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ASCO SPECIAL ARTICLE

Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology clinical practice guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/lung-cancer-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose
The panel updated the American Society of Clinical Oncology (ASCO) adjuvant therapy guideline for resected non–small-cell lung cancers.

Methods
ASCO convened an update panel and conducted a systematic review of the literature, investigating adjuvant therapy in resected non–small-cell lung cancers.

Results
The updated evidence base covered questions related to adjuvant systemic therapy and included a systematic review conducted by Cancer Care Ontario current to January 2016. A recent American Society for Radiation Oncology guideline and systematic review, previously endorsed by ASCO, was used as the basis for recommendations for adjuvant radiation therapy. An update of these systematic reviews and a search for studies related to radiation therapy found no additional randomized controlled trials.

Recommendations
Adjuvant cisplatin-based chemotherapy is recommended for routine use in patients with stage IIA, IIB, or IIIA disease who have undergone complete surgical resections. For individuals with stage IB, adjuvant cisplatin-based chemotherapy is not recommended for routine use. However, a postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks of adjuvant chemotherapy for each patient. The guideline provides information on factors other than stage to consider when making a recommendation for adjuvant chemotherapy, including tumor size, histopathologic features, and genetic alterations. Adjuvant chemotherapy is not recommended for patients with stage IA disease. Adjuvant radiation therapy is not recommended for patients with resected stage I or II disease. In patients with stage IIIA N2 disease, adjuvant radiation therapy is not recommended for routine use. However, a postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiation therapy for each patient with N2 disease. Additional information is available at www.asco.org/lung-cancer-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

Lung cancers are the leading cause of cancer-related deaths for men and women throughout the world. In the United States, approximately 224,000 new lung cancers are expected in 2016, and more than 158,000 individuals are expected to die as a result of the disease.[1] Five-year survival rates range from 67% for T1N0 disease to 23% for patients with T1-3N2 disease.[2] Adenocarcinomas and squamous cell lung cancers, which are the focus of this guideline, comprise approximately 85% of all lung cancers.[2]

This update of the 2007 joint Cancer Care Ontario (CCO)/American Society of Clinical

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update

Guideline Question

What is the role of adjuvant systemic therapy and adjuvant radiation therapy in patients with completely resected stage I to IIIA non–small-cell lung cancers (NSCLCs)?

Target Population

Patients with completely resected stage I to IIIA NSCLCs (completely resected, defined as no macroscopic disease and uninvolved resection margins pathologically after surgery).

Target Audience

Surgical oncologists, medical oncologists, radiation oncologists, and other clinicians who treat patients in the target population.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Adjuvant systemic therapy for NSCLCs:

Recommendation 1.1. Stage IA: Adjuvant chemotherapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Moderate[3]; Strength of recommendation: Strong).

Recommendation 1.2. Stage IB: Adjuvant cisplatin-based chemotherapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks of adjuvant chemotherapy for each patient. Factors other than tumor stage to consider when making a recommendation for adjuvant chemotherapy are outlined after the adjuvant systemic therapy section of this guideline (Type: Evidence based and Panel consensus; Benefits outweigh harms, especially in patients with larger tumors; Evidence quality: Intermediate[3]; Strength of recommendation: Moderate).

Recommendation 1.3. Stages IIA/B and IIIA**:** Adjuvant cisplatin-based chemotherapy is recommended (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: High[3]; Strength of recommendation: Strong).

Adjuvant radiation therapy for NSCLCs:

Recommendation 2.1. Stages IA/B and IIA/B: Adjuvant radiation therapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Intermediate; Strength of recommendation: Strong[2]).

Recommendation 2.2. Stage IIIA (N2): Adjuvant radiation therapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiotherapy for each patient with N2 disease (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: Intermediate[4]; Strength of recommendation: Moderate).

Comparison of the 2016 Updated Recommendations With the Previous 2007 Version of This Guideline

The recommendations for adjuvant systemic therapy or adjuvant radiation therapy contained in this guideline update do not differ substantively from the 2007 version of this guideline in terms of recommendations for or against the delivery of adjuvant therapy options across various stages. This updated version of the guideline does provide direction within the recommendations for a multimodality evaluation that includes a medical oncologist or a radiation oncologist for stage IB and IIIA resected NSCLCs, respectively. Please see Data Supplement 3 for a direct comparison of the 2007 and 2016 recommendations.

Additional Resources

More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/lung-cancer-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to provide additional options to patients, inform medical decisions, and improve cancer care, and that all patients should have the opportunity to participate.

Oncology (ASCO) clinical practice guideline[2] addresses two principal questions in the treatment of patients with completely resected non–small-cell lung cancers (NSCLCs): the overall survival benefit and role of adjuvant systemic therapy, including chemotherapy and newer targeted therapy and immunotherapy options, and adjuvant radiation therapy.

The 2007 joint CCO/ASCO guideline recommended chemotherapy for stage II and IIIA disease but not stage IA. Adjuvant chemotherapy was not routinely recommended in stage IB. Adjuvant radiation therapy was not recommended for patients with stage I or II and also not routinely recommended for those with stage IIIA.[2]

This guideline update incorporates the latest published research on adjuvant therapy in patients with completely resected stage I to IIIA lung cancers. CCO recently updated its systematic review on adjuvant systemic therapy,[3] including longer-term results from key clinical trials, recent trials of targeted therapy and immunotherapy, and subgroup analyses of chemotherapy in patients with stage IB disease with larger tumors. These studies and the latest evidence on adjuvant radiation therapy from the National Cancer Database (NCDB) and the 2015 ASCO endorsement of the American Society for Radiation Oncology (ASTRO) evidence-based recommendations for adjuvant radiation therapy for NSCLC are included in this guideline update. A panel of clinical experts (Appendix Table A1, online only) used this evidence base to reaffirm or modify the recommendations contained in the 2007 CCO/ASCO joint guideline on adjuvant therapy in completely resected NSCLC to verify the relevance of the guideline recommendations. A summary of the key recommendations can be found in the Bottom Line Box.

GUIDELINE QUESTIONS

This clinical practice guideline addresses two overarching clinical questions:

1. What is the benefit of adjuvant systemic therapy in patients with completely resected stage I to IIIA NSCLCs?
2. What is the benefit of adjuvant radiation therapy in patients with completely resected stage I to IIIA NSCLCs?

