Guideline Summary

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

Context

In 2006, the Cancer Care Ontario (CCO) Program in Evidence-based Care and the American Society of Clinical Oncology (ASCO) convened a joint expert panel to produce this Clinical Practice Guideline on adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIa resectable non-small-cell lung cancer (NSCLC).¹ CCO previously published and updated systematic reviews and guidelines on this topic.²⁻⁹

Clinical Questions

This clinical practice guideline addresses two principal questions related to the treatment of patients with completely resected stage I-IIIa NSCLC: (1) what is the role of adjuvant chemotherapy, and is there an overall survival benefit and (2) what is the role of adjuvant radiation therapy, and is there a survival benefit?

For many years, patients with stage I-IIIa NSCLC received surgery alone as standard treatment. But even with complete resection, 5-year survival rates were disappointing, suggesting that NSCLC is commonly a systemic disease at diagnosis. Using adjuvant chemotherapy for patients with complete resected NSCLC stages I-IIIa was controversial because evidence initially failed to show significant survival benefits and produced conflicted results. This has changed for patients with resected NSCLC stages II and IIIa. However, controversy continues regarding postoperative thoracic irradiation for these patients with completely resected early-stage NSCLC. The recommendations are summarized in Table 1.

Chemotherapy

Since the first positive meta-analysis (1995) showing that cisplatin-based chemotherapy regimens improved 5-year overall survival, large randomized controlled trials of these regimens continued to show significant survival benefits. Clear evidence now supports the use of adjuvant cisplatin-based regimens in completely resected NSCLC stages II and IIIa.

Stage IA

Because patients with stage IA disease generally achieve good survival and since very few such patients have been included

in clinical trials, there is little evidence on the effectiveness of adjuvant cisplatin-based chemotherapy for this stage. Adjuvant chemotherapy for patients with stage IA is not recommended.

Stage IB

The role of adjuvant chemotherapy in stage IB disease is less established than for stages II-IIIa. Neither a meta-analysis nor results of four large randomized controlled trials showed significant overall survival benefit with cisplatin-based adjuvant therapy for stage IB. There is some evidence from subgroup analyses that there is a small but nonsignificant overall survival benefit in stage IB and a significant survival benefit for patients with larger primary tumors (≥ 4.0 cm) from adjuvant chemotherapy. However, due to lack of an overall survival benefit for stage IB, the routine use of adjuvant cisplatin-based chemotherapy for patients with this stage of disease is not recommended.

Stage IIA and B

The aforementioned meta-analysis and two randomized controlled trials reported statistically superior overall survival with adjuvant chemotherapy in stage II. This evidence supports using adjuvant cisplatin-vinorelbine-based chemotherapy for patients with completely resected stage II NSCLC.

Stage IIIa

The meta-analysis and two randomized controlled trials report statistically superior overall survival, which supports the use of adjuvant chemotherapy for stage IIIa.

Types of Chemotherapy

An important meta-analysis found a statistically significant survival disadvantage associated with the use of postoperative chemotherapy involving alkylating agents; these agents are not recommended. Most trials used cisplatin-based chemotherapy, which showed significant survival benefit in combination with vinorelbine. The adjuvant chemotherapy reported in the other trials was cisplatin combined with other agents. It is unknown whether other doses or schedules of administering these combinations will produce benefits similar to cisplatin-vinorelbine. Currently, available data do not support using carboplatin; it should not be routinely administered in the adjuvant setting.

Strategies to Improve Doctor-Patient Communication Discussing the Risks and Benefits of Adjuvant Therapy

- People with resected lung cancer have unique concerns including complex medical, psychological, and social issues, and face a stigma unique among cancers. The clinician must consider these issues before discussing the topic of adjuvant chemotherapy and face the challenge of both imparting the gravity of the diagnosis and prognosis and maintaining hope for a cure.
- A clinician can offer an individualized session solely for this discussion, tailored to the way a patient prefers to receive information (eg, numbers, visual aids). Although there is no best way to discuss the topic, people with cancer of different types prefer shared-decision making, with adequate time for decision making.
- The discussion should focus on helping the patient understand his/her prognosis and the risks and benefits of adjuvant therapy. A clinician should be able to discuss: relative risk reduction; absolute survival benefit; treatment-related side effects (short and long-term) and their management; and quality-of-life issues. Due to possible differences from clinical trial participants, clinicians should present individualized descriptions of their risks and benefits.
- The guideline includes graphs representing estimated absolute benefits and risks of treatment with surgery and adjuvant chemotherapy by stage.*
- Due to the evidence discussed in this guideline, therapeutic nihilism toward adjuvant chemotherapy for stage II-III NSCLC should now be abandoned.

NOTE. Few studies address this subject with patients with lung cancer necessitating reference to studies with participants with different cancers. This section of guideline represents consensus that is not evidence-based.

