

## Treatment of Non-small Cell Lung Cancer Stage I and Stage II\*

### ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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**Background:** The surgical treatment of stage I and II non-small cell lung cancer (NSCLC) continues to evolve in the areas of intraoperative lymph node staging (specifically the issue of lymph node dissection vs sampling), the role of sublobar resections instead of lobectomy for treatment of smaller tumors, and the use of video-assisted techniques to perform anatomic lobectomy. Adjuvant therapy (both chemotherapy and radiation therapy) and the use of larger fractions of radiotherapy delivered to a smaller area for nonoperative treatment of early stage NSCLC have shown promising results.

**Methods:** The panel selected the following areas for review based on clinical relevance and the amount and quality of data available for analysis: surgical approaches to resecting early stage NSCLC, methods of lymph node staging at the time of surgical resection, adjuvant chemotherapy in the treatment of early stage NSCLC, and the use of radiation therapy for primary treatment of early stage NSCLC as well as in the adjuvant setting. Recommendations by the multidisciplinary writing committee were based on literature review using established methods.

**Results and conclusions:** Surgical resection remains the treatment of choice for stage I and II NSCLC, although surgical methods continue to evolve. Adjuvant chemotherapy for patients with stage II, but not stage I, NSCLC is well established. Radiotherapy remains an important treatment for either cases of early stage NSCLC that are medically inoperable or patients who refuse surgery. (CHEST 2007; 132:234S–242S)

**Key words:** ablative therapy; adjuvant therapy; chemotherapy; metaanalyses; non-small cell lung cancer; radiotherapy; stage I and II; surgery; video-assisted thoracic surgery

**Abbreviations:** ACCP = American College of Chest Physicians; ACOSOG = American College of Surgeons Oncology Group; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiation therapy; UFT = tegafur/uracil; VATS = video-assisted thoracic surgery

Patients with stage I or stage II non-small cell lung cancer (NSCLC) are considered to have early stage disease. Unfortunately, these two stages combined account for only 25 to 30% of all patients with

lung cancer. Stage I NSCLC is defined by the American Joint Commission on Cancer as a T1 or T2 tumor in the parenchyma of the lung, no more proximal than 2 cm from the carina, and not invading chest wall or parietal pleura. In addition, patients in

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this stage grouping have hilar (N1) and mediastinal (N2) lymph node stations negative for tumor, and no metastatic (M1) disease. Stage II NSCLC is defined as a T1 or T2 cancer with N1 nodal metastasis and no distant metastasis (T1-2N1M0) or a T3 cancer with no nodal or distant metastasis (T3N0M0). Stage IIA consists of T1N1 cancers.

For review, T1 tumors by definition are  $\leq 3$  cm and do not involve the visceral pleura or a main bronchus. N1 denotes metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor. Stage IIB includes T2N1 and T3N0 cancers. T2 denotes a tumor with any of the following features:  $>3$  cm in greatest dimension, or involves a main bronchus  $>2$  cm distal to the carina, or invades the visceral pleura, or is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung. T3 denotes a tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pleura, parietal pericardium, or tumor in the main bronchus  $<2$  cm distal to the carina without involvement of the carina, or associated atelectasis or obstructive pneumonitis of the entire lung.

We refer the reader to the last version of these *Guidelines* for those aspects of the treatment of stage I and stage II NSCLC that were well reviewed there and also for important background information (see previous "Stage I" and "Stage II" chapters, *CHEST* 2003). In the current version of the *Guidelines*, treatment recommendations regarding tumors of the chest wall (T3N0, part of stage IIB), formerly discussed in the chapter on the treatment of stage II NSCLC, are instead included in the chapter on special situations (see chapter on "Special Treatment Issues in Lung Cancer"). Since the last version of these *Guidelines*, a number of trends in the treatment of patients with stage I and stage II NSCLC have become evident. These trends include increased experience with video-assisted thoracic surgical (VATS) lobectomy in the treatment of patients with clinical stage I NSCLC; the growing recognition that patients with smaller tumors ( $\leq 2.0$  cm) are a favorable subset of patients with stage I NSCLC; growing consideration of sublobar resection for patients with small stage I NSCLC; increasing use of stereotactic radiation and other ablative therapies in nonsurgical candidates; and recent controversy about the use of adjuvant chemotherapy for completely resected patients with stage IB NSCLC, among others. These trends and others are the subjects of ongoing or planned

clinical trials. These issues will be covered in this chapter when there are sufficient data to make evidence-based recommendations.

