Complete Summary

GUIDELINE TITLE

Postoperative adjuvant therapy in non-small-cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Weisenburger TH, Komaki RU, Bradley J, Gewanter RM, Gopal RS, Movas B, Rosenzweig KE, Thoms WW Jr, Wolkov HB, Kaiser LR, Schiller JH, Expert Panel on Radiation Oncology-Lung. Postoperative adjuvant therapy in non-small-cell lung cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 13 p. [60 references]

GUIDELINE STATUS

This is the current release of the guideline.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Non-small-cell lung cancer (NSCLC)

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Pulmonary Medicine
Radiation Oncology
Radiology
Thoracic Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of postoperative adjuvant therapy in treatment of patients with non-small-cell lung cancer

TARGET POPULATION

Patients with non-small-cell lung cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Radiotherapy procedure planning
2. Radiation therapy (refer to the "Major Recommendations" field for doses)
3. Chemotherapy
4. Combination of chemo and radiation therapy

MAJOR OUTCOMES CONSIDERED

- Recurrence rates
- Overall and disease-free survival rates
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible.

If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Postoperative Adjuvant Therapy in Non-Small-Cell Lung Cancer

Variant 1: T2 N1 (hilar) with careful mediastinal surgical staging. Negative surgical margins post resection.

Treatment	Appropriateness Rating	Comments
Postop Mediastinal RT plus Chemo		
Chemo	8	
Chemo then RT	5	
Concurrent chemo plus RT	2	
Chemo then concurrent RT plus chemo	2	
RT alone	2	

Treatment	Appropriateness Rating	Comments
Dose Utilized		
30 Gy/10 fractions	2	
40 Gy/20 fractions	2	
45 Gy/25 fractions	3	
50 Gy/25 fractions	8	
50.4 Gy/28 fractions	8	
54 Gy/30 fractions	7	
59.4 Gy/33 fractions	3	
69.6 Gy/58 fractions (bid)	2	
70.2 Gy/39 fractions	2	
Radiotherapy Procedures		
Computer planning	8	
CT-based planning	8	
3D treatment planning	8	
Radiotherapy Technique		
Multifield technique	8	
Complex blocking	8	
AP/PA only	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: T2 N2 with careful mediastinal staging, highest node negative. Negative surgical margins post resection.

Treatment	Appropriateness Rating	Comments
Postop Mediastinal RT plus Chemo		

Treatment	Appropriateness Rating	Comments
Chemo	8	
Chemo then RT	8	
Concurrent chemo plus RT	2	
Chemo then concurrent RT plus chemo	2	
RT alone	2	
Dose Utilized		
30 Gy/10 fractions	2	
40 Gy/20 fractions	2	
45 Gy/25 fractions	2	
50 Gy/25 fractions	8	
50.4 Gy/28 fractions	8	
54 Gy/30 fractions	8	
59.4 Gy/33 fractions	5	
69.6 Gy/58 fractions (bid)	2	
70.2 Gy/39 fractions	2	
Radiotherapy Procedures		
Computer planning	8	
CT-based planning	8	
3D treatment planning	8	
Radiotherapy Technique		
Multifield technique	8	
Complex blocking	8	
AP/PA only	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: T2 N2 with careful mediastinal staging, highest node positive. Negative surgical margins post resection.

Treatment	Appropriateness Rating	Comments
Postop Mediastinal RT plus Chemo		
Chemo	8	
Chemo then RT	8	
Concurrent chemo plus RT	2	
Chemo then concurrent RT plus chemo	2	
RT alone	2	
Dose Utilized		
30 Gy/10 fractions	2	
40 Gy/20 fractions	2	
45 Gy/25 fractions	2	
50 Gy/25 fractions	2	
50.4 Gy/28 fractions	2	
54 Gy/30 fractions	8	
59.4 Gy/33 fractions	8	
69.6 Gy/58 fractions (bid)	2	
70.2 Gy/39 fractions	2	
Radiotherapy Procedures		
Computer planning	8	
CT-based planning	8	
3D treatment planning	8	
Radiotherapy Technique		
Multifield technique	8	

Treatment	Appropriateness Rating	Comments
Complex blocking	8	
AP/PA only	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: T1-2 N0 with careful mediastinal staging. Negative surgical margins post resection.

