

Cancer Care Ontario and American Society of Clinical Oncology Adjuvant Chemotherapy and Adjuvant Radiation Therapy for Stages I-III A Resectable Non–Small-Cell Lung Cancer Guideline

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A B S T R A C T

Purpose

To determine the role of adjuvant chemotherapy and radiation therapy in patients with completely resected stage IA-III A non–small-cell lung cancer (NSCLC).

Methods

The Cancer Care Ontario Program in Evidence-Based Care and the American Society of Clinical Oncology convened a Joint Expert Panel in August 2006 to review the evidence and draft recommendations for these therapies.

Results

Available data support the use of adjuvant cisplatin-based chemotherapy in completely resected NSCLC; however, the strength of the data and consequent recommendations vary by disease stage. Adjuvant radiation therapy appears detrimental to survival in stages IB and II, with a possible modest benefit in stage III A.

Conclusion

Adjuvant cisplatin-based chemotherapy is recommended for routine use in patients with stages IIA, IIB, and III A disease. Although there has been a statistically significant overall survival benefit seen in several randomized clinical trials (RCTs) enrolling a range of people with completely resected NSCLC, results of subset analyses for patient populations with stage IB disease were not significant, and adjuvant chemotherapy in stage IB disease is not currently recommended for routine use. To date, very few patients with stage IA NSCLC have been enrolled onto RCTs of adjuvant therapy; adjuvant chemotherapy is not recommended in these cases. Evidence from RCTs demonstrates a survival detriment for adjuvant radiotherapy with limited evidence for a reduction in local recurrence. Adjuvant radiation therapy appears detrimental to survival in stage IB and II, and may possibly confer a modest benefit in stage III A.

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INTRODUCTION

This clinical practice guideline addresses two principal questions related to the treatment of patients with non–small-cell lung cancer (NSCLC). First, what is the benefit in terms of overall survival and role of adjuvant chemotherapy in patients with completely resected stage I-III A NSCLC? Second, what is the benefit in terms of overall survival and role of adjuvant radiation therapy in patients with completely resected stage I-III A NSCLC?

Lung cancer is the leading cause of cancer death in the western world. In the United States, 213,000 new cases of lung cancer are expected in 2007, and

more than 160,000 individuals are expected to die as a result of the disease.¹ Approximately 85% of all cases of lung cancer are of the non–small-cell type.²

For many years, surgery alone has been the standard treatment for patients with stage I-III A NSCLC. Even with complete resection, 5-year survival rates are disappointing and range from 67% for T1N0 (IA) disease, to 23% for patients with T1-3N2 (III A).³ Relapse most often occurs at distant sites, suggesting that NSCLC is commonly a systemic disease at diagnosis. To improve survival for patients with resectable NSCLC, clinicians have examined the use of chemotherapy and radiation therapy in both the preoperative (neoadjuvant or induction) and postoperative (adjuvant) settings.

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†Deceased. This article is dedicated to Christopher E. Desch, MD, who was the National Medical Director of the National Comprehensive Cancer Network, one of the founding volunteers of the Quality Oncology Practice Initiative for ASCO, and a driving force behind ASCO oncology guidelines. As both an academic and community oncologist, he had a unique perspective, ability, and passion to improve the quality of cancer care.

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Until recently, the benefit of adjuvant chemotherapy in stage I-IIIa NSCLC patients was uncertain. Many small underpowered trials of postoperative chemotherapy failed to demonstrate a significant survival benefit and larger multicenter trials yielded conflicting results. In addition, there has been uncertainty concerning the role of postoperative thoracic irradiation in these patients. Recent data have clarified these issues and this guideline serves to provide an evidence basis for the role of postoperative chemotherapy and radiotherapy in completely resected (R0 resection) stage I-IIIa NSCLC patients. This guideline does not address the role of postoperative therapy for NSCLC patients with positive margins (ie, microscopic residual disease, R1 resection) or macroscopic residual disease (R2 resection), given that the trials that formed the evidence base for this guideline did not include such patients. The use of postoperative tegafur and uracil (UFT) is not included in this guideline; although survival improvement has been reported in postoperative UFT Japanese trials,⁴ there have been no confirmatory trials in Western populations. This guideline did not review randomized neoadjuvant trials and focused only on the use of postoperative chemotherapy. The guideline recommendations are summarized in Table 1.

Clinical Practice Guidelines

Practice guidelines are systematically developed statements to assist practitioners and patients with appropriate health care decisions for specific clinical circumstances.⁵ Attributes of good guidelines include a multidisciplinary process of development and critical review of all relevant evidence. Guidelines may be useful in producing better care and decreasing its cost. Specifically, utilization of clinical practice guidelines may provide improvements in outcomes, improvements in medical practice, a means for minimizing inappropriate practice variation, decision support tools for practitioners, points of reference for medical orientation and education, criteria for self-evaluation, indicators and criteria for external quality review, assistance with reimbursement and coverage decisions, and criteria for use in credentialing decisions.

In formulating recommendations for the use of adjuvant therapy for patients with stage I-IIIa NSCLC, Cancer Care Ontario

(CCO) and the American Society of Clinical Oncology (ASCO) considered these tenets of guideline development, emphasizing review of data from controlled clinical trials. However, it is important to emphasize that practice guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result. **Accordingly, ASCO and CCO consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative therapies in a disease for which better therapy is needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.**

METHODS

Panel Composition

CCO and ASCO convened a Joint Expert Panel consisting of experts in clinical medicine, clinical research, health services research, and related disciplines (biostatistics, medical decision-making, patient-physician communication) with a focus on expertise in lung cancer. Patient representatives were also included on the Panel. The clinical experts represented medical oncology, radiation oncology, and surgical oncology. A steering committee under the auspices of the Health Services Committee (HSC) and the CCO Program in Evidence-Based Care (PEBC) Lung Cancer Disease Site Group (DSG) chose Panel participants for the clinical practice guideline development process. The Panel participants are listed in Appendix Table A1.

Literature Review and Analysis

CCO systematic reviews on adjuvant chemotherapy and adjuvant radiation therapy. The CCO Lung DSG first published a systematic review on the role of adjuvant radiation therapy and chemotherapy in patients with stage II or IIIa resected NSCLC in 1997.⁶ More recently, two separate systematic reviews were undertaken by CCO to update the original systematic review: one on adjuvant chemotherapy for patients with stage I-IIIa completely resected NSCLC, and one on adjuvant radiation in patients with stage II or IIIa completely resected NSCLC. These systematic reviews have been published elsewhere and serve as the primary source of evidence for this practice guideline.⁷⁻¹¹

CCO-ASCO Panel literature review and analysis. CCO-PEBC staff updated the literature searches in August 2006, before the joint CCO-ASCO Panel meeting. Articles were included in the CCO-PEBC systematic reviews of chemotherapy (or radiation therapy) for NSCLC if they were in the following categories:

1. Evidence-based practice guidelines addressing the role of postoperative chemotherapy (or radiation therapy) following complete resection of NSCLC and published since 2000 (to identify trials published since the prior systematic review), or

Table 1. Summary of Recommendations for Adjuvant Cisplatin-Based Chemotherapy and Adjuvant Radiotherapy

Stage	Summary of Recommendations for Adjuvant Cisplatin-Based Chemotherapy
IA	Adjuvant chemotherapy is not recommended.
IB	Adjuvant cisplatin-based chemotherapy is not recommended for routine use.
IIA	Adjuvant cisplatin-based chemotherapy is recommended.
IIB	Adjuvant cisplatin-based chemotherapy is recommended.
IIIA	Adjuvant cisplatin-based chemotherapy is recommended.
General	The use of adjuvant chemotherapy regimens that include alkylating agents is not recommended as these agents have been found to be detrimental to survival.
Summary of Recommendations for Adjuvant Radiotherapy	
IA/B and IIA/B	Adjuvant radiation is not recommended.
IIIA	Adjuvant radiation therapy is not recommended for routine use because of the lack of prospective, randomized clinical trial data evaluating its efficacy. A clinical trial is underway to determine the advisability of its routine use.