## MATERIALS AND METHODS

The Duke Evidence-based Clinical Practice Center searched the literature for studies regarding the issues of lymph node staging vs dissection, surgical treatment of early stage lung cancer, the use of adjuvant chemotherapy in the treatment of early stage lung cancer, and the use of radiation therapy for primary treatment of early stage lung cancer as well as in the adjuvant setting. The Duke Evidence-based Practice Center found insufficient data were available regarding ablative therapies such as radiofrequency ablation, cryotherapy, and ablation of tumors using microwave emitting probes, and these areas were not included in this evidence-based review. They then provided evidence tables, summaries of studies, and references to other recently published guidelines authored by other organizations for the panel members to review. The panel of authors for this chapter devised an initial set of recommendations. A larger multidisciplinary panel including thoracic surgeons, radiation oncologists, pulmonologists, and medical oncologists reviewed these and made additional recommendations. Grades were assigned to each recommendation using a standardized method (see chapter on "Methodology for Lung Cancer Evidence Review and Guideline Development"). The entire document was then reviewed and approved by the Health and Science Policy committee of the American College of Chest Physicians (ACCP) and ultimately the Board of Regents of the ACCP.

## RESULTS

### *Surgical Treatment of Stage I and II NSCLC*

There are no randomized clinical trials comparing surgery alone to radiation therapy alone or chemotherapy alone in the treatment of early stage (stage I and II) NSCLC. The concept that surgery offers the best hope of a cure is based on retrospective data ("clinical experience") as reported in the literature. Based on large series of resected stage I and stage II NSCLC, the prognoses for stage IA, IB, IIA and IIB NSCLC, expressed in terms of 5-year survival rates, are commonly accepted to be 60 to 80% for stage I and 40 to 50% for stage II NSCLC.

Silvestri et al<sup>1</sup> retrospectively reviewed mortality rates of 1,416 patients who underwent lobectomy in South Carolina. Mortality was less for those patients whose operation was performed by a board-certified thoracic surgeon as opposed to a general surgeon (21 of 705 patients [3.0%] for thoracic surgeons, vs 38 of 711 patients [5.3%] for general surgeons). In a large retrospective review of the Medicare database, similar findings were noted.<sup>2</sup> Of 25,545 patients who underwent either lobectomy or pneumonectomy for lung cancer in 1998 to 1999, operative mortality rates were significantly lower for cardiothoracic (5.6%) and general thoracic (5.8%) surgeons than general

surgeons (7.6%). In order to participate in modern, multimodality treatment approaches, thoracic surgeons must be aware of the indications for adjuvant therapies, the required preoperative and intraoperative staging that facilitate that approach, and the available treatment alternatives. No less should be required of programs that offer newer image-guided ablative therapies such as radiofrequency ablation, cryoablation, or stereotactic radiation therapy. At present, surgical resection remains the recommended treatment approach for patients with stage I and II NSCLC. As such, all patients with early stage NSCLC should be seen and evaluated by a thoracic surgeon to determine whether they are a candidate for surgical exploration and resection. Other local therapies such as stereotactic radiation or radiofrequency ablation may be appropriate for patients who are medically inoperable. The use of these techniques in patients who are surgical candidates should not occur outside of the context of a clinical research study.

#### RECOMMENDATIONS

**1. For patients with clinical stage I and II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended.** Grade of recommendation, 1A

**2. For patients with clinical stage I and II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if patients are being considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy (SBRT).** Grade of recommendation, 1B

The Lung Cancer Study Group<sup>3</sup> reported in 1995 the results of a prospective randomized trial comparing limited resection to lobectomy in patients with peripheral T1 lung cancers. In this study, patients treated with limited resection had a threefold increase in local recurrence, a 75% increase in combined local and distant recurrence, and a 50% increase in death with cancer rate. There was no difference in operative mortality between the limited resection and lobectomy treatment groups, although there was a higher rate of postoperative respiratory failure requiring ventilator support in the lobectomy group.