* These guidelines are accompanied by Decision Aid Tools which include these representations. A version of Adjuvant! was produced to make estimates of non-small-cell lung cancer patient outcomes with and without adjuvant therapy.⁷⁻⁹ The American Society of Clinical Oncology produced its own version of such a tool for the publication of these guidelines.

Chemotherapy Dosage

The following dosage of cisplatin-vinorelbine is recommended: 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 patient inconvenience or resource constraints present obstacles to using this schedule of administration, practitioners can adopt one cisplatin-based chemotherapy regimen to use consistently in order to ensure familiarity and maximize patient safety.

Additional Considerations

In trials, most patients tolerated between 60% and 85% of planned adjuvant chemotherapy dosage. A sizable number of patients (generally < one third) experienced grade 3/4 toxicity in trials. Special considerations are warranted for patients with poor performance status or advanced age, who may require a treatment different from the recommendations above.

Radiation Therapy

Evidence from randomized controlled trials demonstrates a survival detriment for adjuvant radiotherapy in stages I-II. There is limited evidence for a reduction in local recurrence. While some nonrandomized evidence supports the use of adjuvant radiotherapy for patients with resected stage IIIA NSCLC, this remains controversial.

Stages I-II

A meta-analysis found a significant adverse effect of postoperative radiotherapy on survival due to long-term detrimental impact on pulmonary and cardiac function, and concluded that the results favored surgery alone. Similarly, postoperative radiotherapy was associated with a worse recurrence-free survival. Some have challenged the findings of this meta-analysis along several lines, including the use of obsolete radiation treatment equipment and the use of what is now considered suboptimal dosages per fraction. Two subsequent trials produced different results from the meta-analysis, though one trial had questionable validity. These trials found no significant survival detriment and also decreased local recurrence. The third trial found a significant survival detriment specific to stage II. Due to these conflicting data, adjuvant radiation for stages I-II is not recommended.

Stage IIIA

While there is some indication of a modest benefit with adjuvant radiation therapy in this stage, evidence is still uncertain because of the lack of prospective, randomized clinical trial data evaluating its efficacy. Data from a meta-analysis and subsequent randomized controlled trials showed no survival detriment. Two nonrandomized studies (nonrandomized analyses did not meet inclusion criteria for the systematic review) showed increased survival and support

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

Stage	T	N	M	Recommendation
Stage IA	1	0	0	Adjuvant chemotherapy is not recommended
Stage IB	2	0	0	Adjuvant cisplatin-based chemotherapy is not recommended for routine use
Stage IIA	1	1	0	Adjuvant cisplatin-based chemotherapy is recommended
Stage IIB	2	1	0	Adjuvant cisplatin-based chemotherapy is recommended
	3	0	0	
Stage IIIA	3	1	0	Adjuvant cisplatin-based chemotherapy is recommended
	1-3	2	0	
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				
Stages IA/B and IIA/B	1-2	0-1	0	Adjuvant radiation is not recommended
Stage IIIA	1-3	2	0	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

the argument that adjuvant radiotherapy may be beneficial when tumor is present in the resected mediastinal lymph nodes. The evidence on the benefits and harms of modern radiotherapy in stage IIIA is incomplete, though a clinical trial to address its role in this stage of disease is underway. Postoperative radiation is not currently recommended for routine use for patients with completely resected stage IIIA NSCLC.

The optimal dose of postoperative thoracic irradiation is not known at this time.

Molecular Markers

Studies have investigated molecular markers as predictors of chemotherapy sensitivity in NSCLC. The panel undertook a selective review of the literature pertaining to seven molecular markers. The majority were investigated for their possible ability to predict cisplatin resistance, including mutations, ERCC1 polymorphisms, and p27. Currently, there is a lack of conclusive evidence showing that any marker is significantly related to clinical outcome.

Limitations of the Guideline

Due to limited data from clinical trials, this guideline does not address postoperative therapy for patients with positive margins or macroscopic residual disease; patients older than 75 years; and patients with stage I disease, incompletely resected stage II or III disease, or resected stage IV disease.

Data are lacking from prospective trials of adjuvant radiotherapy. It is not now possible to make firm recommendations for adjuvant therapy for treating patients in any of these situations.

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is 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 results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because 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.

Methodology

CCO's previously published systematic reviews formed the evidence base for this guideline, to which CCO added updated searches in August 2006. The review included evidence published since CCO's prior systematic review. The results from one (unpublished) large individual patient pooled meta-analysis and data from five large published randomized controlled trials support the adjuvant chemotherapy recommendations. Review of a meta-analysis of nine randomized controlled trials and data obtained from three additional randomized controlled trials support the adjuvant radiation therapy recommendations.

Additional Resources

The full-text version of this guideline was published online in the *Journal of Clinical Oncology* (<http://www.jco.org>). In addition, further resources including a slide set, and Decision Aid Tools, are available through www.asco.org/guidelines/adjuvantnslc. A patient guide is available at the People Living With Cancer Web site (www.plwc.org/patientsguides).

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