METHODS

Guideline Update Development Process

Panel formation. The Expert Panel met via teleconference and Webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the multidisciplinary Expert Panel, with expertise in medical, radiation, and surgical oncology, were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. A patient representative and a representative from the Practice Guidelines Implementation Network were also included on the panel. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication. After the ASCO process was completed, CCO provided approval through its Program in Evidence-based Care approval process.

Systematic literature review. In 2007, ASCO and CCO published a joint guideline on adjuvant chemotherapy and adjuvant radiation therapy for stage I to IIIA resectable NSCLC.[2] CCO recently updated the systematic review on adjuvant chemotherapy, bringing it current to January 2016, and expanded the search strategy to include recent trials of targeted therapy and immunotherapy.[3] That CCO systematic review and accompanying guideline recommendations serve as the basis for the adjuvant systemic therapy portion of this updated CCO/ASCO joint guideline. To improve the currency of the evidence base, a final literature search for any additional adjuvant systemic therapy trials published between January and June 2016 was conducted.

In 2015, ASCO endorsed ASTRO's evidence-based guideline on adjuvant radiation therapy in locally advanced NSCLC,[4,5] with a systematic review that was current to March 2013. The ASTRO systematic review and accompanying guideline recommendations serve as the basis for the adjuvant radiation therapy portion of this guideline. To update the evidence base, a search for any additional adjuvant radiation therapy trials that were published between March 2013 and June 2016 was conducted.

Literature search strategy. MEDLINE was searched using PubMed on June 21, 2016, using keywords and MeSH terms related to NSCLC and chemotherapy, radiation therapy, targeted therapy, and immunotherapy. The complete literature search strategy used in the PubMed database is available in Data Supplement 1. Reference lists of included articles were scanned for additional eligible citations.

Study selection criteria. Publications with the following study designs were eligible for inclusion in the evidence base:

- Systematic reviews of randomized controlled trials (RCTs) with or without meta-analyses,
- Phase III RCTs,
- Observational comparative studies based on the:
  - NCDB, a large, prospectively acquired database that is gathered and maintained by the American College of Surgeons, the Commission on Cancer, and the American Cancer Society;[6]
  - SEER Program database, which collects registry data on cancer cases from various locations and sources throughout the United States (seer.cancer.gov/about).

Studies were considered for inclusion if they reported the following outcomes by TNM stage for comparisons of surgery alone versus surgery plus adjuvant systemic therapy or surgery plus radiation therapy with or without systemic therapy in the target population of patients with completely resected lung cancers (ie, no macroscopic disease and uninvolved resection margins after surgery):

- Overall survival (OS),
- Disease-free survival (DFS),
- Adverse events.

Articles were not considered if they were:

- Published only as an abstract;
- Trials of neoadjuvant (ie, preoperative) chemotherapy;
- Trials of tegafur and uracil;
- Included patients with incomplete resections (ie, had positive margins or macroscopic residual disease);
- Noncomparative study designs, including editorials, commentaries, letters, news articles, case reports, and narrative reviews;
- Non-English language publications.

Data Extraction

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[7] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (Methodology Supplement).

Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/lung-cancer-guidelines, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The Methodology Supplement (available at www.asco.org/lung-cancer-guidelines) provides additional information about the "Signals"[8] approach to updating.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

Guideline Disclaimers

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

ADJUVANT SYSTEMIC THERAPY

The CCO systematic review was current to January 2016 and included phase III RCTs comparing adjuvant systemic therapy with observation, other adjuvant systemic therapy, or adjuvant systemic therapy plus targeted agents in adult patients with completely resected NSCLC.[3] It includes the most recent update of the individual patient data (IPD) NSCLC Collaborative Group (NSCLCCG) meta-analyses, longer-term results, and exploratory analyses from trials that were included in the 2007 CCO/ASCO guideline and two new phase III RCTs. Also included are phase III trials of newer systemic therapy options: epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and immunotherapy.

The PubMed search conducted by ASCO from January 2016 to June 21, 2016, for additional trials of adjuvant systemic therapy found no new articles that met the inclusion criteria; however, one study that had been included in the CCO review as an abstract was fully published in April 2016.

A flow diagram of the search results can be found in Data Supplement 2.

QUALITY ASSESSMENT

Quality assessments conducted by CCO were adopted for this guideline and have been published elsewhere.[3] Briefly, the NSCLCCG meta-analysis scored well on the AMSTAR tool because it included an a priori design and comprehensive literature search, provided characteristics of included studies, and reported on heterogeneity. However, the NSCLCCG authors did not assess the likelihood of publication bias or the quality of the included studies or state any conflicts of interest. In a quality assessment of individual phase III trials of chemotherapy included in the NSCLCCG meta-analysis and CCO review, studies were judged using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology[9] to be at a moderate to high risk of bias due to lack of reporting of allocation concealment during randomization and lack of blinding. Two newer trials that were not included in the meta-analyses were also at risk for bias due to lack of blinding.[10,11] The quality of evidence for trials of immunotherapy and EGFR-TKIs was judged to be moderate due to inconsistency of comparators between trials. Evidence from NCDB or SEER is considered low quality because of the retrospective, nonrandomized nature of the data, which increases the risk of bias in the estimated effect.

KEY EVIDENCE

Adjuvant Chemotherapy

New randomized trial data. The first NSCLCCG meta-analyses of studies of adjuvant chemotherapy were published in 1995,[12] and the previous version of this guideline included the 2007 version,[13]

which included 8,147 patients and 30 RCTs. The 2016 CCO systematic review[3] included the most recent 2010 edition,[14] with the Cancer and Leukemia Group B (CALGB)[15] trial of chemotherapy in patients with stage IB disease and three additional RCTs, bringing the total number of included studies to 34 and patients to 8,447.[14]

The NSCLCCG meta-analyses[14] cover two key comparisons:

1. Surgery plus adjuvant chemotherapy versus surgery alone;
2. Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy.

For the comparison of OS at 5 years with surgery alone compared with surgery plus adjuvant chemotherapy, the NSCLCCG meta-analysis included 26 trials and found a significant advantage for the primary outcome of OS with adjuvant chemotherapy (hazard ratio [HR], 0.86; 95% CI, 0.81 to 0.92; $P < .001$; $I^2 = 4\%$).[14] Likewise, the meta-analysis of 12 trials that compared curative surgery and radiotherapy with or without adjuvant chemotherapy found an HR for OS of 0.88 (95% CI, 0.81 to 0.97; $P = .009$; $I^2 = 0\%$). In the latter analysis, patients with incomplete resections or unclear treatment schedules and those who had undergone neoadjuvant chemotherapy were included. There were no significant differences by patient characteristics, including stage.[14]