- 2. Randomized controlled trials (RCTs) or meta-analyses that
 - (a) compared postoperative chemotherapy (or radiation therapy) versus surgery without chemotherapy (or radiation therapy) in patients with completely resected NSCLC;
 - (b) reported overall survival or disease-free survival as a main outcome; or
 - (c) were published in peer-reviewed journals or reported in a conference abstract.

Articles published in a language other than English were excluded. Articles lacking information on the stage distribution of the study population were also not considered. Studies involving alkylating chemotherapy agents, alone or in combination with nonplatinum agents, or involving immunotherapy were not included. Complete details of the literature search strategies and databases searched in the systematic review for adjuvant chemotherapy (or radiation therapy) are outlined in other publications.⁷⁻¹¹

Consensus Development Based on Evidence

The CCO systematic reviews on adjuvant chemotherapy and radiation therapy were circulated to the CCO-ASCO Joint Panel members in August 2006 for review. The Panel also reviewed the new evidence that had emerged since the completion of the CCO systematic reviews, refined the questions to be addressed by the guideline, and developed recommendations at a meeting at the ASCO Headquarters Office (Alexandria, VA) in August 2006. A draft version of the guideline was circulated to the four coauthors of the Joint Panel in February 2007 for review and approval. Additional work on the guideline was completed via teleconferences with Panel members. A revised version was circulated to all Panel members in April 2007 for final review and approval. The draft guideline was disseminated to practitioners in Ontario, Canada, and in the United States for external review.

External Review

Both the CCO-PEBC and ASCO conducted an external review of the recommendations in this guideline. The initial systematic review and practice guideline developed by CCO were distributed to practitioners in Ontario, Canada, for review in October 2004. Feedback was obtained through a mailed survey accompanying the guideline, in which practitioners could rate a number of items, including the quality of the review, whether or not they agreed with the recommendations, and whether they would follow the recommendations in their own practice. Written feedback was also encouraged. Feedback from external reviewers was also solicited by ASCO. ASCO distributed the guideline draft to six oncologists and two patient advocates and asked them to complete a similar form to that employed in the CCO practitioner feedback process. The content of the guideline and manuscript were reviewed and approved by the ASCO HSC, the ASCO Board of Directors, and by the CCO Report Approval Panel before dissemination.

TNM Staging System for NSCLC

The stages of NSCLC were defined using the TNM staging system (Table 2).

Summary of Outcomes Assessed

The primary outcome of interest was overall survival.

Table 2. Staging for NSCLC Using the TNM System

Stage	T	N	M
I A	1	0	0
I B	2	0	0
II A	1	1	0
II B	2	1	0
	3	0	0
III A	3	1	0
	1-3	2	0

Abbreviations: NSCLC, non-small-cell lung cancer; T, primary tumor; N, regional lymph nodes; M, distant metastasis.

RESULTS

Adjuvant Chemotherapy

Literature search results. The systematic review conducted by members of CCO's Lung DSG identified eight meta-analyses,^{4,12-22} and 16 RCTs involving intravenous platinum-based chemotherapy²³⁻⁴⁰ relevant to this guideline. Detailed summaries of the trial characteristics and results have been published elsewhere.^{7,8} Summaries of the survival outcomes for trials, comparing surgery alone to surgery followed by platinum-based chemotherapy, are presented in Table 3 (small trials with fewer than 150 patients) and Table 4 (large trials with more than 150 patients). Updated publication or abstract results are included where available; the search identified two updates of trials of therapy that were published in abstract form after the completion of the CCO guidelines.^{20,21,38,39}

The Lung DSG decided not to perform a meta-analysis on trials of postoperative chemotherapy because of the availability of a large individual patient data meta-analysis conducted by the NSCLC Collaborative Group in 1995,¹² and updated in 2007.²²

WHAT IS THE ROLE OF ADJUVANT CHEMOTHERAPY IN STAGE I-IIIa COMPLETELY RESECTED NSCLC?

Evidence summary and recommendations. The results from two (unpublished) large-sample individual patient pooled analysis²⁰⁻²² and the reported data from five published RCTs^{33,34,36,38-40} form the basis of the following recommendations on the appropriateness of adjuvant chemotherapy in resected NSCLC.

Overall conclusions. The two recent pooled analyses and three of five RCTs found an overall survival benefit associated with cisplatin-based therapies, and these data support its use in this setting. These studies comprised primarily patients with stages IA-IIIa disease. The following section provides stage-specific clinical guidance that is predicated on subanalyses from these studies.

Stage IA. Adjuvant chemotherapy is not recommended for patients with completely resected stage IA NSCLC. There is little evidence available on the effectiveness of adjuvant cisplatin-based chemotherapy, given that fewer than 350 stage IA patients were included in the reviewed studies.

Stage IB. Adjuvant chemotherapy is not recommended for routine use for patients with completely resected stage IB NSCLC. Neither the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis^{20,21} nor any of the recently published large RCTs (ie, National Cancer Institute of Canada Clinical Trials Group JBR.10 [NCIC-CTG JBR.10],³⁶ Adjuvant Navelbine International Trialist Association trial

Table 3. Randomized Cisplatin-Based Adjuvant Chemotherapy Trials Enrolling Fewer Than 150 Patients

Trial	Stage	% of Patients	Intervention(s)	No. of Patients Assessable	Overall Survival (5 years, %)*	Disease-Free Survival (5 years, %)*
Ichinose et al, 1991 ²³	I	60	S + PAPe/CAP-M/PVds	41	61	54
	II	19	S			
	IIIA	21		45	58	50
Niiranen et al, 1992 ²⁴	I†	90	S + CAP	54	67	65
	II†	2	S	56	56	48
	III†	8				
Feld et al, 1993 ²⁵ LCSG 801	T1N1	16	S + CAP	136	53	NR
	T2N0	84	S	133	57	
Ohta et al, 1993 ²⁶ JCOG	IIIA	100	S + PVds	90	35	37‡
			S	91	41	42‡
Dautzenberg et al, 1995 ²⁷	I	3	S + CAPVcL + RT	138	18	22
	II	26	S + RT	129	19	24
	III	71				
Lee et al, 1995 ²⁸ (abstract)	II	34	S + PE + RT	33	16.6	NR
	IIIA	66	S + RT	32	26.2	
Mineo et al, 2001 ³⁰	pIB	100	S + PE	33	63	59
			S	33	45	30
Lee et al, 2003 ^{31,32} (abstract)	N0-1	79	S + PV + RT	69	NR	72§
	N2	21	S + RT	68		55§
Tada et al, 2004 ³⁵ JCOG 9304	I-III	71	S + PVds	59	28	18.3
	III	29	S	60	36	16.1
Park et al, 2005 ³⁷	IA	18	S + MVbP	59	81	89
	IB	82	S	59	75	65

NOTE. Values in bold are significant at a 95% level of confidence (ie, $P < .05$).