Most clinicians treating lung cancer agree that complete surgical resection of stage I lung cancer offers the best chance for cure. Questions still arise as to the risk-benefit relationship between lobectomy and lesser resections (segmentectomy or wedge resection) in selected groups of patients with stage I

lung cancer. One group of patients in whom limited resection has been advocated includes those with poor pulmonary function (see chapter on “Physiologic Evaluation of Patients With Lung Cancer Being Considered for Resectional Surgery”). Linden et al<sup>4</sup> reported the results of resection in 100 patients with poor lung function (preoperative FEV<sub>1</sub> <35% of predicted). There were no operative (30 days) deaths in 14 lung cancer patients treated with lobectomy via thoracotomy (n = 10) or VATS (n = 4) approaches. A small, case-matched control study by Martin-Ucar et al<sup>5</sup> compared stage I NSCLC patients with a predicted postoperative FEV<sub>1</sub> of <40% treatment with either segmental resection or anatomic lobectomy. In this report of 34 patients,<sup>5</sup> there was identical hospital mortality (5.9%) for the two types of resection. Unlike the Lung Cancer Study Group trial, there was no significant difference in local recurrence or overall survival comparing segmental resection to lobectomy. This trial surprisingly showed an increased incidence of local recurrence in the lobectomy arm and only distant recurrence in the segmentectomy arm, calling in to question the overall validity of the findings.

In a large retrospective review from Japan, Watanabe et al<sup>6</sup> analyzed the data on 3,270 consecutive patients treated with resection for primary lung cancer between January 1987 and December 2002. The authors compared outcomes between 1,615 patients treated in an earlier period (from 1987 to 1996) to 1,655 patients treated in a later period (from 1997 to 2002). The authors reported very low 30-day (0.5%) and in-hospital (0.8%) mortality rates in patients treated with surgical resection for lung cancer between 1997 and 2002. They did not see a significant difference in either 30-day (0.3% vs 0.3%) or in-hospital mortality (1.3% vs 0.9%) between lesser resection and lobectomy. As expected, there was a significantly increased 30-day (3.1%) and in-hospital (5.9%) mortality in patients treated with pneumonectomy.

In a retrospective review of 1,137 patients treated surgically for lung cancer, Jackevicius et al<sup>7</sup> reported on the outcomes of 42 patients treated with limited resection (segmentectomy or wedge) between 1980 and 1997. The overall actual 5-year survival rate was a disappointing 29%. The authors found the best survival among patients with T1N0 cancers treated with surgical resection alone with a median survival in these patients of 45.7 months. The authors found no survival benefit with adjuvant radiation therapy in stage I or II patients. Not surprisingly, patients with N2 stage IIIA disease fared the worst, with a median survival of only 9 months. The authors rightly concluded that limited resection should only be per-

formed in case of T1-2N0 lung cancer. There is no role for limited resection in patients with known N1 or N2 disease.

Tsubota et al<sup>8</sup> reported the early results of a prospective multicenter trial of limited surgical resection of peripheral tumors <2 cm in diameter. The investigators excluded patients with N1 or N2 disease identified by frozen section. There were no perioperative deaths in 55 patients treated with segmentectomy, and the overall 5-year survival was 85%. Local recurrence rate was 4%.

Landreneau et al<sup>9</sup> analyzed the outcomes of a series of patients with peripheral stage IA (T1N0M0) lung cancer treated with open lobectomy (n = 117), open wedge resection (n = 42), or VATS wedge resection (n = 60) between January 1989 and July 1994. Postoperative complications occurred in 16% of patients undergoing VATS wedge resection in contrast to 28% of patients undergoing open wedge resection and 31% of patients treated with open lobectomy. While there was no significant difference in overall survival between patients treated with VATS wedge resection compared to open lobectomy, there was a significant decrease in overall survival for patients treated with open wedge resection. There was a trend toward increased local recurrence in the wedge resection groups (19%) compared to the open lobectomy group (9%), although this difference was not statistically significant. The 5-year actuarial survival in the wedge resection groups (open and VATS) was 48%, vs 67% in the open lobectomy group. All patients in this analysis had T1 (<3 cm) tumors located in the outer third of the lung with no evidence of endobronchial extension and had clear margins on frozen section and intraoperative mediastinal and hilar nodal staging.