Two additional phase III trials were published after the most recent version of the NSCLCCG meta-analysis (Table 1).[10,11] One study compared surgery plus adjuvant carboplatin and paclitaxel versus surgery alone in early-stage NSCLCs.[10] No significant differences were found between groups for DFS (HR, 0.87; 95% CI, 0.54 to 1.38; $P = .54$), which was the primary end point, or OS (HR, 0.99; 95% CI, 0.75 to 1.3; $P = .93$). This study had a lack of power to detect differences between study groups. Sixty-six percent of patients who underwent resection received the planned adjuvant treatment. A smaller trial that was terminated early compared adjuvant chemotherapy with resection alone in stage IIIA-N2 NSCLCs and found significantly poorer outcomes with resection alone for the primary end point of DFS (HR, 1.560; 95% CI, 1.064 to 2.287; $P = .02$), as well as for OS (HR, 1.466; 95% CI, 1.017 to 2.114; $P = .037$).[11] An additional comparison with preoperative chemotherapy was outside the scope of this guideline.

Pooled analyses from randomized trials. In the previous version of this guideline, the Lung Adjuvant Cisplatin Evaluation (LACE) IPD meta-analysis of the five largest trials of cisplatin-based chemotherapy in NSCLCs demonstrated an overall HR for death of 0.89 (95% CI, 0.82 to 0.96; $P = .005$) after a median follow-up of 5.2 years.[16] A recent unplanned subgroup analysis found that there was significant interaction of cisplatin plus vinorelbine chemotherapy and stage (test for trend $P = .02$ for OS and $P = .008$ for DFS).[17] Patients with stage IIIA disease benefited the most from cisplatin plus vinorelbine, followed closely by those with stage II. In stage IB disease, which comprised approximately 34% of the total group, there was no significant effect compared with observation.[17]

Longer-term follow-up of phase III RCTs. Longer-term follow-up was available for JBR.10,[18] CALGB,[15,19] and the International Adjuvant Lung Cancer Trial (IALT),[20] which were included in the NSCLCCG analysis [14] and the previous version of this guideline[2] (Table 2). Detailed characteristics of these trials have been published elsewhere.[2,14] The LACE meta-analysis included earlier results for these trials, demonstrating a significant difference in favor of cisplatin-based chemotherapy after a median follow-up of 5.2 years.[16] In all three trials, OS was no longer significantly different between resected patients treated with or without chemotherapy after median follow-up intervals of 9.3,[18] 7.5,[20] and 9 years,[15,19] respectively. Median DFS was significantly better in the chemotherapy group after longer-term follow-up in the IALT study[20] (Table 2), and in a Cox regression model with disease stage, chemotherapy, and their interaction term, patients with stage II NSCLCs in the JBR.10 study had a significant benefit in survival with chemotherapy (HR, 0.68; 95% CI, 0.50 to 0.92; $P = .01$).[18]

Administrative databases. Morgensztern et al[22] evaluated the role of adjuvant chemotherapy in an NCDB data set of 25,267

Table 1. Summary of Phase III Trials Published Since the Last NSCLCCG Meta-Analysis[14]

Study (author, year)	Stage	No. of Patients	Treatment	Median Follow-Up (months)	OS	DFS
Felip,[10] 2010	Stage IA (> 2 cm), IB, II, or T3N1	211	Paclitaxel 200 mg/m^2 over 3 hours + carboplatin (AUC dose, 6.0 mg/mL/min) for 30-60 minutes *v*	51	Median OS, NR	Median DFS, NR
		212	Observation		HR, 0.99; 95% CI, 0.75 to 1.3; $P = .93$	HR, 0.96; 95% CI, 0.75 to 1.22; $P = .74$
Ou,[11] 2010	Stage III (N2)	38	Vinorelbine 25 mg/m^2 as 10-minute infusions on days 1 and 8 + carboplatin (AUC, 5) administered in 60-minute infusion + G-CSF at each cycle on days 9, 10, and 11 *v*	29	Median OS: Chemotherapy: 33 months; 95% CI, 27.4 to 38.6	Median DFS: Chemotherapy: 32 months; 95% CI, 21.3 to 42.7
		41	Paclitaxel 175 mg/m^2 as 3-hour infusion on day 1 + carboplatin (AUC, 5) administered in 60-minute infusion + G-CSF at each cycle on days 2, 3, and 4 *v*		Observation: 24 months; 95% CI, 15.8 to 32.2	Observation: 24 months; 95% CI, 13.1 to 26.9
		71	Observation		HR, 1.466; 95% CI, 1.017 to 2.114; ***P* = .037**	HR, 1.560; 95% CI, 1.064 to 2.287; ***P* = .02**

NOTE. In this study, an HR greater than one indicates a benefit in the treatment (chemotherapy) group. Bold text indicates a statistically significant result.
Abbreviations: AUC, area under the curve; DFS, disease-free survival; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; NR, not reached; NSCLCCG, Non–Small-Cell Lung Cancer Collaborative Group; OS, overall survival.

Table 2. Longer-Term Impact of Chemotherapy on OS and DFS After Surgery for NSCLC

Study (author, year)	Stage	No. of Patients	Treatment	Median Follow-Up	OS	DFS
JBR.10 (Winton,[21] 2005; Butts,[18] 2010)	T2NO, T1N1, T2N1	242	Cisplatin 50 mg/m^2 on days 1 and 8 every 4 weeks for four cycles + vinorelbine 25 mg/m^2 on day 1 every 3 weeks for 16 weeks *v*	9.3 years (range, 5.8 to 13.8)	Median OS[21]:	Median RFS[21]:
		240	Observation		Chemotherapy: 7.8 years; 95% CI, 6.1 to NR Observation: 6.1 years; 95% CI, 4 to NR Adjusted HR[18]: 0.79; 95% CI, 0.62 to 1.00; *P* = .05	Chemotherapy, NR Observation: 3.9 years
IALT (Arriagada,[20] 2010)	I, II, III	932	Chemotherapy (regimens varied based on center) *v*	7.5 years	Median OS: NR	Median DFS: NR
		935	Observation		HR, 0.91; 95% CI, 0.81 to 1.02; *P* = .10	**HR, 0.88; 95% CI, 0.78 to 0.98; *P* = .02**
CALGB9633 (Strauss,[9,15] 2008; Strauss,[19] 2011)	IB	173	Paclitaxel 200 mg/m^2 over 3 hours + carboplatin at AUC 6 mg/mL per minute for 45 to 60 minutes every 3 weeks for four cycles *v*	9 years	Median OS[19]:	Median DFS[15]:
		171	Observation		Chemotherapy: 8.2 years; 95% CI, NR Observation: 6.6 years; 95% CI, NR HR, 0.82; 90% CI, 0.65 to 1.0; *P* = .084 (one tail)	Chemotherapy: 7.4 years; 95% CI, NR Observation: 4.7 years; 95% CI, NR HR, 0.80; 90% CI, 0.62 to 1.02; *P* = .065

