Treatment of Stage I Non-small Cell Lung Carcinoma

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The American Joint Committee on Cancer defines stage I non-small cell lung carcinoma (NSCLC) as consisting of patients with a T1 or T2 primary tumor designation and no evidence of hilar or mediastinal nodal disease (N0) or metastatic spread (M0). Medically fit patients in this clinical stage category based on conventional staging techniques should be considered for aggressive local therapy, and curative treatment is possible. Surgical resection is the accepted treatment for patients with this stage grouping, and full lobar or greater (lobectomy, pneumonectomy) rather than sublobar (wedge resection, segmentectomy) resection is strongly suggested. There is insufficient data to suggest that one method of resection (open thoracotomy, minimally invasive techniques) is superior to another. The performance of a systematic sampling or full mediastinal lymph node dissection may improve pathologic staging but is unproven therapeutically. There are no data supporting the routine use of chemotherapy in an adjuvant or neoadjuvant setting; however, recent phase II data suggest that neoadjuvant chemotherapy is feasible and safe, and larger phase III trials are now evaluating this modality. Primary radiation therapy should be considered for inoperable patients. The use of neoadjuvant or adjuvant radiation therapy in patients with stage I NSCLC is of unproven benefit. ***(CHEST 2003; 123:181S–187S)***

Key words: chemotherapy; lung cancer; radiation therapy; stage I; surgery

Abbreviation: NSCLC = non-small cell lung cancer

Stage I non-small cell lung carcinoma (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 this stage grouping have hilar (N1) and mediastinal (N2) lymph node stations negative for tumor, and no metastatic (M1) disease. Naruke et al[1] and Mountain[2] published two of the largest series evaluating postsurgical survival in NSCLC. In these studies, > 1,500 patients with stage I NSCLC (1997 American Joint Commission on Cancer system designation) were treated surgically, and survival was retrospectively assessed. Five-year survival for patients with T1N0M0 in these series combined was 71.25% and for patients with T2N0M0 was 57%.

This stage, due to differences in survival statistics, is further subdivided into stage IA (T1N0M0) and stage IB (T2N0M0).[3] Unfortunately, early stage disease is relatively less common at presentation than is more advanced NSCLC. The National Cancer Institute Surveillance, Epidemiology and End Results Program[4] recently published data regarding patients with NSCLC in this country from 1989 to 1996. In this analysis, 15% of patients were found to have "localized" rather than "regional," "distant," or "unstaged" tumors.

Clearly, one should not promise a cure to patients with a diagnosis of NSCLC at any stage. However, there is no doubt that survival following treatment in this disease is stage related, and that patients with lower stage disease represent those with the best chance for curative treatment. With this in mind, the appropriate treatment of patients with earlier-stage disease takes on perhaps even greater importance, as the potential for a lost curative opportunity is greatest. This section will critically evaluate the role of surgery as the accepted primary modality of therapy for this malignancy at this time, as well as the questions of proper use of radiation therapy and chemotherapy in both the neoadjuvant and adjuvant settings. In addition, recommendations for alternative primary therapy for patients who are not surgical candidates will be discussed. Other chapters will deal with the staging evaluation of patients with early stage NSCLC, and stage I small cell lung cancer will be reviewed elsewhere in these guidelines as well.

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Although the majority of guideline recommendations of the American College of Chest Physicians for treatment of this stage of NSCLC are likely to be less controversial than treatment of more advanced stages, the area is a dynamic one, and readers are strongly encouraged to keep abreast of developments over the next several years in treatment of this particular category of patients. It is virtually certain that advances in diagnostic radiology, radiation therapy, and tailored systemic treatment in medical oncology will make these recommendations somewhat obsolete in the foreseeable future.

Surgical Resection for Patients With Stage I NSCLC

What Is the Evidence Regarding Surgical Resection as the Preferred Primary Treatment Modality for Patients With Stage I NSCLC?