Abbreviations: S, surgery; PAPe, cisplatin, adriamycin, pepleomyacin; CAP-M, cyclophosphamide, adriamycin, cisplatin, mitomycin; PVds, cisplatin, vindesine; LCSG, Lung Cancer Study Group; JCOG, Japan Clinical Oncology Group; CAP, cyclophosphamide, doxorubicin, cisplatin; CAPVcL, cyclophosphamide, doxorubicin, cisplatin, vincristine, lomustine; RT, radiotherapy; PE, cisplatin, etoposide; PV, cisplatin, vinorelbine; MVbP, mitomycin, vinblastine, cisplatin.

*Survival values without percentages are median survival values (months).

†All T1-3N0.

‡Percent overall survival at 3 years.

§2-year disease-free survival results.

||All pN2.

[ANITA],⁴⁰ International Adjuvant Lung Cancer Trial [IALT],³⁴ and Adjuvant Lung Project Italy³³ [ALPI]) has shown a significant overall survival benefit for cisplatin therapy in stage IB subgroups. The pooled analysis reported a nonsignificant pooled hazard ratio (HR = 0.93; 95% CI, 0.78 to 1.10) for overall survival across five large trials (the above-mentioned four trials, plus the Big Lung Trial,⁴² which did not meet the inclusion criteria for this report). The (unpublished) Cancer and Leukemia Group B (CALGB) 9633 trial was composed entirely of stage IB patients, and has not observed a significant overall survival advantage for paclitaxel/carboplatin adjuvant therapy (HR = 0.80; $P = .10$).^{38,39} However, the trial reported a significant benefit in terms of disease-free survival and found significant overall and disease-free survival advantages in an unplanned subset analysis of patients with tumors ≥ 4 cm (HR = 0.66; 90% CI, 0.045 to 0.97, and HR = 0.62; 90% CI, 0.44 to 0.89, respectively).³⁹

The recently reported updated Medical Research Council (MRC) meta-analysis did find a significant benefit of adjuvant chemotherapy in stage I disease, but these results may reflect the inclusion of Asian trials, in which a disproportionate number of women with adenocarcinoma were treated with UFT-based regimens.²²

Stage II. Adjuvant cisplatin-based chemotherapy is recommended for patients with completely resected stage II NSCLC. The LACE pooled analysis,^{20,21} updated MRC individual patient data meta-analysis,²² NCIC-CTG JBR.10³⁶ and ANITA⁴⁰ all support the

administration of adjuvant cisplatin-based chemotherapy in combination with vinorelbine. The LACE pooled analysis, ANITA, and NCIC-CTG JBR.10 trial all reported superior overall survival (pooled HR = 0.83 and 95% CI, 0.73 to 0.95; HR = 0.71 and 95% CI, 0.49 to 1.03; and HR = 0.59 and 95% CI, 0.42 to 0.85, respectively).

Stage IIIA. In patients with completely resected stage IIIA NSCLC, adjuvant cisplatin-based chemotherapy is recommended. The LACE meta-analysis^{20,21} found a significant benefit for cisplatin therapy in stage III patients in its pooled analysis (pooled HR = 0.83; 95% CI, 0.73 to 0.95). Two trials (IALT³⁴ and ANITA⁴⁰) reported significant overall survival benefits associated with adjuvant chemotherapy in stage IIIA disease. For the subgroup of stage IIIA patients in ANITA ($n = 325$), HR = 0.69 (95% CI, 0.53 to 0.90), and the result for the IALT trial ($n = 728$) was HR = 0.79 (95% CI, 0.66 to 0.95).

Use of alkylating agents. The use of adjuvant chemotherapy involving alkylating agents is not recommended because it has been found to shorten survival. The 1995 NSCLC Collaborative Group individual-patient meta-analysis ($n = 9,387$) found a statistically significant survival *disadvantage* associated with the use of postoperative chemotherapy involving alkylating agents.¹²

Types of chemotherapy agents and regimens. The majority of published trials utilized cisplatin-based chemotherapy. The CALGB 9633 trial of carboplatin-based therapy has been reported in abstract form only.^{38,39} The adjuvant chemotherapy reported in the other trials

Table 4. Meta-Analyses and Randomized Cisplatin-Based Adjuvant Chemotherapy Trials Enrolling More Than 150 Patients, Published After the 1995 NSCLC Meta-Analysis

Reference	No. of Patients Assessable	Stage	% of Patients	Agent	RT*	Overall Survival							
						Overall		Stage					
						HR	95% CI	IB	95% CI	II	95% CI	IIIA	95% CI
Meta-analyses													
Stewart et al, 2007, ²² NSCLCCG (abstract)	8,147	I	65	NA	No	0.87	0.81 to 0.93	NR		NR		NR	
		II	16										
		IIIA	17										
		IIIB	1										
Pignon et al, 2006, ^{20,21} LACE (abstract)	4,584	IA	8	NA	No	0.89	0.82 to 0.96	0.93	0.78 to 1.10	0.83	0.73 to 0.95	0.83	0.73 to 0.95
		IB	30										
		II	35										
		III	27										
Randomized trials													
Keller et al, 2000, ²⁹ ECOG 3590	488	II	41	PE	Yes	0.93	0.74 to 1.18	NA		NS†		NS†	
		IIIA	58										
Scagliotti et al, 2003, ³³ ALPI	1,088	I	39	MVdsP	Yes	0.96	0.81 to 1.13	0.97‡	0.71 to 1.33	0.80	0.60 to 1.06	1.06	0.82 to 1.38
		II	33										
Arriagada et al, 2004, ³⁴ IALT	1,867	pl	36	P + E/V/ Vb/Vds	Yes	0.86	0.76 to 0.98	0.95§	0.74 to 1.23	0.93§	0.72 to 1.20	0.79§ 	0.66 to 0.95
		pII	24										
		pIII	39										
Winton et al, 2005, ³⁶ NCIC-CTG JBR.10	482	IB	45	PV	No	0.69	0.52 to 0.91	0.79¶	0.77 to 1.95	0.59	0.42 to 0.85	NA	
		IIA	15										
		IIB	40										
Strauss et al, 2006, ^{38,39} CALGB 9633 (abstract)	344	IB	100	TCb	No	0.80#	0.60 to 1.07	0.80#	0.60 to 1.07	NA			NA
Douillard et al, 2006 ⁴⁰ ANITA	829	IB	36	PV	Yes	0.80	0.66 to 0.96	1.10	0.76 to 1.57	0.71	0.49 to 1.03	0.69	0.53 to 0.90
		II	24										
		IIIA	39										

NOTE. Values in bold are significant at a 95% level of confidence (ie, $P < .05$).

Abbreviations: NSCLC, non-small-cell lung cancer; HR, hazard ratio; RT, radiotherapy; CG, collaborative group; NA, not applicable; LACE, Lung Adjuvant Cisplatin Evaluation; ECOG, Eastern Cooperative Oncology Group; P, cisplatin; E, etoposide; NS, value of HR not statistically significantly different from 1.0; ALPI, Adjuvant Lung Project Italy; M, mitomycin; Vds, vindesine; IALT, International Adjuvant Lung Cancer Trial; p, pathologically documented stage; Vb, vinblastine; NCIC-CTG, National Cancer Institute of Canada Clinical Trials Group; V, vinorelbine; CALGB, Cancer and Leukemia Group B; TCb, paclitaxel, carboplatin; ANITA, Adjuvant Navelbine International Trialists Association trial.