NOTE. Bolded text indicates a statistically significant result. Data adapted.[3]
Abbreviations: AUC, area under the curve; CALGB, Cancer and Leukemia Group B; DFS, disease-free survival; HR, hazard ratio; IALT, International Adjuvant Lung Cancer Trial; NSCLC, non–small-cell lung cancer; NR, not reached; OS, overall survival; RFS, recurrence-free survival.

patients who underwent complete resection from 2004 to 2011. Approximately 20% (4,996) received adjuvant chemotherapy, which was associated with significantly improved median survival and OS for all tumor size groups, from 3.1 to 7 cm, grouped by 1-cm intervals, within the T2 stage.

Other Systemic Therapy Options.

Three additional fully published phase III RCTs met the inclusion criteria for the CCO review, including trials of EGFR-TKIs gefitinib[23] and erlotinib[24] and a trial of immunotherapy.[25] One abstract that was included in the CCO review was fully published after the final data search and is included in our results[26] (Table 3).

EGFR-TKIs. The RADIANT (Randomized Double-Blind Trial in Adjuvant NSCLC With Tarceva) trial[24] compared erlotinib versus placebo in a population of patients with completely resected stage IB to IIIA NSCLC whose tumors were not selected by the presence of sensitizing *EGFR* mutations, the robust biomarker that underlies sensitivity of tumors to EGFR-TKIs.[27] Instead, patients were entered if their tumors expressed EGFR protein by immunohistochemistry or *EGFR* amplification by fluorescence in situ hybridization, factors not proven to be predictive of benefit from EGFR-TKIs. No significant differences in DFS or OS were detected in the overall unselected study population. DFS favored erlotinib in patients with an *EGFR* sensitizing mutation (HR, 0.61; 95% CI, 0.384 to 0.981; *P* = .039); however, due to the hierarchic structure of the analysis, this result is not considered significant. There was no overall survival benefit from erlotinib in this subgroup (HR, 1.09; 95% CI, 0.55 to 2.16).

The BR19 trial compared gefitinib versus placebo in a population of patients with completely resected stage IB to IIIA NSCLC whose tumors were not selected by the presence of sensitizing *EGFR* mutations or copy number or EGFR protein expression. Approximately half (500 patients) of the planned sample was accrued. After discontinuation of medication, patients were observed for at least 4 years before the final analysis was performed. The HR for OS, the primary end point, was 1.24 (95% CI, 0.94 to 1.64; *P* = .14), and the HR for DFS was 1.22 (95% CI, 0.93 to 1.61; *P* = .15). There was no benefit for either of the subgroups with *EGFR* wild-type tumors or the 15 tumors (4% of the total sample) with *EGFR* sensitizing mutations.

Immunotherapy. In a single-institution study of 51 patients, Kimura et al[25] investigated adjuvant immunotherapy, which consisted of the adoptive transfer of autologous activated killer T cells and dendritic cells obtained from the patients' own regional lymph nodes. Patients were observed for 5 years. This study showed a significant OS benefit (HR, 0.229; 95% CI, 0.093 to 0.564; *P* = .0013) for the combined immunotherapy plus chemotherapy group.

In the MAGRIT (MAGE-A3 [melanoma-associated antigen-A3] As Adjuvant Non–Small-Cell Lung Cancer Immunotherapy) trial, Vansteenkiste et al[26] found no significant difference in the primary outcome DFS for patients treated with MAGE-A3 immunotherapeutic in a combined population that did or did not receive chemotherapy (HR, 1.02; 95% CI, 0.89 to 1.19; *P* = .74). They also found no difference

Table 3. Phase III RCTs of Targeted Therapy and Immunotherapy

Study (author, year)	Stage	No. of Patients	Median Follow-Up (range)	Treatment	Median OS (range)	HR for OS	Median DFS (range)	HR for DFS
Targeted therapy with EGFR-TKIs								
RADIANT (Kelly,[24] 2015)	Stage IB, II, IIIA (n = 162)	623	47 months	Erlotinib 150 mg/day for up to 2 years v	NR	1.13; 95% CI, 0.881 to 1.448; *P* = .3350	50.5 months	0.90; 95% CI, 0.741 to 1.104; *P* = .3235 (primary end point)
	EGFR mutation positive	350		Placebo (> half received chemotherapy)	NR		48.2 months	
BR19 (Goss,[23] 2013)	Stage IB, II, IIIA (n = 15)	251	5 years (0.1-6.3)	Gefitinib 250 mg/day for 2 years *v*	5 years (4.4-not calculable)	1.24; 95% CI, 0.94 to 1.64; *P* = .14 (primary end point)	4.2 years (3.2-not calculable)	1.22; 95% CI, 0.93 to 1.61; *P* = .15
	EGFR mutation positive	252		Placebo	NR		NR	
Immunotherapy*								
Kimura,[25] 2015	Stage IB, II to IV	51	32 months	Four courses per month of chemotherapy (regimens varied) + activated killer T cells and dendritic cells 1 week after each course of chemotherapy, then once a month for 6 months after resection, then every 2 months until 2 years after resection *v*	NR	0.229; 95% CI, 0.093 to 0.564; **P = .0013**	RFS: Vaccine + chemotherapy: 16.56 months (9-32.01)	RFS: 0.423; 95% CI, 0.241 to 0.743; **P = .0027**
		52		Four courses of chemotherapy†	47.5 months (26.3-NR)		Chemotherapy: NR	
Immunotherapy‡								
MAGRIT (Vansteenkiste,[26] 2016)	Stage IB to IIIA MAGE-A3 positive	1,515 (784 also received chemotherapy)	38.1 months (MAGE-A3)	13 muscular injections of recMAGE-A3 with AS15 immunostimulant (MAGE-A3 immunotherapeutic) with or without chemotherapy *v*	Median OS in overall population:	1.04; 95% CI, 0.86 to 1.24; *P* = .6994	Median DFS in overall population:	1.02; 95% CI, 0.89 to 1.19; *P* = .74
		757 (392 also received chemotherapy)	39.5 months (placebo)	Placebo with or without chemotherapy	MAGE-A3: Median not reached Placebo: Median not reached Median OS in patients who did not receive chemotherapy: MAGE-A3: median NR Placebo: median NR	1.00; 95% CI, 0.78 to 1.29; *P* = .9824	MAGE-A3: 60.5 months; 95% CI, 57.2 to undefined Placebo: 57.9 months; 95% CI, 55.7 to undefined Median DFS in patients who did not receive chemotherapy: MAGE-A3: 58.0 months; 95% CI, 56.6 to undefined Placebo: 56.9 months (44.4- undefined)	0.97; 95% CI, 0.80 to 1.18; *P* = .76

NOTE. Bold *P* values indicate a statistically significant difference between intervention and control groups.

