used.	LQE	Strong	100
Statement E. Patients with microscopic residual (R1) primary disease (ie, positive margin) and/or microscopic (ie, extracapsular 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) to improve local control.	LQE	Strong	93
Statement 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) to improve local control.	LQE	Strong	93
Key Question #5: When is neoadjuvant radiation therapy before surgery indicated for the curative-intent treatment of locally advanced non-small cell lung cancer?			
Statement A. There is no level 1 evidence recommending the use of induction radiation therapy (or chemoradiation therapy) followed by surgery for patients with resectable stage III NSCLC.	HQE	Strong	93
Statement B. In those patients who are selected for a trimodality approach, preoperatively planned lobectomy (as opposed to pneumonectomy) based on best surgical judgment is preferable because it was associated with survival benefit in the exploratory post-hoc INT 0139 analysis.	MQE	Strong	93
Statement C. No definitive statement can be made about best patient selection criteria for the trimodality therapy, although no weight loss, female gender, and 1 (vs more) involved nodal station were associated with improved outcome in INT 0139.	MQE	Strong	93
Statement D. The ideal preoperative radiation therapy dose is currently not known; however, a minimum of 45 Gy should be delivered consistent with the INT 0139 trial.	LQE	Strong	93
Statement E. Preoperative conventionally fractionated doses up to 60 Gy may be associated with reasonable mediastinal clearance rates, although no significant correlation with improved overall survival has been demonstrated.	LQE	Strong	86

HQE, high quality of evidence; INT, Intergroup; LA, locally advanced; LQE, low quality of evidence; MQE, moderate quality of evidence; NSCLC, non-small cell lung cancer; PORT, postoperative radiation therapy.

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."[3] 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."[3] 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

KQ4: What are the indications for adjuvant postoperative radiation therapy for the curative-intent treatment of locally advanced non-small cell lung cancer?

Guideline statements and evidence summary

A. Phase 3 studies and meta-analyses of postoperative radiation therapy (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 with observation strategies **(a medium quality of evidence [MQE], recommendation rated as "strong")**.

B. Phase 3 studies and meta-analyses of PORT in completely resected (R0) LA NSCLC with N0-1 disease demonstrate inferior survival when compared with observation strategies; therefore, PORT therapy for this patient population is not routinely recommended **(MQE, recommendation rated as "strong")**.

The role of PORT for resected lung cancer has been investigated in prospective trials as early as the 1960s, with the first randomized controlled trial of PORT of relevance to current practice published in 1980. Results from these trials, in which PORT was administered across a range of resected lung cancer stages (I-III), had suggested local control benefits to the addition of PORT, but overall survival outcomes were inconclusive.[5-13] To clarify the role of PORT in resected lung cancer, the Meta-analysis Group of the British Medical Research Council Clinical Trials Unit established the PORT Meta-analysis Trialists Group C to study the role of PORT by undertaking a meta-analysis of individual patient data from the published randomized trials. Results of this British Medical Research Council meta-analysis were first published in 1998 and suggested an overall survival detriment to the addition of PORT for all stages of resected NSCLC.[14] This analysis was updated in 2005 and 2010, reflecting new clinical trial data without any change to the conclusion of the metaanalysis.[14-16] In summary, the last review has reported on 2343 patients from 11 trials and noted a significant adverse effect of PORT on survival, with a hazard ratio of 1.18 (18% relative increase in the risk of death).[15] The authors further noted that this detrimental effect is most pronounced for patients with stage I/II (N0-N1 nodal disease). For stage III (N2) patients (ie, LA NSCLC), there is no clear evidence of an adverse effect on survival, but there is an observed benefit in local recurrence, with an absolute 24% reduction with PORT therapy seen in the meta-analysis. Any use of PORT in N0/N1 R0 resected patients should be in the context of clinical trials using advanced imaging and radiation targeting technologies to see if the risk/benefit ratio for this treatment can be shifted.

C. Because level 1 evidence supports the administration of adjuvant CT for completely resected (R0) LA NSCLC based on improvements in overall survival compared with patients on observation, any PORT therapy should be delivered sequentially after CT in order not to interfere with standard of care CT **(a low quality of evidence [LQE], recommendation rated as "strong")**.