*Radiotherapy was administered to some patients, by center choice.

†The values and/or CIs were not reported in the publications.

‡Stage I tumors.

§Values reported in a separate publication.⁴¹

||Stage III tumors. In the IALT trial, 91% of stage III patients were stage IIIA.

¶The values and CIs were calculated using data available in the report, and may be approximate (eg, extracted from a figure).

#90% CI.

included in this guideline consisted of platinum-based regimens, and included cisplatin, mitomycin, and vindesine; cisplatin and etoposide; cisplatin and vinorelbine; cisplatin and vinblastine; cisplatin and vindesine; and carboplatin and paclitaxel (Table 5). NCIC-CTG JBR.10, IALT, and ANITA trials achieved a statistically and clinically significant survival benefit for adjuvant chemotherapy using vinorelbine combined with cisplatin. The LACE meta-analysis found an overall survival benefit associated with the cisplatin plus vinorelbine combination (HR = 0.80; 95% CI, 0.70 to 0.91) that was marginally (though not statistically significantly) better than that of other drug combinations ($P = .10$).^{20,21} The updated MRC meta-analysis²² found an overall survival benefit for chemotherapy (HR = 0.86; 95% CI, 0.81 to 0.93; $P < .000001$), with 22 of 30 trials or approximately 70% of patients receiving a cisplatin-based regimen. Analysis by type of regimen did not vary or significantly alter the hazard rate. It is unknown whether other doses and schedules of administration of these agents will produce similar benefits. One of the drawbacks to a recommen-

dation favoring the cisplatin plus vinorelbine regimen used in both the NCIC-CTG JBR.10 and ANITA trials is that it involves weekly administration of vinorelbine during 16 weeks (four cycles). Analysis of compliance with adjuvant chemotherapy in the NCIC-CTG JBR.10 trial found the median administered dose of cisplatin was 84% of the maximum intended, whereas the median administered dose of vinorelbine was only 52%.⁴⁶ Patients were less likely to complete chemotherapy if they had undergone pneumonectomy, were older, or were female. A recent randomized trial published in abstract form has demonstrated that, in advanced NSCLC, the more convenient 3-week cycle of vinorelbine on days 1 and 8 and cisplatin on day 1 has better tolerance and similar efficacy to the regimen administered in the adjuvant setting described above.⁴⁷ The Panel recommends the use of the cisplatin plus vinorelbine in the dose and schedule that yielded the greatest survival benefit in NCIC-CTG JBR.10 (ie, cisplatin 50 mg/m² on days 1 and 8 every 4 weeks for four cycles, and vinorelbine 25 mg/m² weekly for 16 weeks for four cycles). However, if

Table 5. Chemotherapy Regimens Delivered in Major Trials

Trial	No. of Patients	Agent	Dose (mg/m ² /d)
ALPI	1,088	Cisplatin Mitomycin Vinblastine	100 every 3 weeks for 3 cycles 8 every 3 weeks for 3 cycles 3 every 3 weeks for 3 cycles
IALT	1,867	Cisplatin Vinorelbine* Vinblastine† Etoposide‡	80-120 every 3 or 4 weeks for 3 or 4 cycles 30 every week to last cisplatin administration 4 every week for 5 weeks, then every 2 weeks until last cisplatin administration 100 days 1-3 with each cisplatin
CALGB 9633	344	Carboplatin Paclitaxel	AUC 6 every 3 weeks for 4 cycles 200 every 3 weeks for 4 cycles
NCIC-CTG JBR.10	482	Cisplatin Vinorelbine	50 day 1 and 8 every 4 weeks for 4 cycles 25 every week for 16 cycles
ANITA	840	Cisplatin Vinorelbine	100 every 4 weeks for 4 cycles 30 every 4 weeks for 4 cycles

NOTE. Regimens displayed in bold were associated with statistically significant survival results.

Abbreviations: ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; CALGB, Cancer and Leukemia Group B; AUC, area under the curve 6 mg/mL-minute; NCIC-CTG JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10; ANITA, Adjuvant Navelbine International Trialist Association trial.

*27% of patients received vinorelbine and cisplatin.

†11% of patients received vinblastine and cisplatin.

‡57% of patients received etoposide and cisplatin.

patients' inconvenience or resource constraints preclude the use of this schedule of administration, the Panel recommends that practitioners adopt one cisplatin-based chemotherapy regimen to use consistently to ensure familiarity and optimize patient safety.

Currently available data do not support the use of carboplatin and it should not be administered routinely in the adjuvant setting.

Additional considerations. Most trials report delivery of between 60% and 85% of the planned adjuvant chemotherapy dosage in the postoperative NSCLC setting. A sizable number of patients experienced grade 3/4 toxicity in trials (generally < one third, though nearly three fourths in the JBR.10 trial). However, treatment-related deaths were uncommon (range, < 2%). Special considerations should be given to patients with poor performance status or advanced age, who may require treatment different from the above recommendations. An unplanned analysis of results from patients in the JBR.10 trial found an overall survival benefit for patients older than age 65 years, without an increase in treatment-related toxicity or hospitalization.⁴⁸ There is little evidence available on the treatment of persons older than age 75 years; very few individuals of this age were included in the reported trials.

Adjuvant Radiation Therapy

Literature search results. Evidence from a meta-analysis of nine RCTs evaluating postoperative radiation therapy and data obtained from three additional RCTs published after this meta-analysis were reviewed. The Postoperative Radiotherapy (PORT) meta-analysis⁴⁹ included information on 2,128 patients and 1,368 deaths, and assessed the effect of postoperative radiotherapy on overall and recurrence-free survival, and recurrence rates. The degree of heterogeneity among trials was also assessed. In their systematic review,⁹ the CCO-PEBC Lung DSG assessed this evidence and expanded it with data from additional trials retrieved in an updated literature search (Table 6). Data from a nonrandomized subanalysis of the ANITA trial⁴⁰ and retrospective data from the Surveillance, Epidemiology, and End Results (SEER) study⁵⁰ were also considered.

WHAT IS THE ROLE OF ADJUVANT RADIATION IN STAGE I-III A COMPLETELY RESECTED NSCLC?

Evidence Summary and Recommendations

Stages I and II. Postoperative thoracic radiation is not recommended for patients with completely resected stage I or II NSCLC. The PORT meta-analysis^{49,51} included information on 2,128 patients and 1,368 deaths, and found a significant adverse effect of postoperative radiotherapy on survival (combined HR = 1.21; 95% CI, 1.08 to 1.34); subset analyses suggested a trend toward greater negative effects for lower nodal status. These effects were due to long-term detrimental impact on pulmonary and cardiac function. Similarly, recurrence-free survival was also worsened by postoperative radiotherapy (combined HR = 1.13; 95% CI, 1.02 to 1.26). In both of these analyses, there was no evidence of heterogeneity among trials ($P = .11$ and $.15$, respectively). The authors concluded that the pattern of results favored surgery alone. Local recurrence rates tended to be lower for patients receiving radiotherapy, although this result was significant in only one trial. The results of three trials published after the meta-analysis (for which some data were included in the PORT meta-analysis) conflicted somewhat with the PORT meta-analysis results. Two trials found no significant survival detriment with radiation,^{43,45} although one trial had questionable validity.⁴⁵ The third trial found a significant survival detriment (5-year survival rates of 30% and 43% for adjuvant radiation and surgery alone, respectively; $P < .05$). Subgroup analyses showed that the detrimental effect was specific to stage II.⁴⁴ Both of the trials showing no survival detriment found decreased local recurrence associated with radiation (6% v 23.6%⁴³ and 12.7% v 33.2%; $P < .01$)⁴⁵

Stage IIIA. In patients with completely resected stage IIIA NSCLC, postoperative radiation is controversial and is not recommended for routine use because of the lack of prospective, randomized clinical trial data evaluating its efficacy. A clinical trial is underway to determine the advisability of its routine use.