Abbreviations: DFS, disease-free survival; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; MAGE-A3, melanoma-associated antigen-A3; MAGRIT, MAGE-A3 As Adjuvant Non–Small-Cell Lung Cancer Immunotherapy; NR, not reached; OS, overall survival; RADIANT, Randomized Double-Blind Trial in Adjuvant NSCLC With Tarceva; RFS, recurrence-free survival.

*Adoptive transfer of autologous activated killer T cells and dendritic cells.

†Stage IIIA patients received two courses of induction chemotherapy before surgery.

‡MAGE-A3 cancer immunotherapeutic.

in DFS in the subset of patients who did not receive chemotherapy (HR, 0.97; 95% CI, 0.80 to 1.18; $P = .76$). Because there was no difference between groups, the study was unable to identify a biomarker that would enable selection of patients for this treatment.

Adverse Events

In the LACE meta-analysis of cisplatin-based chemotherapy, the rate of overall grade 3 to 4 toxicity was 66% among 1,190 patients in four trials for which this information was available.[16] With data from five trials, the rate of grade 4 toxicity was 32%. The most frequent toxicity was neutropenia (grade 3, 9%; grade 4, 28%); however, the rate was highly variable across trials, likely due to differing methods of surveillance and data collection. There were 19 chemotherapy-related deaths (0.9%) reported. Butts et al[18] reported that no unexpected late toxicity or increase in second malignancies from adjuvant chemotherapy were observed.

A meta-analysis of randomized and nonrandomized studies found that the overall rate of grade 3 or greater adverse events with EGFR-TKI adjuvant therapy was 42.3% (95% CI, 39.1 to 45.6).[28]

RECOMMENDATIONS

CLINICAL QUESTION 1

What is the OS benefit of adjuvant systemic therapy in patients with completely resected stage I to IIIA NSCLCs?

Recommendation 1.1

Stage IA: Adjuvant chemotherapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Moderate[3]; Strength of recommendation: Strong).

Recommendation 1.2

Stage IB: Adjuvant cisplatin-based chemotherapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks for adjuvant chemotherapy for each patient (Type: Evidence based and Panel consensus; Benefits outweigh harms, especially in patients with larger tumors; Evidence quality: Intermediate[3]; Strength of recommendation: Moderate).

Recommendation 1.3

Stages IIA/B and IIIA: Adjuvant cisplatin-based chemotherapy is recommended (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: High[3]; Strength of recommendation: Strong).

Factors Other Than Tumor Stage to Consider in Recommending Adjuvant Chemotherapy

Beyond stage, many tumor-specific variables have been studied to determine their utility in delineating prognosis for patients with resected lung cancers, and the results of a selective review of the literature pertaining to prognostic characteristics are provided in this section. Many of these studies are in patients with stage I tumors. The ability of these features to estimate prognosis, assist in the recommendation of adjuvant therapy, or predict the benefit of adjuvant chemotherapy remains unknown. Although post hoc analyses of completed adjuvant chemotherapy studies have identified some putative genetic predictors of response, none have been validated prospectively.

Resected tumor size between 3 and 7 cm. In patients with resected lung cancers and no nodal spread, the 5-year survival rate declines with increasing tumor size: 3 to 4 cm, 74%; 4 to 5 cm, 65%; and 5 to 7 cm, 57%.[29] Survival data in a cohort of 25,267 patients with resected T2N0M0 tumors in the NCDB demonstrated that adjuvant chemotherapy was associated with improved median survival and 5-year OS for all tumor size groups with the T2 stage.[22] Earlier subgroup analyses of completed randomized adjuvant chemotherapy trials demonstrated survival improvement with chemotherapy for patients with tumors $\geq$ 4 cm.[15,18]

Histopathologic features. The presence of selected histopathologic features has been associated with higher recurrence risk and poorer prognosis, including perineural invasion,[30] tumor necrosis,[30] vascular invasion,[31] and/or lymphatic invasion.[31,32] The presence of visceral pleural invasion, regardless of T stage, upstages tumors $<$ 3 cm to pT2a.[33,34] A study of resected stage I lung adenocarcinomas found mitotic index (zero to 10 $v >$ 10 mitoses per 10 high-powered fields) to be an independent prognostic marker.[35] In addition, the following risk levels are associated with International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society adenocarcinoma subtypes[36-42]:

- Micropapillary or solid: high risk;
- Acinar, papillary, or invasive mucinous: intermediate risk;
- Minimally invasive or lepidic: low risk.

Presence of oncogenic drivers. Mutations in *KRAS* are not predictive for benefit from adjuvant chemotherapy.[18,43,44] The results with adjuvant EGFR-TKIs in patients with *EGFR*-mutant cancers have been discussed under Key Evidence.

Presence of determinants of DNA repair capacity. Multiple genes, particularly those related to DNA repair, have been studied for their impact on prognosis and chemosensitivity, such as *ERCC1*,[45,46] *RRM1*,[46] and *BRCA1*. Biomarker-selected adjuvant trials, including the completed SWOG feasibility study[47] and the Spanish *BRCA1*-directed trial (reported to be negative) and the trials of *ERCC1* and *RRM1* to select patients with advanced disease for benefit,[48] have all been unsuccessful.