Fernando et al<sup>10</sup> reported on a multicenter retrospective outcome study of 291 patients with stage IA (T1N0) NSCLC treated with either sublobar resection (n = 124) or lobar resection (n = 167). Brachytherapy was used in 48% (n = 60) of the sublobar resection cases. Brachytherapy decreased the local recurrence rate in the sublobar resection group from 17% (11 of 64 patients) to 3.3% (2 of 60 patients). There was no survival difference between sublobar and lobar resection in tumors <2 cm in diameter. In contrast, median survival was significantly better for patients with larger tumors (2 to 3 cm) undergoing lobar resection group (70 months) than for similar patients treated with sublobar resection (44.7 months).

Birdas et al<sup>11</sup> retrospectively reviewed the outcomes of 167 patients with stage IB lung cancer treated with lobectomy (n = 126) or sublobar resection (n = 41) with <sup>125</sup>I brachytherapy over the resection staple line. The local recurrence rate was similar

between the sublobar with brachytherapy group (4.8%) and the lobectomy group (3.4%). At 4 years, the disease-free survival was equivalent for sublobar (43.0%) and lobectomy (42.8%) patients. Overall survival did not differ for sublobar patients (54.1%; median, 50.2 months) and lobectomy patients (51.8%; median, 56.9 months; p = 0.38).

Currently, the American College of Surgeons Oncology Group (ACOSOG) is conducting a phase III clinical trial (ACOSOG Z4032) designed to determine whether the addition of <sup>125</sup>I brachytherapy to sublobar resection improves local control in patients with stage I NSCLC compared to sublobar resection alone. Eligible patients must be considered to be at high risk for standard surgical therapy (lobectomy) based on well-defined criteria including decreased lung function or other comorbid factors.

## RECOMMENDATIONS

**3. In patients with stage I and II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sublobar resections (wedge or segmentectomy).** Grade of recommendation, 1A

**4. In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection because of comorbid disease or decreased pulmonary function, sublobar resection is recommended over nonsurgical interventions.** Grade of recommendation, 1B

As thoracic surgeons have gained further experience with VATS techniques, they have been applied at an increasing number of centers for the performance of anatomic lung resections (lobectomy and segmentectomy) in patients with clinical stage I NSCLC.<sup>12</sup> Data from an exploratory early series<sup>13</sup> have found VATS resection safe and with complication rates similar to that of open lobectomy. More recently, large series<sup>14</sup> have reported long-term follow-up confirming that VATS lobectomy can achieve cure rates similar to those performed via thoracotomy.

## RECOMMENDATION

**5. In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy), the use of VATS by surgeons experienced in these techniques is an acceptable alternative to open thoracotomy.** Grade of recommendation, 1B



The extent of lymph node evaluation at the time of surgical resection of stage I and stage II NSCLC continues to be a matter of debate. Clinical practice varies from visual inspection alone to radical lymphadenectomy. Questions remain regarding the extent of lymph node removal (sampling vs dissection) or the minimum number of lymph node stations or nodes sampled.

Two randomized trials<sup>15,16</sup> have found no difference in overall survival in patients undergoing lymphadenectomy compared to those undergoing lymph node sampling at the time of resection for NSCLC. In contrast, a third randomized trial by Wu et al<sup>17</sup> found improved survival for patients with clinical stage I to III NSCLC who underwent resection with mediastinal lymph node dissection rather than sampling.

The Cochrane collaboration reviewed 11 randomized trials with a total of 1,910 patients who underwent treatment for early stage (I to IIIA) lung cancer. From a pooled analysis of three trials, they reported that 4-year survival was superior in patients who underwent resection and complete mediastinal lymph node dissection compared with those undergoing resection and lymph node sampling, with the hazard ratio estimated to be 0.78 (95% confidence interval, 0.65 to 0.93;  $p = 0.005$ ).<sup>18</sup>

Data from a prospective, multiinstitutional, randomized trial<sup>19</sup> conducted by the ACOSOG have been reported. This trial was designed to determine if survival after lung resection was impacted by lymph node dissection versus lymph node sampling (ACOSOG Z0030). Preliminary analysis has found no difference in operative mortality based on lymph node procedure. Lymph node dissection was associated with longer operative time and greater volume of postoperative chest tube drainage. However, length of hospital stay did not differ between the two surgical approaches (median stay, 6 days). Both lymph node dissection and sampling are safe procedures and provide critical staging information that will influence recommendations regarding postoperative adjuvant therapy. At present, there is insufficient information to recommend one technique as superior.