In a subgroup analysis of patients with stage III/N2 disease, there was no statistical evidence of an adverse effect in the PORT

Table 6. Results of RCTs Published After the PORT Meta-Analysis

Reference	Median Follow-Up (years)	Intervention	No. of Patients Randomly Assigned	Survival		Local Recurrence Rate (%)
				Median (years)	5-Year Rate (%)	
Mayer et al, 1997 ⁴³	3.6	Surgery + RT	83	NR	29.7	6.0
		Surgery	72	NR	20.4	23.6
Dautzenberg et al, 1999 ⁴⁴	5.7	Surgery + RT	373	2.3	30.0*	22.5†
		Surgery	355	3.5	43.0	28.5
Feng et al, 2000 ⁴⁵	NR	Surgery + RT	134‡	NR	43.4	12.7§
		Surgery	162‡	NR	40.5	33.2§

NOTE. The differences between values in bold are significant at a 95% level of confidence (ie, $P < .05$).

Abbreviations: RCT, randomized controlled trial; PORT, Postoperative Radiotherapy; NR, not reported; RT, radiotherapy.

*Adjustments were made for age, sex, T, N, histologic type and surgery, and stratification by protocol, resulting in an adjusted RR for survival of 1.28. Discrepant 95% CIs and P values were reported: 1.07 to 1.54, $P = .008$ in the report text and 1.04 to 1.58, $P = .018$ in the relevant table.

†The authors noted that the decrease in local recurrence in those treated with radiotherapy was not significant (RR, 0.85; 95% CI, 0.64 to 1.14; $P = .28$, log rank), although it was unclear if this analysis was based on local recurrence rates or recurrence-free survival data.

‡These are the number of assessable patients in each group. There were 183 patients randomly assigned to PORT and 182 patients randomly assigned to surgery alone.

§Rates of thoracic relapse.

meta-analysis.⁴⁹ In subsequently published trials⁴³⁻⁴⁵ (for which some data were included in the PORT meta-analysis), none has found a significant survival detriment for stage III disease. The benefits or harms of modern radiotherapy in stage IIIa disease have not yet been studied in a prospective randomized trial, although a trial is currently ongoing in Europe. Results from a nonrandomized subanalysis (ANITA)⁴⁰ and from SEER⁵⁰ suggest benefit of PORT in stage IIIa disease and should be clarified in ongoing phase III trials. The large ($n = 7,465$) SEER retrospective study found superior survival rates associated with radiotherapy in N2 disease (HR = 0.855; 95% CI, 0.762 to 0.959).⁵⁰ In addition, a nonrandomized subanalysis of the ANITA trial, comparing 5-year overall survival in N2 patients who did or did not receive postoperative radiotherapy, found higher survival rates in patients receiving radiotherapy in both the observation and chemotherapy arms (21% v 17% and 47% v 34%, respectively; statistical tests of comparison were not conducted).⁴⁰

Radiation dosage. The majority of studies cited used doses ranging from 30 to 60 Gy, typically provided in 2- to 2.5-Gy fractions. The optimal dose of postoperative thoracic irradiation is not known at this time.

STRATEGIES TO HELP PHYSICIANS IMPROVE COMMUNICATION WITH PATIENTS

The Panel recognizes the challenge of discussing adjuvant therapy with lung cancer patients. This section of the guideline is intended to help doctors inform their patients of the benefits and risks of adjuvant therapy, while addressing the unique concerns of lung cancer patients, to reach a shared decision on whether to proceed. Few studies have addressed doctor-patient communication in lung cancer patients, and even fewer involve patients with curable lung cancer. Therefore, this section of the guideline represents consensus that is not evidence-based.

Patients with resected NSCLC often have complex medical, psychological, and social issues that their physician must take into account before discussing adjuvant therapy. Many patients have pain, impaired breathing, or fatigue related to thoracotomy. Patients with lung cancer may have underlying debility due to smoking-related

illness, and many have depression or psychological distress as a result of their lung cancer diagnosis—a disease with a decidedly bad reputation.^{52,53} Furthermore, lung cancer carries a unique social stigma due to its association with cigarette smoking, which increases stress and impairs communication with family, friends, and caregivers.⁵⁴ Smoking cessation, which is mandatory in lung cancer patients to improve outcome, may result in increased stress in patients who are addicted to nicotine.⁵⁵ Increasingly, lung cancer is a disease of the elderly, who may be more susceptible to the toxic adverse effects of chemotherapy, and, from an actuarial standpoint, more likely to die of something other than lung cancer than a younger patient with similar stage disease.

The physician must consider these complex issues when discussing the benefits and risks of adjuvant therapy, recognizing patients who may be unprepared, overzealous, or unmotivated to proceed with additional therapy. Given this complexity, there clearly is no best way to discuss this topic with a patient, and each session must be individualized. Studies involving patients with a variety of cancer types have found that patients are most satisfied if they perceive an effort by their physician to share decision-making and have adequate time to make their decision.⁵⁶⁻⁵⁹ One way to accomplish the latter is to offer a session dedicated solely to the discussion of adjuvant treatment options.

Patients with lung cancer who lack precise understanding of their prognosis tend to overestimate their probability of cure.⁶⁰ To improve communication, it is important to determine the patient's level of understanding early in the interview by asking an open-ended question such as, "Tell me what you know about your lung cancer?" The discussion of adjuvant therapy is especially difficult because it involves informing patients who hope they are free of cancer about their risk of recurrence and death. Conversely, the discussion may be especially rewarding in that the goal of adjuvant therapy, in fact, is cure.⁶¹ The challenge is in deciding how to impart the gravity of the patient's diagnosis and prognosis while maintaining the hope for cure. It is important first to ask the patient how he or she would like to hear information regarding the risk of recurrence, and the potential benefit of additional therapy. Some patients prefer general terms, versus specific use of numbers, or visual aids (charts or graphs).

For patients who prefer numbers, the physician should be able to quote both the relative reduction in the risk of death (ie, the HR), as

well as absolute survival benefit of the therapy. Studies of communication in patients with breast cancer have found that quoting absolute survival benefit is easier for patients to understand compared with relative risk reduction.⁶² Those patients who are quoted relative risk reduction are significantly more likely to endorse chemotherapy, but less likely to demonstrate a true understanding of the benefit.⁶²

Absolute survival benefit of adjuvant chemotherapy can be estimated by multiplying (1 - HR) of a clinical trial by the proportion of patients who are dead at 5 years in the control arm of the clinical trial. For example, if the HR = 0.80 and 50% of patients die in 5 years in the control arm, then the absolute reduction in death rate is approximately 0.20 × 50% = 10%. Conversely, if the HR is more than 1.0 (as in the stage IB subgroup of NCIC-CTG JBR.10 and ANITA), then the death rate will increase by that proportion.