Treatment	Appropriateness Rating	Comments
Postop Mediastinal RT plus Chemo		
Chemo	5	
Chemo then RT	1	
Concurrent chemo plus RT	1	
Chemo then concurrent RT plus chemo	1	
RT alone	1	
Dose Utilized		
30 Gy/10 fractions	1	
40 Gy/20 fractions	1	
45 Gy/25 fractions	1	
50 Gy/25 fractions	1	
50.4 Gy/28 fractions	1	
54 Gy/30 fractions	1	
59.4 Gy/33 fractions	1	
69.6 Gy/58 fractions (bid)	1	

Treatment	Appropriateness Rating	Comments
70.2 Gy/39 fractions	1	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: T3 N0 with chest wall invasion, with mediastinal node staging. Negative surgical margins post resection.

Treatment	Appropriateness Rating	Comments
Postoperative RT chest wall primary site	8	
Postoperative RT mediastinum	2	
Postop RT plus Chemo		
Chemo	8	
Chemo then RT	8	
Concurrent chemo plus RT	2	
Chemo then concurrent RT plus chemo	2	
RT alone	2	
Dose Utilized		
30 Gy/10 fractions	2	
40 Gy/20 fractions	2	
45 Gy/25 fractions	2	
50 Gy/25 fractions	7	
50.4 Gy/28 fractions	7	
54 Gy/30 fractions	8	
59.4 Gy/33 fractions	8	

Treatment	Appropriateness Rating	Comments
69.6 Gy/58 fractions (bid)	2	
70.2 Gy/39 fractions	2	
Radiotherapy Procedures		
Computer planning	8	
CT-based planning	8	
3D treatment planning	8	
Radiotherapy Technique		
Multifield technique	8	
Complex blocking	8	
AP/PA only	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: T1-3 N0 with mediastinal node staging. Positive margins.

Treatment	Appropriateness Rating	Comments
Postoperative RT chest wall primary site	8	
Postoperative RT mediastinum	2	
Postop RT plus Chemo		
Chemo then RT	5	
Concurrent chemo plus RT	8	
Chemo then concurrent RT plus chemo	6	
RT alone	5	

Treatment	Appropriateness Rating	Comments
Dose Utilized		
30 Gy/10 fractions	2	
40 Gy/20 fractions	2	
45 Gy/25 fractions	2	
50 Gy/25 fractions	7	
50.4 Gy/28 fractions	7	
54 Gy/30 fractions	8	
59.4 Gy/33 fractions	8	
69.6 Gy/58 fractions (bid)	2	
70.2 Gy/39 fractions	2	
Radiotherapy Procedures		
Computer planning	8	
CT-based planning	8	
3D treatment planning	8	
Radiotherapy Technique		
Multifield technique	8	
Complex blocking	8	
AP/PA only	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 7: T2 N2 limited sampling of clinically positive nodes, postop FEV1 = 700 ml. Negative surgical margins post resection.

Treatment	Appropriateness Rating	Comments
Postop Mediastinal RT plus Chemo		

Treatment	Appropriateness Rating	Comments
Chemo	8	
Chemo then RT	6	
Concurrent chemo plus RT	2	
Chemo then concurrent RT plus chemo	2	
RT alone	2	
Dose Utilized		
30 Gy/10 fractions	2	
40 Gy/20 fractions	2	
45 Gy/25 fractions	2	
50 Gy/25 fractions	3	
50.4 Gy/28 fractions	3	
54 Gy/30 fractions	8	
59.4 Gy/33 fractions	8	
69.6 Gy/58 fractions (bid)	2	
70.2 Gy/39 fractions	2	
Radiotherapy Procedures		
Computer planning	8	
CT-based planning	8	
3D treatment planning	8	
Radiotherapy Technique		
Multifield technique	8	
Complex blocking	8	
AP/PA only	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Postoperative Radiotherapy

The role of postoperative radiotherapy (PORT) in patient with non-small-cell lung cancer (NSCLC) has been debated for many years. The populations of patient studied have been heterogeneous with respect to histology, tumor (T) and nodule (N) stage, surgical staging, and treatment parameters. In addition, within this group of patients there are important prognostic indicators such as whether the lymph nodes are involved with tumor intranodally or extranodally, the number of lymph node regions involved, subcarinal or subaortic lymph node involvement, clinical evidence of mediastinal lymph node involvement, mediastinoscopic evidence of lymph node involvement, and possibly the cell type. Few studies have reported on many of these indicators.