Adjuvant CT and radiation therapy have been extensively evaluated over the past several decades to determine the potential additive impact to important clinical outcomes. Currently, adjuvant CT has become the standard of care for patients with completely resected stage II and III NSCLC after the results from multiple randomized trials, later validated by meta-analyses, demonstrated a benefit for addition of platinum-based CT after resection of LA NSCLC, which leads to absolute overall survival improvements at 5 years of between 5% and 15%.[17-24] Given the demonstrated overall survival associated with CT and lack of overall survival benefit with radiation therapy (for RO N2 disease), adjuvant radiation therapy should be delivered sequentially after CT in order not to interfere with CT delivery because of a risk of combined chemoradiation side effects that can lead to potential treatment breaks or deintensification.

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 used **(LQE, recommendation rated as "strong")**.

E. Patients with microscopic residual (R1) primary disease (ie, positive margin) and/or microscopic (ie, extracapsular extension) nodal disease may be appropriate candidates for PORT (given either concurrently or sequentially with CT) with conventionally fractionated doses in the range of 54 Gy to 60 Gy (in 1.8-2.0 Gy/day fraction size) 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 CT) with conventionally fractionated doses of at least 60 Gy (in 1.8-2.0 Gy/day fraction size) to improve local control **(LQE, recommendation rated as "strong")**.

The differentiation of adjuvant PORT for resected disease from postoperative radiation therapy for positive margin disease, extracapsular nodal extension, or gross residual primary or nodal disease (R1-microscopic disease or R2-macroscopic disease) is important. Notwithstanding the absence of randomized evidence, in these high-risk R1 and R2 situations, treatment with PORT is an established indication because of the high risk of locoregional relapse

in these patients. In the context of an R1/R2 resection, the use of concurrent chemoradiation therapy can be considered. This needs to be done carefully given the potential morbidity of PORT, including radiation pneumonitis and fibrosis, and the likelihood that this risk is further increased by the use of concurrent CT. Overall, the risk/benefit ratio for concurrent versus sequential approaches in the postoperative setting is not clear. PORT doses in clinical practice for R1 disease are typically 54-60 Gy and at least 60 Gy in R2 disease (in 1.8-2.0 Gy daily fractions).[25,26] 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 used consistent with clinical trials investigating this treatment indication.

KQ5: When is neoadjuvant radiation therapy before surgery indicated for the curative-intent treatment of locally advanced non-small cell lung cancer?

Guideline statements and evidence summary

A. There is no level I evidence recommending the use of induction radiation therapy (or chemoradiation therapy) followed by surgery for patients with resectable stage III NSCLC **(HQE, recommendation rated as "strong")**. The Intergroup (INT) 0139 phase 3 randomized clinical trial,[27] comparing trimodality therapy with the definitive concurrent chemoradiation therapy, demonstrated no survival benefit to the trimodality arm (median survival, 23.6 months vs 22.2 months), with improved progression-free survival of 12.8 versus 10.5 months. The study enrolled 396 eligible medically operable, good performance status patients with T1-3N2M0 NSCLC, without any limitation on mediastinal nodal size. Three quarters of all patients had a single mediastinal station involved and 20% had 2 involved stations. CT in both arms consisted of cisplatin and etoposide and the radiation therapy doses were 45 Gy and 61 Gy conventionally fractionated (1.8 Gy/fraction) in the preoperative versus definitive chemoradiation therapy arms, respectively. In the surgical arm, nonprogressing patients underwent thoracotomy. Overall, 88% of all patients were eligible for thoracotomy and 71% had a complete surgical excision; 5.5% had incomplete resection; and only 4.5% had no resection (for total of 81% actually undergoing thoracotomy). Among those requiring pneumonectomy, perioperative mortality was 26%; 50% for those who had a complex right pneumonectomy.

B. In those patients who are selected for trimodality approach, preoperatively planned lobectomy (as opposed to pneumonectomy), based on best surgical judgment is preferable because 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 1 (vs more) involved nodal station were associated with improved outcome in INT 0139 **(MQE, recommendation rated as "strong")**.

Despite the lack of survival difference between arms in INT 0139, other clinical trials were conducted or are ongoing.[28-32] The enthusiasm for these trials can be justified by the belief that it was the excessive and unexpected mortality of the pneumonectomy patients in the INT 0139 study that diluted the potential survival advantage in the surgical arm. This hypothesis is supported by the exploratory unplanned analysis of the INT 0139 data, demonstrating that patients who underwent lobectomy after induction chemoradiation therapy experienced an improved survival benefit when compared with patients matched (by performance status, age, sex, and T stage) from the definitive chemoradiation therapy arm (median survival of 33.6 months vs 21.7 months and 5-year survival rates of 36% vs 18%, respectively).[27] In this analysis, patient survival in this surgical arm was not hindered by the observed low lobectomy-related mortality of 1%. Such survival is notable in the multi-institutional setting, pre–positron emission tomography era and with 2-dimensional radiation therapy. In comparison, the best median reported so far in the cooperative group setting for patients with stage IIIA/B NSCLC (60-Gy arm of the Radiation Therapy Oncology Group [RTOG] 0617 study)[33] is 28.7 months, with 2% treatment-related mortality. In the RTOG 0617 trial, 90% of patients were staged with positron emission tomography and all received modern 3-dimensional radiation therapy or intensity modulated radiation therapy. A direct comparison of survival between the INT 0139 and RTOG 0617 is obviously flawed and speculative in nature because patients in INT 0139 represented, per definition, a more favorable, resectable stage IIIA–only population (presumably with an overall lower disease burden).