#### RECOMMENDATION

**6. In patients undergoing resection for stage I and II NSCLC, it is recommended that intraoperative systematic mediastinal lymph node sampling or dissection be performed for accurate pathologic staging.** Grade of recommendation, 1B

No randomized trials comparing sleeve lobectomy

to pneumonectomy have been reported in the literature. The data available consist of retrospective reviews of the outcomes in patients treated with sleeve lobectomy compared with matched or unmatched control subjects treated with pneumonectomy. For example, Suen et al<sup>20</sup> reported a series of 58 patients with NSCLC treated with sleeve lobectomy or pneumonectomy. After sleeve lobectomy, the operative mortality was 5.2% and the overall 5-year survival rate was 37.5%. For patients treated with pneumonectomy, operative mortality rate was 4.9% and the overall 5-year survival rate was 35.8%.

#### RECOMMENDATIONS

**7. For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy.** Grade of recommendation, 1B

**8. For patients with N1 lymph node metastases (stage II NSCLC) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy.** Grade of recommendation, 1B

#### *Adjuvant Chemotherapy*

Despite complete resection, many stage I and II NSCLC patients experience recurrence. The majority of these relapses are distant, and studies have addressed the role of postoperative chemotherapy. Although the majority of randomized trials have included a range of surgical stages, there are sufficient data to make recommendations about the use of adjuvant chemotherapy in stage I and II NSCLC. Several excellent reviews<sup>21–23</sup> of this topic are available.

For patients with completely resected stage IA NSCLC, postoperative chemotherapy is not recommended. There are very little data available on this subset of patients because most randomized adjuvant trials have excluded patients with stage IA disease extent. From the lung adjuvant cisplatin evaluation metaanalysis,<sup>24</sup> there was no benefit for postoperative adjuvant cisplatin-based chemotherapy among 347 stage IA NSCLC patients.

For patients with stage IB NSCLC, the majority of recent studies<sup>25–27</sup> have not found a statistically significant benefit for this subset of patients. One study<sup>28</sup> has reported benefit, although the results were so different from the other trials as to call into question the validity of its findings. The lung adjuvant cisplatin evaluation metaanalysis<sup>24</sup> found a trend toward improvement in survival in 1,371 stage IB patients randomized to postoperative cisplatin-based

chemotherapy over surgery alone, with an 8% reduction in the risk of death associated with chemotherapy, but this difference was not statistically significant. The Cancer and Leukemia Group B investigators conducted an exploratory analysis of the effectiveness of adjuvant paclitaxel/carboplatin chemotherapy in those patients with primary tumors >4 cm. In this analysis,<sup>27</sup> there continued to be a statistically significant benefit for these stage IB patients.

Studies from Japan have evaluated the use of oral uracil/tegafur (UFT) as an adjuvant therapy to surgery in early stage NSCLC. UFT, a fluoropyrimidine, is a well-tolerated oral agent. Results from these randomized adjuvant trials have been mixed. The single largest trial<sup>28</sup> randomized completely resected stage I adenocarcinoma patients to oral UFT for 2 years or no postoperative therapy. With a median follow-up of >6 years, the 5-year survival rates were 88% in the UFT group and 85% in the control group ( $p = 0.047$ ). Subset analyses found the greatest benefit in the T2N0, stage IB patients. Of concern was the lack of benefit for disease-free survival.<sup>29</sup> A metaanalysis<sup>30</sup> of the effectiveness of adjuvant UFT has also been conducted. This included results from 2,003 patients and compared outcome of single-agent adjuvant oral UFT to surgery alone. UFT was associated with a significant improvement in overall survival (hazard ratio, 0.74; 95% confidence interval, 0.61 to 0.88;  $p = 0.001$ ).<sup>30</sup> There are no confirmatory data on the use of adjuvant oral UFT outside of Japan. Although the results are encouraging, oral UFT or another oral fluoropyrimidine cannot be recommended as adjuvant therapy at this time.