To date, there have been no large randomized trials evaluating surgical resection vs other treatment modalities for stage I NSCLC. However, a comparison of data from trials evaluating independent and combined modalities, and an examination of rates of postsurgical survival strongly suggest that surgical resection should be viewed as the preferred primary modality. Chemotherapy as a primary treatment modality in stage I NSCLC has not been extensively studied, but combination adjuvant and neoadjuvant studies published to date do not demonstrate any significant survival benefit over surgical resection alone. This being noted, the majority of patients that succumb to NSCLC following surgical resection fail with distant metastatic disease, arguing against the use of surgery alone.

Numerous randomized trials evaluating the use of more active modern systemic chemotherapy agents (cisplatin-based) in the adjuvant setting with reasonable clinical staging criteria have been performed. Although these trials were not specifically designed to treat stage I patients, a large number in this category were randomized. Although relatively well tolerated, no significant survival benefits were noted in any of these individual trials.[5–7] When the use of adjuvant chemotherapy in NSCLC has been evaluated by meta-analysis, it has been shown that the use of alkylating agents favors surgery alone, but that the use of cisplatin-based regimens are found to have a 5% approximate benefit. Although modest, this degree of benefit may prove clinically useful considering the prevalence of the disease.[8] Interestingly, there have been two randomized trials evaluating the use of adjuvant chemotherapy in NSCLC patients utilizing tegafur alone or in combination with other chemotherapeutic agents vs surgery alone. Significant improvement in survival and disease free survival were noted in both of these trials.[9,10] There has been a recent resurgence of interest regarding the use of neoadjuvant chemotherapy based in part on results of smaller stage IIIA trial results and the availability of more active conventional chemotherapy agents.[11,12] A successful feasibility and toxicity study of neoadjuvant chemotherapy was recently completed for patients with stages IB or IIIA, and randomized trials are in progress.[13] Several molecular and cellular marker studies in NSCLC suggest that there may be a large degree of biological heterogeneity for tumors within the stage I grouping. These markers may provide for identification of patients with a higher propensity for recurrence or metastasis, and possibly benefit from chemotherapy.[14]

Studies evaluating the use of adjuvant or neoadjuvant radiation therapy in early stage lung carcinoma have not proven to add to the survival benefit of surgical resection alone, and a meta-analysis has suggested that adjuvant radiation therapy may have an adverse effect in stage I disease, with similar adverse effect noted in at least one randomized neoadjuvant study[15,16] A comparison of survival rates of patients treated with radiation therapy alone for NSCLC due to medical inoperability or refusal of surgical care to those undergoing surgical resection indicates an approximate 25 to 35% improvement in survival in patient undergoing surgical resection.[17–19] It is important, however, to consider several caveats regarding the findings of adjuvant and neoadjuvant radiation therapy to date. Many of these studies have utilized older modalities such as cobalt irradiation. The use of newer modalities as primary therapy such as proton and stereotactic techniques appear to be much more promising, although not studied in a randomized fashion.[20,21] And finally, the survival of medically unfit patients may be influenced by the underlying nonmalignant disease. The use of adjuvant radiation therapy in patients with positive resection margins has not been carefully studied, but there is a suggestion of benefit.[22]

Who should routinely treat patients with NSCLC? Interestingly, multiple recent reports strongly suggest that a higher volume of lung cancer treatment at a given institution as well as the degree of specific specialty training have a significant positive influence on the attitudes of clinicians regarding lung cancer treatment, the treatments administered, and the success of treatment, including surgical resection.[23–26]

Recommendations

1. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, surgery alone is the

preferred treatment modality. Level of evidence, fair; benefit, substantial; grade of recommendation, B

2. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, a complete surgical resection (clear surgical margins) is to be achieved if possible in all cases. Level of evidence, good; benefit, substantial; grade of recommendation: A
3. All patients considered surgical candidates should be evaluated for surgical resection by surgeons trained and board certified or board eligible in thoracic surgery. Level of evidence, good; benefit, substantial; grade of recommendation, A
4. Patients with positive resection margins should be evaluated for additional local treatment modalities (surgical re-resection or radiation therapy). Level of evidence, fair; benefit, moderate; grade of recommendation, B
5. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the use of neoadjuvant chemotherapy has been shown to be feasible, but is not recommended outside the setting of a clinical trial. Level of evidence, poor; benefit, small/weak; grade of recommendation, I
6. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the use of adjuvant chemotherapy is not recommended outside the setting of a clinical trial. Level of evidence, fair; benefit, none/negative; grade of recommendation, D
7. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the routine use of neoadjuvant or adjuvant radiation therapy should not be performed. Level of evidence, good; benefit, none/negative; grade of recommendation: D

What Is the Evidence to Support Full Anatomic Resection (Lobectomy, Pneumonectomy) Over Lesser Resections (Wedge Resection, Segmentectomy) for Stage I NSCLC?

Full anatomic resection is defined as a resection of either a complete lobe of the lung (lobectomy) or the entire lung (pneumonectomy). Either of these procedures require dissection and division of hilar vascular and bronchial structures. Virtually all shared vascular, lymphatic, and vascular divisions are removed as a unit. *Wedge resection* refers to the removal of a nonanatomic portion of the lung, usually performed as removal of a "wedge" of parenchymal with tumor near the pleural surface. Technically, a segmentectomy is an anatomic resection of a bronchopulmonary segment; however, hilar dissection is not usually required. Both of these lesser operations require division of the lung parenchyma across shared lobar vasculature, lymphatics and bronchi, theoretically increasing the risk of local recurrence. Multiple single institution nonrandomized studies were performed in the 1980s and 1990s that suggested that there was a substantial risk of recurrence (14 to 23%) of early stage NSCLC when a wedge or segmental resection was performed.[27–31] A large retrospective study was published in 1995 evaluating subanatomic resections (n = 61) and full anatomic resection (n = 511) in patients with stage I NSCLC.[32] In this study, patients with lesser resections demonstrated a 5- and 10-year survival of 59% and 35%, as compared to 77% and 79% in those undergoing full anatomic resection.[32] Finally, a prospective, randomized controlled trial was completed by the Lung Cancer Study Group and reported in 1995.[33] In this study, 250 patients were allocated to either approach. The authors determined that the lung cancer recurrence rate was 75% greater in the limited resection due to a tripling of local tumor recurrence, and that there was a 50% increase in death with cancer.[33]

In the case of patients with adequate pulmonary function undergoing thoracotomy but not anatomic parenchymal resection, sublobar pulmonary resection may be an alternative in stage I NSCLC. Operative mortality in this setting has been reported to be $< 5\%$, and overall survival when compared to anatomic resection is approximately 10% lower.[27–31]

Recommendations

8. Patients with stage I NSCLC who are medically fit for conventional surgical resection should undergo lobar or greater resection (lobectomy, pneumonectomy) rather than sublobar (wedge or bronchopulmonary segment) resections. Level of evidence, good; benefit, substantial; grade of recommendation, A
9. Patients with stage I (IA and IB) NSCLC who may tolerate operative intervention but not a lobar or greater lung resection due to comorbid disease or compromised pulmonary function should undergo sublobar (wedge or bronchopulmonary segment) resection. Level of evidence, poor; benefit, substantial; grade of recommendation, C

What Is the Evidence To Support Either Conventional Thoracotomy or Minimally Invasive Approaches to Anatomic Resection for Stage I NSCLC?

The use of thoracoscopic or minimally invasive sublobar resection for NSCLC would not be anticipated to have any better outcome than those discussed earlier via open thoracotomy. In recent years, a number of investigators have compared the use of thoracoscopic or minimally invasive anatomic resection to that of standard open thoracotomy. Although a large number of trials have been published, the majority are retrospective in nature.[34–39] There is a prevalent suggestion of an improvement in postoperative pain, but this has not been durable in all studies. In addition, minimally invasive techniques have not always been evaluated against comparatively "less invasive" (*ie*, small incision or muscle-sparing) conventional surgical procedures. The short and intermediate survival do not appear to be different than with open procedures. However, it is reasonable to consider that without a large prospective randomized study, survival cannot be assessed without significant bias, and that even postoperative pain assessment can be biased without the benefit of blinding of investigators and/or patients.