The extent of surgical resection and staging is also important. In one surgical series of 102 patients with no clinical evidence of mediastinal adenopathy at thoracotomy, 24% had pathologically positive nodes. Approximately 27% to 36% of the patients with mediastinal lymph node disease will have no involvement of the lobar or hilar lymph nodes. If resection of clinically negative mediastinal lymph nodes is not performed, it is possible that more substantial amounts of subclinical disease will be present in the mediastinal lymph nodes, which might alter the clinical course. One study evaluated the extent of mediastinal surgical resection in 373 patients accrued to ECOG 3590, a randomized trial of adjuvant therapy in patients with completely resected stages II and IIIa NSCLC. Systematic sampling (SS) was performed in 187 patients and mediastinal lymph node dissection (MLND) in 186 patients. In this non-randomized comparison, SS was comparable to MLND in determining nodal staging, though complete MLND found a greater number of positive nodes, and MLND was associated with an improved survival compared with SS in patients with right-sided NSCLC.

A number of studies, both retrospective and prospective, have compared PORT with no further treatment in patients following resection for NSCLC. The retrospective studies as a group may suffer from selection bias since in a given study it is possible that the radiotherapy group was systematically selected to be healthier or sicker than the group not given radiation therapy. All of these studies include patients who have undergone complete resection of at least all gross disease. Only three studies employed systematic mediastinal staging. The Lung Cancer Study group (LCSG) 773 only included selected patients who had complete resections, described as having negative margins and the most proximal node negative. Patients who had positive margins or the highest node positive were treated in LCSG 779, which compared radiotherapy to radiotherapy with chemotherapy consisting of cytoxan, adriamycin, and cisplatin (CAP).

PORT in patients without evidence of lymphatic metastasis appears to have no significant survival benefit, although one recent, small study interestingly noted a "trend". For patients with lymph node metastases, several retrospective studies indicate that for epidermoid carcinoma, PORT significantly increases survival. One study did not show an increase in survival with PORT, but the groups were not

comparable, since 52% of the patients who received PORT had T3 or N2 involvement vs. only 24% in the surgery only group. In addition, systematic mediastinal lymph node evaluation had not been performed, leading to a potential bias of uneven distribution of subclinical N2 involvement. The randomized prospective trial by the LCSG Study 773 showed a substantial decrease in local recurrences as the first site of recurrence, indicating that the desired effect of control of intrathoracic disease had been achieved, but without a significant increase in survival. The study, however, only contained 44 patients with mediastinal metastatic disease. In this N2 group there was a significantly reduced overall recurrence rate, but not an increased survival, in those treated with radiotherapy. As stated by the authors, this is a subgroup in which radiation may provide a survival benefit.

One study reported on 155 patients with pT1-3, N0-2, metastasis (M)0 NSCLC (all histologies) who were randomized to receive 50–56 Gy to the ipsilateral hilum plus mediastinum. The overall 5-year survival rates were 29.7% in the treated group and 20.4% in the observation arm (NS). There was decreased local recurrence in the treated group. Another study retrospectively analyzed 224 patients from the Mayo Clinic with NSCLC, all histologies, metastatic to ipsilateral lymph nodes (stage IIIA), who had gross total resections. The authors compared the local recurrence and overall survival rates of the 88 patients who received PORT with those who did not. They reported actuarial local recurrence and survival rates of 17% vs. 60% and 43% vs. 22%, respectively.

A meta-analysis (PORT Meta-analysis Trialists Group) found a significant adverse effect of PORT in stage I/II, N0-N1 patients, but not in stage III or N2 patients. The authors interpreted the meta-analysis to show that "postoperative radiotherapy is detrimental to patients with early stage completely resected NSCLC and should not be routinely used for such patients" and that "the role of postoperative radiotherapy in the treatment of N2 tumors is not clear and may warrant further research." This study has been heavily criticized for a number of reasons. The accompanying editorial stated that "radiotherapy is a subtle and complex business and several factors need to be considered (i.e., technique, beam energy, volume of tissue irradiated, total dose, dose per fraction, interval between fractions, and overall treatment time). To assert that radiotherapy is harmful without considering these crucial variables is equivalent to concluding, on the basis of uncontrolled experience with tincture of foxglove, that all inotropic agents are too dangerous for clinical use." Several authors have been critical of the inclusion of series of patients treated with cobalt, posterior spinal cord blocks, and large volumes and doses and the inclusion of early stage disease. Criticisms have also mentioned the inclusion not only of patients in the meta-analysis that had been excluded from analysis in the original report, but also patients from unpublished trials as possible confounding factors. The authors of the meta-analysis replied that the possible explanation of the detrimental effects as being due to the volume of lung treated or dose delivered goes "beyond the scope of the actual data." To avoid bias, they stated that all relevant trials should be included, regardless of publication status, and that all patients in the trial should be analyzed on an intention to treat basis. They "disagreed that there is no controversy in the treatment of stage I patients." They acknowledged that the radiotherapy techniques were heterogeneous and that more modern techniques are available but stated that there are no studies with these newer techniques and