Data for the use of adjuvant cisplatin-based chemotherapy in stage II NSCLC are strong. The International Adjuvant Lung Trial, National Cancer Institute of Canada JBR.10, and Adjuvant Navelbine International Trialists Association studies all found significant benefit for the use of adjuvant chemotherapy in the general population of NSCLC studied, as well as in the stage II patient subsets.<sup>31</sup> The lung adjuvant cisplatin evaluation metaanalysis<sup>24</sup> of the 1,616 stage II patient subset found a 27% reduction in the risk of death (hazard ratio, 0.83; 95% confidence interval, 0.73 to 0.95).

## RECOMMENDATIONS

**9. For patients with completely resected stage IA NSCLC, the use of adjuvant chemotherapy is not recommended for routine use outside the setting of a clinical trial.** Grade of recommendation, 1A

**10. For patients with completely resected stage IB NSCLC, the use of adjuvant chemotherapy is not recommended for routine use.** Grade of recommendation, 1B

**11. For patients with completely resected stage II NSCLC and good performance status, the use of platinum-based adjuvant chemotherapy is recommended.** Grade of recommendation, 1A

## *Definitive Radiation Therapy for Stage I and II NSCLC*

While surgery is the preferred treatment for early stage lung cancer, for those patients who are not candidates for surgery because of comorbid conditions ("medically inoperable") or who refuse surgery, experience has generally shown that radiotherapy is effective in obtaining local control with some longer-term survivors. Data suggest that medically inoperable patients still mainly die from lung cancer despite their other medical problems, so treatment of the tumor is justified as opposed to supportive care. Qiao et al<sup>32</sup> reviewed 18 articles between 1988 and 2000. Local recurrence was noted to be the predominant mode of failure and occurred at a median rate of 40%. Median survival in these studies was 18 to 33 months.

Accelerated therapy (54 Gy in 12 days) was superior to conventional radiotherapy (60 Gy in 6 weeks) in the randomized phase III continuous hyperfractionated accelerated therapy study conducted in the United Kingdom.<sup>33</sup> A subset of 169 patients with stage I/II NSCLC were included. Four-year survival was significantly improved with continuous accelerated hyperfractionated radiation therapy (18% vs 12%).

More recently, radiation oncologists have administered radiotherapy in larger doses, fewer fractions, and smaller fields first with three-dimensional conformal therapies and more recently with the use of SBRT, with relatively large series reported from Japan and smaller series from the United States.<sup>34,35</sup> Onishi et al<sup>34</sup> noted local recurrence rates of 14.5% (9.7% for T1 tumors and 20.0% for T2 tumors) during follow-up (median, 24 mo). In a series of 70 patients, Timmerman et al<sup>35</sup> noted excessive toxicity when treating central tumors, but reported 2-year freedom from severe toxicity of 83% for patients with peripheral lung tumors. A 3-month major response rate of 60% was reported. Kaplan-Meier estimated local control rate at 2 years was 95%. Data are awaited from Radiation Therapy Oncology Group trial 0236, a phase II trial of SBRT in the treatment of patients with medically inoperable stage I/II NSCLC, which recently achieved its accrual goals and closed.

## RECOMMENDATION

**12. For patients with stage I or II NSCLC who are not candidates for surgery (“medically inoperable”) or who refuse surgery, curative intent fractionated radiotherapy is recommended.** Grade of recommendation, 1B

### *Adjuvant (Postoperative) Radiation Therapy for Stage I and II NSCLC*

Postoperative radiotherapy after complete resection of stage I or II NSCLC has been proposed with the goal of decreasing local recurrence rates and improving long-term survival. The Cochrane collaboration had recently updated its well-known postoperative radiotherapy metaanalysis.<sup>36</sup> The current metaanalysis is based on the results of 10 randomized control trials and 2,232 patients. There continues to be evidence that postoperative radiotherapy is associated with a decrease in survival for patients with stage I (N0) and stage II (N1) NSCLC. Critics note that the metaanalysis includes a number of older studies that used radiotherapy methods that are known to be inferior to current standards.