Recommendation

10. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the use of video-assisted surgical techniques for lobar or greater NSCLC resection may be associated with less postoperative pain; however, there are insufficient data at this time to recommend this type of procedure as an alternative to conventional techniques. Level of evidence, poor; benefit, small/weak; grade of recommendation, I

What Is the Evidence To Support Nodal Dissection in Patients With Stage I NSCLC Rather Than Other Approaches for Evaluation of Involvement of Mediastinal Lymph Nodes?

The issues to consider in regard to mediastinal lymph node evaluation at the time of anatomic resection are the differential benefit to definitive staging and survival and the potential associated morbidity. The options for mediastinal lymph node evaluation are many, and include no mediastinal lymph node dissection whatsoever, mediastinal lymph node sampling, conventional mediastinal lymph node dissection (systematic sampling) and radical *en bloc* resection of mediastinal lymph nodes and surrounding mediastinal fat and other structures.

The question of morbidity has not been carefully assessed; however, in a retrospective analysis of systematic nodal dissection vs nodal sampling, no differences in operative time or blood loss were noted.[40] Likewise, no significant differences in morbidity were noted when radical *en bloc* nodal dissection was compared to conventional lymph node dissection.[41] The theoretical survival benefit of mediastinal lymph node dissection in patients who by definition have no positive nodes at pathologic examination is not intuitive. In regard to the relationship of survival to method of mediastinal nodal evaluation for all comers with the disease, the results are conflicting. One report has demonstrated a survival difference for patients with stage II and III NSCLC undergoing a conventional dissection rather than sampling, but no data exist in this regard for stage I disease, and this was a nonrandomized report.[40] A similar dilemma arises in the stage I grouping in regard to staging benefit from mediastinal nodal dissection if one considers pathologic stage only. However, it is pertinent to note that many patients are upstaged by surgery, and that in a study evaluating retrospectively the use of sampling vs systematic dissection that more positive nodal stations were identified.[40] A number of authors claim that no nodal dissection whatsoever should be undertaken in patients with small peripheral tumors, or that a sampling at most should be performed. These investigators demonstrate similar survival in stage I NSCLC with these characteristics with or without full nodal dissection.[42,43] However, this is countered by numerous studies demonstrating the inability of clinical evaluation, regardless of stage, to accurately predict mediastinal nodal involvement.[17,40,44] Randomized trials evaluating these questions in stage I disease do not exist. Interestingly, a number of investigators are evaluating the use of "sentinel" lymph node sampling of mediastinal nodal stations in an effort to obviate the need for systematic dissection, but this is an investigational tool at best at this time.[45,46] Finally, the advent of more sensitive and specific nonoperative staging modalities, such as positron emission tomography and other newer imaging approaches, may render mediastinal lymph node dissection unnecessary as a staging endeavor in the near future.

Recommendations

11. All patients undergoing resection for stage I NSCLC (IA and IB) should have intraoperative systematic surgical mediastinal lymph node evaluation for accurate pathologic staging. Level of evidence, fair; benefit, substantial; grade of recommendation, B

Treatment of Nonoperative Candidates With Stage I NSCLC

What Is the Evidence To Support the Use of Radiation Therapy as the Primary Treatment Modality in Patients With Stage I NSCLC Who Are Unable Medically or Unwilling To Undergo a Surgical Procedure?

Although anatomic resection is the preferred local treatment modality for stage I NSCLC, a subset of patients either refuse or are medically unfit for surgical treatment. These patients may also benefit from some form of local control modality—such as definitive radiation therapy or subanatomic resection as outlined in the previous section. A number of studies have evaluated the use of radiation therapy in this cohort, with survival averaging approximately 30% at 5 years.[17–19] A recent meta-analysis was performed to evaluate this paradigm. Utilizing criteria that required patients to receive > 40 Gy in 20 fractions over 4 weeks or its radiobiological equivalent, 1 randomized trial and 35 nonrandomized trials were identified.[47] The cancer-specific survival was 13 to 39% at 5 years in the studies evaluated, and overall survival at 2 years with continuous hyperfractionated accelerated radiotherapy (37%) was superior to 60 Gy over 6 weeks (24%). Although supporting radiation therapy over best supportive care, one criticism of the literature put forth by the authors is a lack of randomized trials, and trials comparing palliative vs immediate curative intent radical irradiation.