Gene signatures. Genomic assays (microarrays and polymerase chain reaction based) have been used to identify high- and low-risk disease subsets.[49-52] These separately developed signatures have little overlap in genes analyzed, and all require prospective validation before they can be recommended for use. One of these has been further combined with the subtype of adenocarcinoma to create a combined score for recurrence.[53] A predictive gene signature derived from JBR.10 specimens demonstrated a benefit from chemotherapy in the signature defined high-risk cohort and not in the low-risk subset.[54]

Adjuvant Radiation Therapy

The evidence base until March 2013 for postoperative radiotherapy (PORT) in patients with completely resected stage IIIA

to N2 NSCLCs is described in the 2015 ASCO endorsement of the ASTRO guideline "Adjuvant Radiation Therapy in Locally Advanced Non-small Cell Lung Cancer."[4] Since that endorsement, there has been no new evidence that would alter the recommendation against PORT in patients with stage I or II disease. New or updated research has been published in the population of patients with stage IIIA disease; the search for additional studies published between March 2013 and June 21, 2016, found an update to the IPD meta-analysis by the Medical Research Council PORT Meta-analysis Trialist Group, using newer statistical methodology[55]; three studies based on data from the NCDB[6,56,57] and one systematic review that compared outcomes in stage IIIA-N2 NSCLC for patients who did or did not receive PORT)[58,59] were also included. The quality and results of these studies are discussed subsequently.

Quality Assessment

The evidence base for adjuvant radiation therapy in resected stage IIIA-N2 disease was determined to be of moderate quality according to the ASTRO systematic review, which used the American College of Physicians methodology for assessment of study quality.[4]

Key Evidence

A 2013 update with 11 trials (2,343 patients) showed a detrimental effect of PORT for OS (HR, 1.18; 95% CI, 1.07 to 1.31; P = .001), and for local (HR, 1.12; 95% CI, 1.02 to 1.24; P = .02), distant (HR, 1.13; 95% CI, 1.02 to 1.25; P = .02), and overall (HR, 1.09; 95% CI, 1.0.99 to 1.21; P = .08) recurrence-free survival.[55] An analysis by stage of eight trials, using the sixth edition of the TNM staging system and updated methodology found that while PORT still seemed to be detrimental in patients with stage I or II disease, the result by stage was no longer significant (P = .12).[55] These authors recommended that PORT not be routinely used until supporting evidence from trials using modern PORT techniques was available.

Billiet et al[58,59] conducted a non-IPD meta-analysis using a heterogeneous mix of studies of PORT in patients with stage I to III NSCLCs that were published between 1980 and 2002. For all types of therapy beams combined (ie, cobalt or linear accelerators or a combination of both), there was a nonsignificant difference in OS (relative risk [RR], 1.07; 95% CI, 0.89 to 1.29; P = .45); however, local tumor failure was significantly reduced in the group that received surgery plus PORT versus PORT alone (RR, 0.42; 95% CI, 0.27 to 0.67; P = .001; I^2 = 74.8%). A subgroup analysis of OS for surgery plus PORT with linear accelerators versus surgery alone, which included four studies with 439 patients, did not find an OS difference (RR, 0.85; 95% CI, 0.59 to 1.22; P = .38) but did find a significant difference in local tumor failure favoring surgery plus PORT versus surgery alone (RR, 0.31; 95% CI, 0.12 to 0.79; I^2 = 49.2%).

Three NCDB studies met the inclusion criteria[6,56,57] (Table 4). These comparative, observational studies assessed more contemporary delivery of PORT for N2 disease, relative to the studies included in the Medical Research Council PORT meta-analysis.[60] In Mikell et al,[6] where 82% of patients received adjuvant chemotherapy, there was a significant difference in OS in favor of the adjuvant radiation therapy group on multivariable analysis (HR, 0.89; 95% CI, 0.79 to 1.00; P = .046). Robinson et al[57] assessed so-called modern PORT in patients with resected NSCLCs with N2 extent who received adjuvant chemotherapy. The HR for OS significantly favored the PORT group on multivariable analysis (HR, 0.888; 95% CI, 0.798 to 0.988; P = .029). In an older cohort of patients with stage II to IIIA NSCLCs in which 34% received chemotherapy, there was no significant difference in OS between PORT versus no PORT on multivariable analysis (HR, 0.96; 95% CI, 0.88 to 1.05; P = .337); however, there was a significant benefit of PORT compared with no PORT when the analysis was restricted to patients who had received a dose of 45 to 54 Gy (5-year OS: HR, 0.85; 95% CI, 0.76 to 0.94; P < .001), and no improvement in OS was seen with PORT in patients receiving more than 54 Gy.[56]

Adverse Events

The three NCDB studies lacked outcome data for toxicity, treatment compliance, and quality of life.[6,56,57] The most commonly encountered adverse events with radiation therapy have previously been reported in a meta-analysis to be mild esophagitis, dysphagia, and odynophagia.[61] In that study, cough and pneumonitis requiring steroid therapy were the most common pulmonary toxicities, radiation myelitis was reported in one patient, and no severe late complications were noted. Late complications were few, although analysis of this outcome was likely limited by the follow-up duration.[61] The adverse effect of PORT on cardiac events has not been adequately studied.

CLINICAL QUESTION 2

What is the OS benefit of adjuvant radiation therapy in patients with completely resected stage I to IIIA NSCLCs?

Recommendation 2.1

Stage IA/B and IIA/B: Adjuvant radiation therapy is not recommended (Type: Evidence based and Panel consensus; Harms outweigh benefits; Evidence quality: Intermediate; Strength of recommendation: Strong[2]).

Recommendation 2.2

Stage IIIA: Adjuvant radiation therapy is not recommended for routine use. A postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiotherapy in patients with N2 disease (Type: Evidence based and Panel consensus; Benefits outweigh harms; Evidence quality: Intermediate[4]; Strength of recommendation: Moderate).

Strategies to Improve Communication With Patients Considering Adjuvant Chemotherapy

This section is intended to help health care practitioners discuss the benefits and risks of adjuvant therapy and address the unique concerns of persons with lung cancers to reach a shared decision. Few studies have addressed physician-patient communication specifically in patients with lung cancers, and even fewer have involved patients with curable lung cancers. These recommendations represent consensus with low evidence quality.