that "modern techniques would need to be very much improved to overturn the clear detriment observed."

Several authors have reported that more recent studies of radiotherapy given after surgery have been associated with no apparent increased mortality. One study reported no increase in intercurrent deaths in a retrospective review of 208 patients treated postoperatively with modern treatment planning and appropriate case selection. Another study compared PORT with concurrent chemotherapy/PORT. They noted no increase in death from intercurrent disease when the study groups were compared with matched controls generated from population statistics. A randomized study of PORT in 104 resected stage I patients also noted acceptable toxicity.

Several studies have been published since the original PORT meta-analysis evaluating survival. One study randomized 366 N1 and N2 patients to 60 Gy or observation. They reported that the overall 5-year survival rate was 42.9% in the surgery/radiotherapy group and 40.5% in the surgery alone group. Another study noted a decrease in local recurrence rate (2.2% vs. 23%) and a "promising trend" of increased overall survival at 5 years (67% vs. 58%) with radiotherapy. This study was included in the latest update of the PORT meta-analysis, but the conclusions have not changed with regard to the benefit or toxicity of PORT, though the hazard ratio for toxicity is slightly less.

One may conclude from these studies that PORT will likely significantly reduce the risk of loco-regional relapse in patients who have metastases to either hilar or mediastinal lymph nodes. There will be no significant increase in survival in patients with negative lymph nodes or positive hilar nodes in patients with negative mediastinal node dissections if PORT is given. If there is an increase in survival in those patients with positive mediastinal nodes, it is likely to be small because of the tendency of these patients to develop disseminated disease. A definitive recommendation for the use of PORT cannot be made even in stage IIIA patients. LCSG 773 unfortunately did not contain a sufficient number of patients with mediastinal metastatic disease to detect a difference in survival with any power, and, therefore, the definitive randomized study has yet to be performed for these patients. Many of the larger studies of patients with mediastinal disease have routinely used PORT, and it seems reasonable in view of the decrease in local recurrence and possible survival benefit to consider PORT in those patients with positive mediastinal nodes, and in patients who have hilar node metastases, but have not had lymph node sampling of the mediastinum. It is important that PORT be optimized with 3D conformal techniques in view of the potential morbidity/mortality of such treatment.

Chest Wall Tumors

Tumors invading the chest wall occur in approximately 5% of patients. The prognosis is worse when there is more than parietal pleural involvement and, as in NSCLC in other sites, when lymph nodes are involved. There are no randomized studies comparing surgery alone to surgery with PORT in completely resected patients, nor are there likely to be because of the infrequency of the problem. To assess the value of PORT, one should evaluate well-staged patients who have no lymph node involvement. One study reported on 93 patients operated on for lung cancer involving the chest wall from 1960 to 1980. Sixty-six had complete en bloc

resections, and of these, 31 had T3 N0 disease. Sixteen were selected to receive PORT. The reasons for selection are not stated. The actuarial survival rate at 5 years was the same whether or not radiotherapy was given (53.3% vs. 54.4%). There were no data on local recurrence patterns. Another study reported on 125 patients operated between 1974 and 1983 who had NSCLC invading the chest wall excluding superior sulcus tumors. PORT was planned only for patients who had nodal involvement. Forty-five patients were completely resected and had T3 N0 disease. The probability of survival at five years for these 45 patients was 56%. There were 32 patients with T3 N1-2 disease completely resected, 21 of whom received PORT. The 5-year survival rate for them was 21%. Local recurrence data are not given. In a study of 35 patients treated between 1969 and 1981, 83% of whom had en bloc resections, twenty-one patients had T3 N0 M0 tumors and were completely resected. Seven of the nine (78%) who received treatment were alive at 5 years compared to only 3 of the 14 (21%) who received no radiotherapy. None of the 13 patients who received radiotherapy recurred locally, while 6 of 22 (27%) who weren't irradiated failed locally. In NSCLC, as in other sites, radiotherapy is likely to benefit patients with a high risk of loco-regional disease who do not have a high risk of metastatic involvement. In patients with any indication of increased risk of local failure, such as close margins, and with no or minimal nodal disease, radiotherapy is likely to reduce the risk of loco-regional relapse and may increase survival.