Figure 1 is a graphical representation of estimated absolute risk and benefit for 100 patients with NSCLC treated with surgery and adjuvant chemotherapy, based on reported, stage-specific HR and death rate in the control arm of each clinical trial. This series of graphs is intended to help physicians understand the absolute risk and benefit of adjuvant chemotherapy for the various stages of NSCLC based on all available data, and should not be interpreted by patients independently. These graphs separate the patient sample into four groups: those who die within 5 years whether they receive chemotherapy or not (light blue), those who live without receiving chemotherapy (yellow), those who live because of chemotherapy (dark blue), and those who die because of chemotherapy (red). When the LACE data are used to estimate absolute benefit, adjuvant chemotherapy increases 5-year survival from 64% up to 67% for stage IB NSCLC, from 39% up to 49% for stage II NSCLC, and from 26% up to 39% for stage III NSCLC.

With the physician providing immediate guidance and interpretation, a graph such as this may help patients achieve a better understanding of absolute risk and benefit. The Panel recognizes the potential importance of patient decision-aid tools, and stage-specific handouts derived from this figure (generated from the LACE meta-analysis, the last row of the figure), are available for clinicians at www.asco.org. The Panel also recognizes that software applications

are available on the Internet that may aid clinicians in developing similar decision-aid tools for patients with NSCLC.⁶³⁻⁶⁵ A version of Adjuvant! has been produced to make estimates of NSCLC patient outcomes with and without adjuvant therapy.^{65,65a,65b} We have for the publication of these guidelines produced our own version of such a tool. There are no studies to test whether these decision-aid tools have a positive impact on patient compliance, or the outcome of patients with lung cancer. In fact, such a stark, graphical representation of the high risk of death, especially in stage II-III disease, may have a negative psychological impact in certain patients. On the other hand, there is no more honest way to impart realistic hope, and to motivate patients to participate in adjuvant therapy in the face of the risks and adverse effects.

When physicians recommend adjuvant therapy, it is not sufficient to provide only data regarding the risk of death. Information that may affect the patient's quality of life is also relevant, and can sometimes be of equal or greater importance than extending survival. Physicians should discuss potential short- and long-term adverse effects of treatment with patients, along with measures that can be taken to obviate or ameliorate these effects if they do occur. The physician should be able to cite the proportion of patients treated in clinical studies who experienced toxicity, including treatment-related death.

In the ANITA and NCIC-CTG JBR.10 trials of vinorelbine and cisplatin, the percentages of patients experiencing WHO grade 3 to 4 effects were 15% to 28% for fatigue, 10% to 27% for nausea and/or vomiting, 10% to 15% for anorexia, 7% to 14% for anemia, 1% to 11% for infection, 7% to 9% for febrile neutropenia, 0% to 5% for hair loss, and 3% for peripheral neuropathy.^{36,40} A split dose of cisplatin (ie, 50 mg/m² delivered on days 1 and 8 of a 4-week cycle) was administered in the NCIC-CTG JBR.10 trial and seems to lower the risk of nausea and fatigue in comparison to a single 100 mg/m² dose (eg, as provided in the ANITA trial). In these trials, toxicity-related mortality was less than 1%. The administration of agents may produce discomfort for patients, such as vein irritation due to vinorelbine infusion. With regard to adjuvant radiation treatment, the risks of grade 3 to 4 toxic adverse effects reported in prospective studies include respiratory toxicity (4%) and esophageal toxicity (2%).⁴⁴

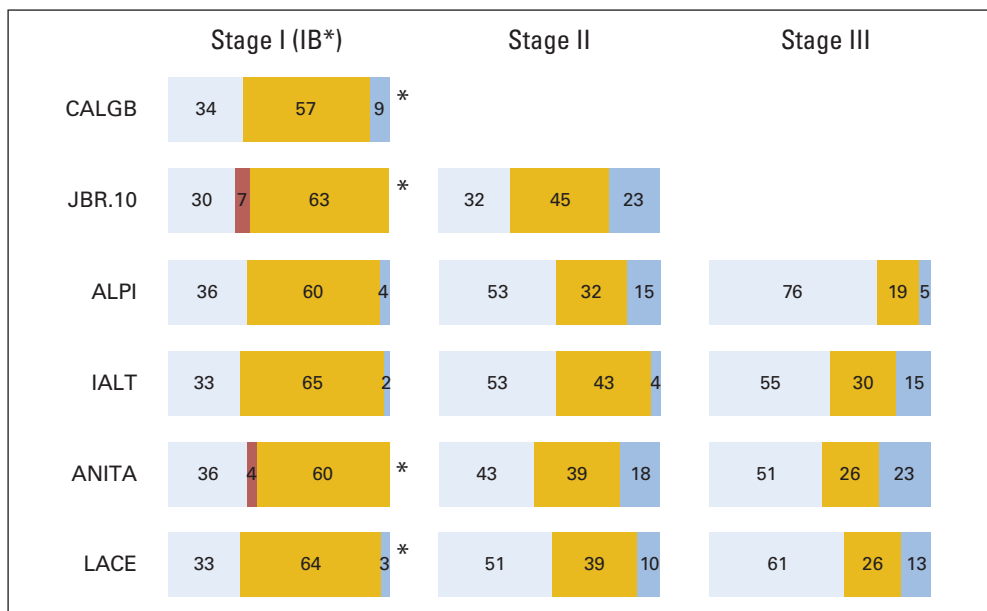


Fig 1. Graphical representation of estimated absolute risk and benefit for 100 patients with non-small-cell lung cancer treated with surgery and adjuvant chemotherapy, based on reported, stage-specific hazard ratio and death rate in the control arm of each clinical trial. (*) Indicates those trials that included only stage IB, ALPI and IALT were open for IA and IB. CALGB, Cancer and Leukemia Group B; NCIC-CTG JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10; ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; ANITA, Adjuvant Navelbine International Trialist Association trial; LACE, Lung Adjuvant Cisplatin Evaluation.

Risk of adverse effects and/or complications should be presented from most common to least common, with serious adverse effects included. Providing percentage figures as described above can help patients put these risks into perspective. It is important to realize that the median age of patients enrolled onto the published studies was 60 years, with performance status 0 to 1 and no significant comorbid disease. Therefore, it is often difficult to generalize the clinical trial data and apply it to an individual patient who may be elderly, have comorbid illness, have poor performance status, or lack social support. Special care should be taken to inform patients of potential permanent effects (such as neuropathy), and to point out the personal circumstances that may increase the risk of adverse events. In the end, the patient should be presented with a personalized description of his or her individual risks and benefits.

For the physician leading a discussion of adjuvant therapy for NSCLC, there are important gaps in the available data. There currently are little or no data to support adjuvant chemotherapy for patients older than age 75 years, patients with stage I disease, incompletely resected stage II or III disease, resected stage IV disease, or patients who have complete resection of pure bronchioloalveolar carcinoma. Bronchioloalveolar carcinoma carries a better prognosis than invasive NSCLC and was excluded systematically from study in ANITA and NCIC-CTG JBR.10. At this time, the Panel cannot make recommendations for adjuvant chemotherapy for patients in any of these situations. However, the practicing oncologist is faced with these decisions on a daily basis. When there is a lack of data, the oncologist may be uncertain of the best medical course of action, and shared decision-making with the patient is never more important than in these circumstances.