Newer advances in radiation therapy, such as three-dimensional conformal techniques and intensity-modulated radiation therapy stereotactic-guided proton beam promise to improve these results in the short term, as well as the use of combination therapies with biological modifiers of radiation cellular response.[20,21,48] The reader is urged to follow the literature carefully.

Recommendation

12. Patients with stage I NSCLC deemed medically unable to tolerate operative intervention or refusing surgical resection and having no medical contraindication to radiation therapy should receive this modality as definitive treatment. Level of evidence, fair; benefit, substantial; grade of recommendation, B

In addition to the articles referred to in the text of this chapter, several preexisting lung cancer treatment guidelines were utilized as reference material in the creation of these recommendations.[45–48]

Summary Statement

In most patients, stage I NSCLC is readily treatable, and favorable outcomes are possible. There are good data to support the treatment recommendations put forth in this chapter, and following these recommendations is likely to make the treatment of patients with this stage grouping of NSCLC more efficient as well as efficacious.

Summary of Recommendations

1. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, surgery alone is the preferred treatment modality. Level of evidence, fair; benefit, substantial; grade of recommendation, B
2. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, a complete surgical resection (clear surgical margins) is to be achieved, if possible in all cases. Level of evidence, good; benefit, substantial; grade of recommendation, A
3. All patients considered surgical candidates should be evaluated for surgical resection by surgeons trained and board certified or board eligible in thoracic surgery. Level of evidence, good; benefit, substantial; grade of recommendation, A
4. Patients with positive resection margins should be evaluated for additional local treatment modalities (surgical re-resection or radiation therapy). Level of evidence, fair; benefit, moderate; grade of recommendation, B
5. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the use of neoadjuvant chemotherapy has been shown to be feasible, but is not recommended outside the setting of a clinical trial. Level of evidence, poor; benefit, small/weak; grade of recommendation, I
6. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the use of adjuvant chemotherapy is not recommended outside the setting of a clinical trial. Level of evidence, fair; benefit, none/negative; grade of recommendation, D
7. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the routine use of neoadjuvant or adjuvant radiation therapy should not be performed. Level of evidence, good; benefit, none/negative; grade of recommendation, D

8. Patients with stage I NSCLC who are medically fit for conventional surgical resection should undergo lobar or greater resection (lobectomy, pneumonectomy) rather than sublobar (wedge or bronchopulmonary segment) resections. Level of evidence, good; benefit, substantial; grade of recommendation, A
9. Patients with stage I (IA and IB) NSCLC who may tolerate operative intervention but not a lobar or greater lung resection due to comorbid disease or compromised pulmonary function should undergo sublobar (wedge or bronchopulmonary segment) resection. Level of evidence, poor; benefit, substantial; grade of recommendation, C
10. For patients with clinical stage I (IA and IB) NSCLC and no medical contraindication to operative intervention, the use of video-assisted surgical techniques for lobar or greater NSCLC resection may be associated with less postoperative pain; however, there are insufficient data at this time to recommend this type of procedure as an alternative to conventional techniques. Level of evidence, poor; benefit, small/weak; grade of recommendation, I
11. All patients undergoing resection for stage I NSCLC (IA and IB) should have intraoperative systematic surgical mediastinal lymph node evaluation for accurate pathologic staging. Level of evidence, fair; benefit, substantial; grade of recommendation, B
12. Patients with stage I NSCLC deemed medically unable to tolerate operative intervention or refusing surgical resection and having no medical contraindication to radiation therapy should receive this modality as definitive treatment. Level of evidence, fair; benefit, substantial; grade of recommendation, B

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