Patient selection is crucial, taking into account performance status as well as pulmonary and cardiovascular function tests. In addition to the individual surgical and anesthesia expertise, high-volume centers have reported better results.[34] A mandatory coverage of the bronchial stump, keeping patients "dry" both during the surgical procedure as well in the postoperative period, seems to limit the incidence of acute respiratory distress syndrome. One group of investigators[35] recommends the benefit of delivering no greater than 1 L of fluids during surgery, avoiding high oxygen concentrations (thus avoiding barotrauma), and severely limiting postoperative fluid administration and maintaining a considerable negative fluid balance.

D. The ideal preoperative radiation therapy 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 2 Gy/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")**.

Historically, the radiation therapy doses used in the preoperative setting were limited to 45-50 Gy, mostly from safety concerns. With the advent of modern radiation therapy techniques, such as 3-dimensional conformal radiation therapy/intensity modulated radiation therapy and image guided radiation therapy, dose escalation of daily standard fractionated preoperative radiation therapy becomes a potentially attractive approach to improve mediastinal pathologic complete response (pCR) rates. Several single-institution studies reported acceptable safety and efficacy of using definitive radiation therapy doses of 59-60 Gy with concurrent CT, with high nodal pCR rates (defined as conversion from N2 to N0/N1).[35-37] These results seem to compare favorably with the pCR rates reported after radiation therapy doses of 45-50 Gy; however, both patient selection and appropriate presurgical restaging are important factors to consider before the implementation of such therapy.

In the RTOG 0229 phase 2 study,[28] 57 eligible stage III NSCLC patients with pathologically proven N2 or N3 nodes received 61.2 Gy concurrently with weekly carboplatin and paclitaxel CT, followed by surgery within 8 weeks from chemoradiation therapy completion and further consolidation CT. The projected primary endpoint of the study was mediastinal pCR improvement from 50% to 70%. Of 57 eligible patients, 56 completed induction therapy and proceeded to surgery, with 65% (37/57) undergoing resection (76% R0 and 24% R1). The mediastinal pCR was documented in 63% (27/43) of patients who underwent nodal reevaluation. Median survival for those with mediastinal pCR was not reached and was 33 months for those with residual nodal disease.

The RTOG 0229 results confirm a high rate of nodal tumor clearance following high-dose preoperative RT, demonstrating at the same time the real-life challenges of conducting a complex trimodality trial in a multi-institutional setting. Despite careful initial patient selection, 5/56 patients eligible for resection were found unresectable; 5 were medically inoperable; 2 had distant progression; and 6/19 with persistent N2 disease did not undergo resection based on the decision of the surgeon. The controversy of whether patients not achieving nodal clearance should undergo surgery remains unresolved, although data from INT 0139 indicate that the median survival time for patients with persistent N2 disease who did not have surgical resection was 7.9 months versus 26.4 months for those with the residual N1-N3 status who did have surgery.[27]

Conclusion

A consensus and evidence-based clinical practice guideline for the adjuvant radiotherapeutic management of LA NSCLC has been created to address 2 questions including the indications of postoperative radiation therapy and indications of preoperative radiation therapy. 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. For patients who have undergone surgical resection, no high-level evidence exists for the routine use of postoperative radiation therapy; however, it can be used to optimize local control in situations with positive margins, gross primary/nodal residual disease, or N2 (mediastinal) involvement. No high-level evidence exists for the routine use of preoperative induction chemoradiation therapy; however, modern surgical series and a post-hoc analysis of the INT 0139 trial suggest that a survival benefit may exist if patients are properly selected and surgical techniques/postoperative care is optimized.