In the past, nihilism on the part of clinicians regarding the benefits of chemotherapy in patients with NSCLC impaired enrollment onto clinical trials of adjuvant therapy. There is evidence that the attitudes of patients and/or physicians may have an impact on treatment compliance. For example, during the NCIC-CTG JBR.10 trial, patients treated in the United States demonstrated better treatment compliance than patients in Canada—a difference that was more likely cultural than medical in origin.⁴⁶ Fewer than half of patients randomly assigned to adjuvant cisplatin-based chemotherapy on these clinical trials completed all four planned cycles on time and at full doses.^{34,36,40}

The guideline Panel concludes that therapeutic nihilism toward adjuvant chemotherapy for stage II-III NSCLC should now be abandoned. The findings and recommendations contained in this guideline provide clinicians with the evidentiary basis for a firm commitment to treat these patients. Furthermore, the guideline includes suggestions for how to communicate this knowledge more effectively to lung cancer patients. The strategies of increasing patient understanding and compliance ultimately should lead to improved patient outcomes for adjuvant chemotherapy in stage II-III NSCLC.

RESULTS OF EXTERNAL REVIEWS

This manuscript was reviewed by members of ASCO in June 2007 using a standardized feedback instrument. The feedback of reviewers was positive and there was little disagreement with the Panel's recommendations. One notable area of disagreement concerned the recommendation for radiotherapy in stage IIIA patients. Some reviewers suggested modifying the recommendation to allow for radiotherapy

in stage IIIA (eg, in N2 patients). The Panel, and some other reviewers, felt that a recommendation against routine use better reflected current evidence and the original recommendation was retained. Details of the feedback and the Panel's responses are available on request to guidelines@asco.org.

The CCO-PEBC also conducted external reviews for its systematic reviews and practice guidelines on adjuvant chemotherapy^{7,8,10} and adjuvant radiotherapy^{9,11} before the preparation of this manuscript. Practitioners from Ontario, Canada, provided feedback through two separate mail surveys. The response rates were moderate to high (57 of 138 [41%] for adjuvant chemotherapy, and 69 to 110 [63%] for adjuvant radiation therapy), and approval of the reports was high (> 80%).

MOLECULAR MARKERS IN NSCLC

Molecular markers have been investigated as predictors of chemotherapy sensitivity in NSCLC, and the results of a selective review of the literature pertaining to markers are provided in this section. The Panel concludes that no markers have been shown conclusively to have a significant relationship with clinical outcomes, particularly overall survival.

Mutations in *KRAS* are found in approximately 20% to 30% of NSCLC cases, and have been investigated in a number of studies as a predictor of resistance to chemotherapy or radiation therapy, although the evidence is insufficient and results are inconclusive at this time.⁶⁶ The NCIC-CTG JBR.10 trial prospectively assessed *KRAS* status in 450 participants (93%) as a predictor of survival, and did not observe a benefit of adjuvant vinorelbine/cisplatin chemotherapy in the subgroup of 48 patients (11%) with *KRAS* mutations.³⁶ Increased expression of the DNA repair gene *ERCC1* is associated with cisplatin resistance. Analysis of 761 patients who participated in the IALT study found that patients with *ERCC1*-negative tumors appeared to benefit from adjuvant chemotherapy, whereas patients with *ERCC1*-positive tumors did not.⁶⁷ Analysis of cell cycle regulators and Ki-67 has been assessed in tumor specimens from 778 IALT participants.⁶⁸ Expression of p16, cyclin D1, cyclin D3, cyclin E, and Ki-67 did not correlate with benefit from adjuvant therapy. However, NSCLC patients with p27-negative tumors appeared to benefit most from adjuvant cisplatin-based chemotherapy after complete resection. Similarly, *BRCA1* overexpression is associated with cisplatin resistance,⁶⁹ although this association has not yet been studied in the context of a randomized trial. Recent reports have detailed efforts to develop molecular profiles of resected NSCLC using gene arrays, which may accurately predict prognosis and identify high-risk patients for adjuvant therapy.^{67,68} The NCI Director's Challenge is a collaborative effort involving several academic centers and coordinated by the US National Cancer Institute (<http://dc.nci.nih.gov>). By pooling gene array data from centers, it is hoped that a large data set will be available to identify significantly prognostic gene signatures in early-stage adenocarcinoma. Future studies will be needed to determine whether microarray profiling can identify the patient subgroups most suitable for adjuvant therapy.

DISCUSSION

During the last two decades, the poor prognosis for patients undergoing surgical resection for NSCLC has prompted investigations

of adjuvant chemotherapy and radiation after complete surgical resection. Initially, these investigations did not demonstrate a consistent survival benefit, leaving doubt about the value of these treatments in the face of their associated toxicities. The first large individual patient data meta-analysis, published by the NSCLC Cooperative Group in 1995, reported that studies using cisplatin-based regimens demonstrated a 5% improvement in 5-year overall survival, with an HR of 0.87 and a nonsignificant $P = .08$, for the 1,394 patients included. The updated NSCLC Cooperative Group individual patient data meta-analysis from 2007 included 8,147 patients from 30 randomized trials, and found an HR of 0.86 and $P < .000001$, and an absolute benefit of chemotherapy of 4% at 5 years and 5% at 8 years.²² Large, randomized, controlled trials of cisplatin-based adjuvant chemotherapy have shown significant survival benefits. Although there remains some uncertainty with regard to the most appropriate chemotherapy regimen to use, there is clear evidence to support the use of adjuvant cisplatin-based regimens in completely resected NSCLC. The data from both pooled analyses and individual trials is strongest both statistically and clinically for stages II and IIIA, for which the Panel recommends routine use of adjuvant chemotherapy. Its role in stage IB disease is less established. Subgroup analyses in stage IB patients from major trials have found a small but nonsignificant overall survival benefit. The CALGB 9633 study, which has been presented but not published, has found a nonsignificant survival benefit for carboplatin-based therapy in stage IB patients; subgroup analysis of patients with larger primary tumors (≥ 4.0 cm) demonstrated a significant benefit.

A major point of contention in this debate over the appropriateness of chemotherapy in stage IB patients has to do with the presence of a statistically significant overall survival benefit for the study patients as a whole in three major trials (IALT, NCIC-CTG JBR.10, ANITA), but the absence of a statistical benefit in IB subgroup analyses. Subset analyses have only power to detect substantially larger effects on the end point of interest, not a smaller effect.⁷⁰⁻⁷² This situation illustrates a dilemma in deriving stage-specific clinical guidelines from randomized trials enrolling a range of surgically staged patients. Such trials provide valuable evidence on the efficacy of interventions, but may not have sufficient sample size within subgroups to generate statistically conclusive results for their primary outcomes. To detect an HR of 0.93 (LACE meta-analysis) with statistical certainty (power of 0.9) for stage IB patients with a presumed 5-year survival of 64% (surgery arm of the ANITA trial), a randomized trial would

require in excess of 5,700 patients.⁷³ The uncertainty of benefit in stage IB disease is highlighted further by comparing the absolute risk reduction (ARR) and number of patients needed to treat (NNT) to prevent one death across disease stages (Table 7). The ARR for stages II and IIIA is approximately 7%, whereas the reduction in stage IB cases is smaller, at only 2.3%, and is statistically uncertain. These values can be interpreted further: a clinician providing therapy to patients with stage II or IIIA disease can expect to prevent one death at 5 years for every 15 patients treated. However, assuming the survival HR estimate for stage IB disease were to be validated in larger trials, a clinician would need to treat 43 patients to prevent one death.