Table 4. Studies of the NCDB in Patients With Resected Pathologic N2 NSCLC

Study (author, year)	Date of Diagnosis	Stage	Receipt of Chemotherapy	Median Follow-Up Time	Covariates in Multivariable Analysis	Intervention *v* Control Group	No. of Patients	Survival (intervention *v* control group)	
								OS	Median OS (months)
Mikell,[6] 2015	2004-2006	IIIA-N2	Adjuvant, 82%; neoadjuvant, 9.1%; unknown, 9.1%	NR	Sex, age, insurance, income, urban status, histology, T stage, No. of regional nodes positive, No. of regional nodes examined	EBRT with LINAC and 3D CRT v No PORT	918 1,197	HR, 0.89; 95% CI, 0.79 to 1.00; ***P* = .046**	42 38 ***P* = .048**
Robinson,[57] 2015	2006-2010	IIIA-N2	Yes (standard adjuvant chemotherapy)	22 months	Age, facility type, sex, income, urban status, comorbidity score, tumor size, multiagent chemotherapy, type of surgery, receipt of PORT	Assumed PORT (≥ 45 Gy) with CT simulation and at least LINAC-based 3D CRT *v* No PORT	1,850 2,633	HR, 0.888; 95% CI, 0.798 to 0.988; ***P* = .029**	45.2 40.7
Corso,[56] 2015	1998-2006	IIIA-N2	34.3% of overall sample received chemotherapy	7.5 years	Histology, age, sex, comorbidity score, type of surgery, receipt of chemotherapy, tumor site, tumor size, nodal stage, receipt of PORT	PORT ≥ 54 Gy *v* No PORT PORT 45 to 54 Gy *v* No PORT	1,444 27,122 1,985 27,122	HR, 0.96; 95% CI, 0.88 to 1.05; *P* = .337 HR: 0.85 (0.76-0.94, ***P* < 0.001**)	NR

NOTE. Bold *P* values indicate a statistically significant difference between intervention and control groups.

Abbreviations: 3D, three dimensional; CRT, chemoradiotherapy; CT, computed tomography; HR, hazard ratio (HR < one indicates result favoring PORT); LINAC, linear accelerator; NCDB, National Cancer Database; NR, not reported; NSCLC, non–small-cell lung cancer; OS, overall survival; PORT, postoperative radiation therapy.

A discussion of adjuvant chemotherapy in persons with resected lung cancers must cover the complex medical, psychological, and social issues faced by these individuals. Many patients have pain, impaired breathing, or fatigue related to surgery. Most patients with lung cancers have underlying debility due to smoking-related illnesses and psychological distress as a result of their lung cancer diagnosis.[62-64] Smoking cessation, a necessary component of the care of persons with lung cancers, can result in at least a short-term increase in stress in patients as they withdraw from nicotine.[65] Furthermore, a majority of persons with lung cancers in the United States are age older than 70 years, increasing the likelihood of significant comorbidities and the attendant greater susceptibility to the adverse effects of chemotherapy and radiation therapy. From an actuarial standpoint, many elderly patients may be more likely to die as a result of causes other than lung cancer than younger patients with similar stage disease, and a discussion of competing health risks is essential.

Practitioners must consider these complex issues when discussing the benefits and risks of adjuvant therapy, recognizing some patients may be unprepared, overzealous, or unmotivated to proceed with additional therapy after major surgery. There is no one way to discuss this topic, and each session must be individualized. Studies have found that patients are most satisfied if they perceive an effort by their physician to share decision making and are afforded sufficient time to make their decision.[66-68] One way to accomplish the latter is to offer a session dedicated solely to the discussion of adjuvant treatment.

Patients with lung cancers who lack a precise understanding of their prognosis tend to overestimate their probability of cure.[69] One way to determine the patient's level of understanding is to ask an open-ended question early in the dialogue, such as, "Tell me what you know about your lung cancer?" The discussion of adjuvant therapy is especially difficult because it involves informing patients about their risk of recurrence and death while they are clinically free of cancer. Many patients conclude they are cured because of postoperative discussions with their surgeon where they were told all visible disease was removed and the completeness of the surgery was confirmed by the pathology report describing clear margins. On the other hand, the discussion may be especially rewarding in that the goal of adjuvant therapy is cure.[70] The challenge is balancing a clear assessment of the patient's prognosis while maintaining hope. It is important to ask the patient how he or she would like to hear information regarding his or her risk of recurrence and the potential benefit of additional therapy. Some patients prefer general terms, others numbers, charts or graphs. A factual discussion between the oncologist, the patient, and the care team is critical. If a graphical representation like that in Figure 1 is used, the medical oncologist should guide the patient through it. Thoracic surgeons can facilitate this discussion by referring patients to a medical oncologist with expertise in lung cancers. After evaluating the patient with N2 disease extent and leading a discussion on the risks and benefits of adjuvant chemotherapy, the medical oncologist can facilitate a discussion of postoperative radiation therapy by arranging a referral to a radiation oncologist with expertise in lung cancers. For patients who prefer numbers, the physician can quote both the relative reduction in the risk of death (ie, the HR), as well as absolute survival benefit of the therapy. Studies have found that quoting absolute survival benefit is easier for patients to understand compared with RR reduction.[71] Patients quoted RR reduction are significantly more likely to agree with the recommendation for chemotherapy but less likely to demonstrate a true understanding of the benefit.[71]

Figure 1 is a graphical representation of estimated absolute risk and benefit for 100 patients with lung cancers treated with surgery and adjuvant chemotherapy, based on reported, stage-specific 5-year survival rates in the control arms of each clinical trial. This series of graphs is intended to help physicians and patients understand the absolute mortality risk and benefit of adjuvant chemotherapy for the various stages of lung cancers based on all available data and is best presented to patients with direct physician guidance. These graphs separate the patient sample into four groups: those who die within 5 years, whether they receive

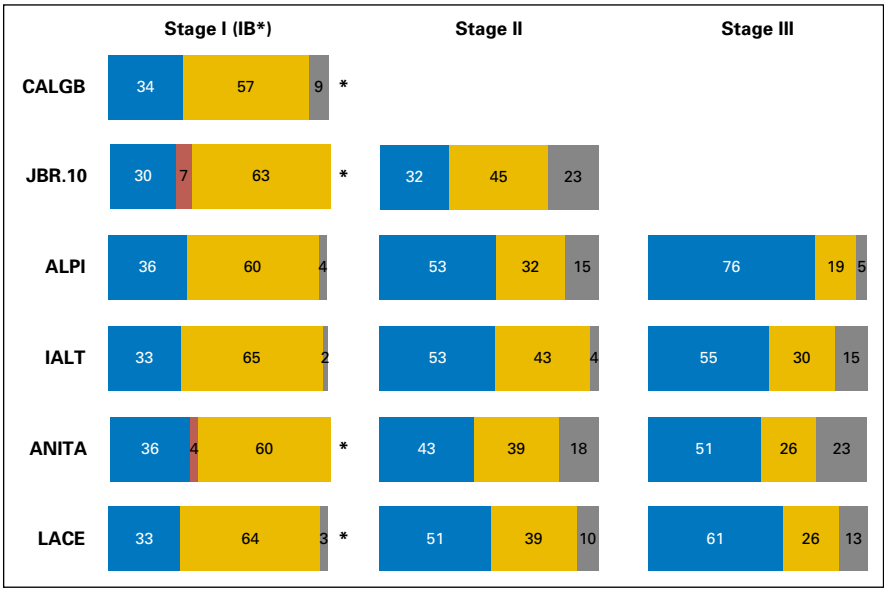

Fig 1. Predicted outcome of 100 patients treated with surgery and adjuvant chemotherapy. These graphs separate a representative 100 patients with resected lung cancers by stage into four groups: those who die within 5 years whether they receive chemotherapy or not (blue), those who live without receiving chemotherapy (gold), those who live because of adjuvant chemotherapy (gray), and those who die because of chemotherapy (red). ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B; IALT, International Adjuvant Lung Cancer Trial; LACE, Lung Adjuvant Cisplatin Evaluation. (*) Trials that included stage IB. ALPI and IALT were open for IA and IB.