Dose

The question of what the appropriate dose is in the postoperative setting has not been addressed in a randomized trial. The required dose for sites of potential occult disease may vary depending on the probability of residual disease, the number of sites at risk, the number and radiosensitivity of clonogens present, and the desired control rate. Additionally, since the benefit of PORT has been somewhat controversial, it is not surprising that there is a lack of dose response data on which to make definitive recommendations. One group of researchers comments that most of the recurrences in their retrospective review occurred at or below a dose of 50 Gy, suggesting that higher doses may be necessary. LCSG 773, which demonstrated a significantly reduced incidence of local recurrence as the first site, called for 50 Gy to the mediastinum. It must be remembered that this group of patients was meticulously staged, with perhaps less risk of substantial subclinical disease remaining compared to patients without mediastinal staging. It would seem that a minimum of 50 Gy would be required, with consideration of higher doses depending on individual circumstances.

Postoperative Chemotherapy

The potential benefit of postoperative chemotherapy without or with PORT has been evaluated in quite a number of randomized trials. The LCSG randomized 141 completely resected stage II and III adenocarcinoma and large cell carcinoma patients to chemotherapy with cyclophosphamide, doxorubicin, and platinum (CAP) or intrapleural Bacille Calmette Guerin (BCG) and levamisole (LCSG 772). There was an increase in disease-free survival and a trend toward increased overall survival that approached significance. The LCSG studied postoperative CAP chemotherapy vs. observation in patients with completely resected stage I disease. There was an increase in disease-free survival but no difference in overall survival. One study randomized patients with completely resected stage III

disease to vindesine and platinum vs. no adjuvant therapy. The authors found no difference in recurrence pattern, recurrence-free survival, or overall survival. Another study did report a significant increase in overall survival in patients with completely resected T1-3 N0 M0 disease when CAP chemotherapy was given. The control arm contained a higher number of pneumonectomy cases, however, and when these cases were excluded from analysis the increase in survival disappeared. The Non-small Cell Lung Cancer Collaborative Group published a meta-analysis in 1995 evaluating the effect of chemotherapy on NSCLC. The analysis of postoperative chemotherapy included 14 trials and 4,357 patients. Five trials used alkylating agents; eight used cisplatin-containing regimen, and three used Tegafur or Uracil/Tegafur (UFT). The authors noted a significantly decreased survival in the studies employing alkylating agents and no change with fluorouracil (5-FU) regimens. Platinum-based chemotherapy produced a non significant but intriguing improvement in survival of 5% at 5 years.

There have been some negative trials since then that have not supported the use of adjuvant chemotherapy. One study reported on 119 pN2 patients comparing cisplatin/vindesine vs. no further treatment after resection. The five-year overall survival rates were 28.2% in the treated group and 36.1% in the control group. A number of other studies, most using platinum based regimes have demonstrated a small but definite increase in recurrence free and overall survival rates. The International Adjuvant Lung Cancer Trial (IALT) compared no further treatment to one of four schedules of cisplatin plus either vinorelbine, vindesine, vinblastine, or etoposide in 1,867 completely resected patients with stages I to III NSCLC. There was a 5.1% and a 4.1% increase in disease-free and overall 5-year survival rates, respectively. The North American intergroup trial included 482 patients with stages IB and II randomized to observation or adjuvant chemotherapy with vinorelbine and cisplatin after complete resection. The 5-year survival rate improved from 54% to 69% with adjuvant chemotherapy. The hazard ratio for recurrence was 0.60. Planned subgroup analyses indicated that most of the advantage was in the patients with stage II disease and that the benefit for stage IB patients was present but not statistically significant. The authors stated that the numbers of patients and events in the stage IB group were small and the test for stage-by-treatment interaction was not significant, and therefore that "it is important not to place too much emphasis on this subgroup analysis." The CALGB 9633 study reported the results of the study at ASCO in 2004. Three hundred and forty-four patients with stage IB were randomized following complete resection to observation or adjuvant treatment with paclitaxel and carboplatin for 4 cycles. At a median follow-up of 34 months, the 4-year overall survival rates were 59% in the observation arm and 71% in the treatment arm. The hazard ratio for death from any cause was 0.62 and for lung cancer mortality was 0.51. The Adjuvant Navelbine International Trialist Association (ANITA) study results were reported at ASCO in 2005. They compared adjuvant cisplatin/navelbine to observation in 840 patients with stages IB to IIIA disease. Five-year survival was improved in stages II and IIIA but not in stage IB.