Clinicians may choose to rely on scientifically robust overall results that confirm therapeutic efficacy but contribute less to clinical decision-making, or base decisions on subgroup analyses that provide more clinically relevant, but less scientifically certain evidence. In the context of the stage IB results described earlier, the trials were designed to answer the question: does cisplatin-based therapy produce a survival benefit in patients with resected NSCLC? The results of several trials confirm that the answer to that question is yes. Does that result apply unequivocally to every subpopulation of patients included in these trials? We do not know, given that the trials were not designed to answer this question. At this time, the available evidence does not support the routine use of adjuvant chemotherapy in stage IB. Additional large studies are necessary to confirm with certainty the role of chemotherapy in stage IB NSCLC. In the interim, clinical algorithms may aid in selection of appropriate stage I patients for adjuvant chemotherapy.⁷⁰

Postoperative radiation traditionally has been an adjuvant treatment to improve local control, though it is now used less frequently. In 1998, the PORT meta-analysis reported that postoperative radiotherapy shortened patient survival in stage I and II patients, although not in stage III disease. The findings of the PORT meta-analysis have been challenged along several lines; for example, most of the included studies involved the use of obsolete radiotherapy devices (ie, cobalt-60 units), whereas linear accelerators are now the standard, and several studies used what are now considered suboptimal dosages per fraction.⁷⁵ No subsequently published trial has demonstrated a significant survival detriment in stage IIIA cases. More recently, results from nonrandomized subanalyses of two studies have added to the debate. First, the large ($n = 7,465$) SEER database found increased survival rates associated with radiotherapy in N2 disease (HR = 0.855; 95% CI, 0.762 to 0.959).⁵⁰ Second, a subanalysis of the ANITA trial comparing

Table 7. Number of Patients Needed to Treat to Detect an OS Benefit at 5 years

Stage	OS (untreated; %)*	HR		ARR		NNT	
		Value	95% CI†	Value	95% CI‡	No.	95% CI
IB	64	0.93	0.78 to 1.10	2.3	6.6 to -2.8	43	15 to ∞ , ∞ to -36§
II	39	0.83	0.73 to 0.95	6.8	1.9 to 11.3	15	9 to 53
IIIA	26	0.83	0.73 to 0.95	6.7	1.8 to 11.4	15	9 to 55

Abbreviations: OS, overall survival; HR, hazard ratio; ARR, absolute risk reduction; NNT, number needed to treat to prevent one death; ANITA, Adjuvant Navelbine International Trialists Association trial; LACE, Lung Adjuvant Cisplatin Evaluation.

*OS rates at 5 years for control arm patients (untreated) in the ANITA trial.⁴⁰

†HRs of OS at 5 years from the LACE pooled analysis.^{20,21}

‡Calculated using the methods described by Altman and Andersen (1999) for ARR using HRs.⁷⁴

§The symbol ∞ refers to an infinite number of patients. An HR of 1 indicates that OS rates are equivalent between trial arms, and values > 1 suggest that the survival rate is greater in the control arm. In the case of stage IB patients, the 95% CI of the HR contains 1, and translated into NNT, an HR of 1 suggests that no number of treated patients will lead to a prevention of one death (ie, infinity). The portion of the HR > 1 is translated into an upper limit of 36 patients needed to treat to harm, which reflects the fact that under a scenario of treatment inferiority relative to observation, providing chemotherapy produces, rather than prevents, deaths.

5-year overall survival in N2 patients who did or did not receive postoperative radiation found higher survival rates in stage IIIa patients receiving radiation in both the observation and chemotherapy arms (21% v 17%, and 47% v 34%, respectively; statistical tests of comparison were not conducted). Taken together, these results suggest that the benefit of postoperative radiation, in terms of eliminating microscopic mediastinal lymph node disease, may outweigh the increased mortality risk generated by the radiotherapy itself.

It is important to note that the results of the retrospective SEER study did not meet the inclusion criteria for the systematic review, and that radiotherapy was provided according to center choice (and not by randomization) in the ANITA trial. Nevertheless, these results support the argument that adjuvant radiotherapy may be beneficial in cases where tumor is present in the resected mediastinal lymph nodes. The use of postoperative radiation in stage IIIa disease is controversial, and although there is some indication of a modest benefit, evidence on this issue is still uncertain. The Panel felt adjuvant radiation should not be recommended for routine use in patients with stage IIIa disease. The Panel is aware that other organizations, such as American College of Radiology, have offered different recommendations regarding the use of postoperative radiation in patients with NSCLC.⁷⁶

The Panel encourages clinicians to participate in ongoing trials of adjuvant chemotherapy or radiotherapy. More information on ongoing trials is available from the Cancer Trials Support Unit (www.ctsu.org), and the National Cancer Institute of Canada (www.ncic.cancer.ca).

GUIDELINE AND CONFLICTS OF INTEREST

All members of the Expert Panel complied with the ASCO policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies with products that might be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

REVISION DATES

At annual intervals, the Panel cochairs will determine the need for revisions to the guidelines based on an examination of current litera-

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ture. If new information suggests that substantive modifications are warranted, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revised guidelines to the HSC, the ASCO Board, and the CCO Report Approval Panel for review and approval.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** David R. Spigel, Genentech (C); Frances A. Shepherd, Pierre Fabre (C), GlaxoSmithKline (C) **Stock Ownership:** None **Honoraria:** Peter M. Ellis, Bristol-Myers Squibb; Frances A. Shepherd, Pierre Fabre, GlaxoSmithKline **Research Funding:** Christopher G. Azzoli, Genentech Biooncology, Sanofi-aventis, Allos Therapeutics; David R. Spigel, Genentech, Sanofi-aventis **Expert Testimony:** None **Other Remuneration:** None

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Appendix

Table A1. CCO-ASCO Guideline on Adjuvant Therapy for Stages I-IIIa NSCLC Panel

Panel Member	Institution
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William K. Evans, MD, Co-Chair	Juravinski Cancer Centre at Hamilton Health Sciences
Mark G. Kris, MD, Co-Chair	Memorial Sloan-Kettering Cancer Center
Katherine M.W. Pisters, MD, Co-Chair	M.D. Anderson Cancer Center
Frances A Shepherd, MD, Co-Chair	University Health Network, Princess Margaret Hospital
Christopher G. Azzoli, MD	Memorial Sloan-Kettering Cancer Center
Gail Darling, MD	University Health Network, Princess Margaret Hospital
Peter M. Ellis, MD	Juravinski Cancer Centre at Hamilton Health Sciences
Laurie E. Gaspar, MD	University of Colorado at Denver Health Sciences Centre
Harvey I. Pass, MD	NYU School of Medicine and NCI Cancer Centre
David R. Spigel, MD	The Sarah Cannon Cancer Center
John R. Strawn, MD	Patient Advocate
Yee C. Ung, MD	Toronto-Sunnybrook Regional Cancer Centre

Abbreviations: CCO, Cancer Care Ontario; ASCO, American Society of Clinical Oncology; NSCLC, non-small-cell lung cancer.