References

1. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):40.
2. Santos ES, Castrellon A, Blaya M, Raez LE. Controversies in the management of stage IIIA non-small-cell lung cancer. *Expert Rev Anticancer Ther.* 2008;8:1913-1929.
3. Loblaw DA, Prestrud AA, Somerfield MR, et al. American Society of Clinical Oncology Clinical Practice Guidelines: Formal systematic review-based consensus methodology. *J Clin Oncol.* 2012;30:3136-3140.
4. Qaseem A, Snow V, Owens DK, Shekelle P. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of methods. *Ann Intern Med.* 2010;153:194-199.
5. Park J. Postoperative adjuvant therapy for stage IIIA non-small cell lung cancer. *J Thorac Oncol.* 2007;2:S651.
6. Feng QF, Wang M, Wang LJ, et al. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: A randomized trial. *Int J Radiat Oncol Biol Phys.* 2000;47:925-929.
7. Dautzenberg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. *Cancer.* 1999;86:265-273.
8. Mayer R, Smolle-Juettner FM, Szolar D, et al. Postoperative radiotherapy in radically resected non-small cell lung cancer. *Chest.* 1997;112:954-959.
9. Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, Yosef HM, Machin D. The role of post-operative radiotherapy in non-small-cell lung cancer: A multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease. Medical Research Council Lung Cancer Working Party. *Br J Cancer.* 1996;74:632-639.
10. The Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group. *N Engl J Med.* 1986;315:1377-1381.
11. Van Houtte P, Rocmans P, Smets P, et al. Postoperative radiation therapy in lung caner: A controlled trial after resection of curative design. *Int J Radiat Oncol Biol Phys.* 1980;6:983-986.
12. Meta-analysis Trialist Group PORT. Postoperative radiotherapy in non-small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet.* 1998;352:257-263.

13. Debevec M, Bitenc M, Vidmar S, et al. Postoperative radiotherapy for radically resected N2 non-small-cell lung cancer (NSCLC): Randomised clinical study 1988–1992. *Lung Cancer.* 1996;14:99-107.
14. Burdett S, Stewart L. Postoperative radiotherapy in non-small-cell lung cancer: Update of an individual patient data meta-analysis. *Lung Cancer.* 2005;47:81-83.
15. PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002142.pub2/abstract. 2010. Accessed February 13, 2015.
16. Walasek T, Kowalska T, Reinfuss M, et al. The effectiveness of postoperative external beam radiotherapy for incompletely resected non-small cell lung cancer. *Pneumonol Alergol Pol.* 2003;71:488-495.
17. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: Two meta-analyses of individual patient data. *Lancet.* 2010;375:1267-1277.
18. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: Updated survival analysis of JBR-10. *J Clin Oncol.* 2010;28:29-34.
19. Douillard J-Y, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. *Lancet Oncol.* 2006;7:719-727.
20. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon J-P, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med.* 2004;350:351-360.
21. Arriagada R, Dunant A, Pignon J-P, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. *J Clin Oncol.* 2010;28:35-42.
22. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008;26:3552-3559.
23. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst.* 2003;95:1453-1461.
24. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med.* 2005;352:2589-2597.
25. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer, version 2.2013. *J Natl Compr Canc Netw.* 2013;11:645-653.
26. Decker RH, Wilson LD. Postoperative radiation therapy for non-small cell lung cancer. *Semin Thorac Cardiovasc Surg.* 2008;20:184-187.
27. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. *Lancet.* 2009;374:379-386.
28. Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02–29: A phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys.* 2012;84:456-463.
29. Radiation Therapy Oncology Group. Randomized phase II study of pre-operative chemoradiotherapy +/− panitumumab (IND #110152) followed by consolidation chemotherapy in potentially operable locally advanced (stage IIIA, N2+) non-small cell lung cancer. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0839. Accessed August 29, 2013.
30. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: A randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol.* 2008;9:636-648.
31. Friedel G, Budach W, Dippon J, et al. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: A single-center study. *J Clin Oncol.* 2010;28:942-948.
32. Betticher DC, Hsu Schmitz S-F, Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: A multicenter phase II trial. *J Clin Oncol.* 2003;21:1752-1759.
33. Bradley J, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617. *J Clin Oncol.* 2013:31. [abstract 7501].
34. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med.* 2003;349:2117-2127.
35. Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg.* 2004;78:1200-1205. [discussion 1206].
36. Maurizi G, D'Andrilli A, Anile M, et al. Sleeve lobectomy compared with pneumonectomy after induction therapy for non-small-cell lung cancer. *J Thorac Oncol.* 2013;8:637-643.
37. Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. *Eur J Cardiothorac Surg.* 2009;35:718-723.