Postoperative adjuvant chemotherapy with a platinum-based regimen is clearly beneficial for stage II and IIIA patients and probably also for IB patients. The benefit for stage IB patients will be clearer with longer follow-up of the CALGB study. It seems reasonable to offer postoperative chemotherapy to these patients, particularly those with good performance status, rapid recovery from surgery, and no major comorbid diseases who have undergone complete resection.

Surgery/Chemotherapy with PORT

The value of adding PORT after or concurrently with postoperative chemotherapy or after neoadjuvant chemotherapy remains little studied and poorly defined. Two of the positive postoperative chemotherapy trials, IALT and ANITA, allowed PORT in a non randomized fashion. The radiotherapy in these studies was given after the chemotherapy. LCSG Study 791 compared radiotherapy (split course) to the same radiotherapy concurrently with CAP in patients with NSCLC who had incomplete resections (positive margins or involvement of the most proximal lymph node in the mediastinum). There was an increase in recurrence-free survival in the chemotherapy arm, but overall survival was not increased. One study randomly compared postoperative vindesine and platinum with mediastinal radiotherapy to mediastinal radiotherapy alone in 72 patients with stage III disease (28 of whom were incompletely resected). There was no difference in recurrence-free or overall survival rates. Another study reported on 267 patients (259 with stage II or III disease) who in a randomized trial received either radiotherapy of 60 Gy to the mediastinum or CAP plus vincristine and lomustine for three cycles, then the same radiotherapy. There was no difference in disease-free or overall survival. The RTOG recently reported a phase II trial of 88 resected stage II and IIIA patients. They all received concurrent radiotherapy and carboplatin and paclitaxel. The toxicities were considered acceptable, and the survival was favorable when compared to ECOG 3590 (median survival of 56.3 months vs. 33.7 months, respectively). The local failure rates were similar between the studies. However, this was not a randomized trial. The authors stated that a randomized trial is warranted based on their promising results.

PORT appears to increase local control in patients who have also received chemotherapy, and it is reasonable to consider using it in patients who have mediastinal nodal involvement and who are felt to be at high risk of local recurrence. Again, it is important that PORT be optimized in view of the potential morbidity/mortality of such treatment.

Abbreviations

- AP/PA, anterior-posterior/posterior-anterior
- Bid, twice a day
- Chemo, chemotherapy
- CT, computed tomography
- FEV1, forced expiratory volume in 1 second
- RT, radiation therapy
- TN, primary tumor, regional lymph node

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate postoperative adjuvant therapy for patients with non-small-cell lung cancer

Subgroups Most Likely to Benefit

In non-small-cell lung cancer (NSCLC), as in other sites, radiotherapy is likely to benefit patients with a high risk of loco-regional disease who do not have a high risk of metastatic involvement. In patients with any indication of increased risk of local failure, such as close margins, and with no or minimal nodal disease, radiotherapy is likely to reduce the risk of loco-regional relapse and may increase survival.

POTENTIAL HARMS

Toxicity associated with chemotherapy and radiation therapy

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Weisenburger TH, Komaki RU, Bradley J, Gewanter RM, Gopal RS, Movas B, Rosenzweig KE, Thoms WW Jr, Wolkov HB, Kaiser LR, Schiller JH, Expert Panel on Radiation Oncology-Lung. Postoperative adjuvant therapy in non-small-cell lung cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 13 p. [60 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Lung

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Thomas H. Weisenburger, MD; Ritsuko U. Komaki, MD; Jeff Bradley, MD; Richard M. Gewanter, MD; Ramesh S. Gopal, MD; Benjamin Movas, MD; Kenneth E. Rosenzweig, MD; William W. Thoms, Jr, MD; Harvey B. Wolkov, MD; Larry R. Kaiser, MD; Joan H. Schiller, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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