chemotherapy or not (blue); those who live without receiving chemotherapy (gold); those who live because of chemotherapy (gray); and those who die because of chemotherapy (red). Using the LACE data to estimate absolute benefit, adjuvant chemotherapy raises 5-year survival from 64% up to 67% for stage IB, from 39% up to 49% for stage II, and from 26% up to 39% for stage IIIA disease extent.

With the physician providing guidance and interpretation, graphs such as these may help patients gain a better understanding of absolute risk and benefit. Software applications are available on the Internet that may further aid clinicians and patients in this process.[72,73] There are no studies to test whether these decision-aid tools have an impact on compliance, understanding, or outcome in patients with lung cancers.

The guideline panel concludes that therapeutic nihilism toward adjuvant chemotherapy for stage IB to IIIA lung cancers should be abandoned. The recommendations contained in this guideline provide clinicians with the evidence that justifies presenting the option of adjuvant chemotherapy to all patients. We are confident that increasing understanding of the benefits and risks, employment of adjuvant strategies in all patients where evidence justifies their use, and better compliance with guidelines can cure more individuals with stage IB to IIIA lung cancers.

DISCUSSION

Little new evidence has been published regarding adjuvant chemotherapy in early-stage lung cancers since the previous version of this guideline.[74] Cisplatin-based adjuvant chemotherapy was recommended for routine use in patients with stage II or IIIA disease extent and for consideration in patients with stage IB NSCLCs. A pooled exploratory analysis based on two RCTs found a nonsignificant trend for increased chemotherapy effect on OS with larger tumor size in patients with no nodal spread.[43] Additionally, an exploratory subgroup analysis of the NSCLCCG meta-analysis found no significant difference in the effect of adjuvant chemotherapy on survival by stage and concluded that in the absence of comorbidities and contraindications to chemotherapy, adjuvant platinum-based chemotherapy should be considered when there is a high risk of recurrence (ie, in stage IB, II, and III disease).[75] This update recommends that physicians discuss the benefits and risks of adjuvant chemotherapy with patients with node-negative NSCLCs. This is a moderate-strength recommendation. This review found no unexpected late toxicities.[18]

No completed trials have been designed to specifically compare survival outcomes with and without adjuvant EGFR-TKIs in patients whose tumors harbor sensitizing *EGFR* mutations. Two phase III trials on their effectiveness were included in this review. A trial of gefitinib that included 15 patients with sensitizing *EGFR* mutations failed to show a survival benefit.[23] A second trial of erlotinib that included 161 patients with tumors with sensitizing *EGFR* mutations demonstrated a large effect on DFS (median, 46 *v* 29 months; $P = .039$); however, this finding was not considered significant, because of a hierarchic statistical design. A meta-analysis[28] included these two trials as well as a phase II RCT and two retrospective comparative studies. This meta-analysis did not meet our inclusion criteria, because of the inclusion of retrospective data, and should be interpreted with caution. However, it showed that the treatment effect of EGFR-TKIs varied by *EGFR* mutation rate, and in the population of patients with *EGFR* mutations, the HR for DFS significantly favored the treatment group (HR, 0.48; 95% CI, 0.36 to 0.65). There was no significant difference in OS. These data were considered insufficient to justify the routine use of EGFR-TKIs in patients with tumors with sensitizing *EGFR* mutations. Several trials are currently under way that assess EGFR-TKIs in patients who have *EGFR* mutation–positive tumors, for example, trials of gefitinib versus placebo (clinicaltrials.gov identifier NCT01405079) and erlotinib versus cisplatin plus vinorelbine (clinicaltrials.gov identifier NCT01410214)[76] and ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial), which includes a platform to test adjuvant crizotinib, erlotinib, and nivolumab (clinicaltrials.gov identifiers NCT02201992 and NCT02193282).[77]

We await the publication of a phase III RCT enrolling 1,501 patients (Intergroup trial E1505), which found that the addition of angiogenesis inhibitor bevacizumab to chemotherapy failed to improve DFS or OS for individuals with surgically resected early-stage NSCLCs compared with chemotherapy alone.[78]

A phase III immunotherapy trial using T cells and dendritic cells included in this review demonstrated an OS benefit for combined immunotherapy and chemotherapy[25]; however, the panel felt the results of this 51-patient single-institution trial were insufficient to recommend this approach. Immune checkpoint inhibitors inhibiting programmed death-1 or programmed death-ligand 1 have demonstrated significant activity in advanced NSCLCs and are now being evaluated in the adjuvant setting.[3]

Studies of large databases have explored the use of PORT in stage IIIA-N2 disease,[79] where there has been suggestion of better local control. However, due to the retrospective nature of these studies, these data are considered insufficient to justify routine use of PORT. In concert with ASTRO, ASCO recommends that adjuvant chemotherapy followed by adjuvant radiation therapy may be used to improve local control in patients with resected NSCLCs with mediastinal lymph node spread (N2).[5] A postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiotherapy in patients with N2 disease.

In conclusion, this guideline updates the strength of the recommendations for adjuvant chemotherapy and adjuvant radiation therapy in patients with stage IB and IIIA disease, respectively. It also includes studies of targeted treatments. It is critical that a multidisciplinary team address the recommendation of adjuvant therapies in each patient with resected stage I to IIIA NSCLC. There is unanimous consensus among the guideline panel that close collaboration among medical oncologists, radiation oncologists, thoracic surgeons, radiologists, and pathologists will ensure the best possible outcome for every patient with a resected NSCLC.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic

disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[80-83] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs; this highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, providing adequate services in the face of limited resources, as well as the challenge of discriminating between multiple guideline products from various sources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update

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Appendix

Table A1. Guideline Update Expert Panel Membership

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