Analyzing similar data for patients with stage II and III NSCLC, Cancer Care Ontario found that postoperative radiation therapy was “mainly detrimental to survival in patients with stage II NSCLC,” while no benefit or detriment was seen for postoperative radiation therapy administered to patients with completely resected stage III NSCLC.<sup>37</sup>

## RECOMMENDATIONS

**13. For patients with completely resected stage IA or IB NSCLC, postoperative radiotherapy is associated with a decreased survival and is not recommended.** Grade of recommendation, 1B

**14. For patients with completely resected stage II NSCLC, postoperative radiotherapy decreases local recurrence but a survival benefit has not been clearly shown; therefore, postoperative radiotherapy is not recommended.** Grade of recommendation, 1B

## CONCLUSIONS

Although there are no clinical trials comparing surgical resection to other forms of therapy for treating stage I and II lung cancer, extensive clinical experience indicates that the best chance

of cure for these tumors comes with surgical resection. Operative outcomes have been found to be better with thoracic surgeons performing lung resection than general surgeons. In patients who can tolerate conventional surgical resection, lobectomy is preferred over sublobar resections. In patients who cannot tolerate conventional surgical resection, sublobar resection is recommended over nonsurgical interventions. For the appropriately trained thoracic surgeon, VATS is an acceptable alternative to open thoracotomy. Whether VATS or open thoracotomy are performed, either systematic mediastinal lymph node sampling or lymph node dissection is recommended at the time of surgical resection. Sleeve lobectomy is preferred over pneumonectomy, when technically possible, in patients with either centrally advanced disease or N1 metastases. Cisplatin-based adjuvant chemotherapy is recommended for completely resected stage II, but not stage I, NSCLC. Curative intent radiotherapy is recommended for patients with stage I or II NSCLC that is either medically inoperable or in patients who refuse surgery. Radiotherapy is not recommended postoperatively after complete surgical resection.

## SUMMARY OF RECOMMENDATIONS

**1. For patients with clinical stage I and II NSCLC and no medical contraindication to operative intervention, surgical resection is recommended.** Grade of recommendation, 1A

**2. For patients with clinical stage I and II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if they are being considered for nonsurgical therapies such as percutaneous ablation or SBRT.** Grade of recommendation, 1B

**3. In patients with stage I and II NSCLC who are medically fit for conventional surgical resection, lobectomy or greater resection are recommended rather than sublobar resections (wedge or segmentectomy).** Grade of recommendation, 1A

**4. In patients with stage I NSCLC who may tolerate operative intervention but not a lobar or greater lung resection due to comorbid disease or decreased pulmonary function, sublobar resection is recommended over nonsurgical interventions.** Grade of recommendation, 1B



**5. In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy), the use of VATS by surgeons experienced in these techniques is an acceptable alternative to open thoracotomy.** Grade of recommendation, 1B

**6. In patients undergoing resection for stage I and II NSCLC, it is recommended that intraoperative systematic mediastinal lymph node sampling or dissection be performed for accurate pathologic staging.** Grade of recommendation, 1B.

**7. For patients with centrally or locally advanced NSCLC in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy.** Grade of recommendation, 1B

**8. For patients with N1 lymph node metastases (stage II NSCLC) in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy.** Grade of recommendation, 1B

**9. For patients with completely resected stage IA NSCLC, the use of adjuvant chemotherapy is not recommended for routine use outside the setting of a clinical trial.** Grade of recommendation, 1A

**10. For patients with completely resected stage IB NSCLC, the use of adjuvant chemotherapy is not recommended for routine use.** Grade of recommendation, 1B

**11. For patients with completely resected stage II NSCLC and good performance status, the use of platinum-based adjuvant chemotherapy is recommended.** Grade of recommendation, 1A

**12. For patients with stage I or II NSCLC who are not candidates for surgery ("medically inoperable") or who refuse surgery, curative intent fractionated radiotherapy is recommended.** Grade of recommendation, 1B

**13. For patients with completely resected stage IA or IB NSCLC, postoperative radiotherapy is associated with a decreased survival and is not recommended.** Grade of recommendation, 1B

**14. For patients with completely resected stage II NSCLC, postoperative radiotherapy decreases local recurrence but a survival benefit has not been clearly shown; therefore, postoperative radiotherapy is not recommended.** Grade of recommendation, 1B

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