Non-small Cell Lung Cancer*

Role of Surgery for Stages I-III

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Survival following surgical resection of non-small cell lung cancer (NSCLC) has improved since the 1960s, although the 5-year survival rate remains low. This article provides an overview of the role of surgery for NSCLC stages I-III, with a focus on optimizing long-term survival in those patients with resectable disease. Topics explored include diagnosis and staging, indications for resection, types of resection, and indications for adjuvant therapy. A review of the literature indicates a clear survival advantage for complete resection, and is suggestive of an advantage for mediastinal lymph node dissection (vs lymph node sampling) and neoadjuvant therapy (vs adjuvant therapy).

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Abbreviations: FDG = 2-[fluorine-18]fluoro-2-deoxy-D-glucose; NSCLC = non-small cell lung cancer; PET = positron emission tomography

In the past 40 years, there have been no major advances that significantly modified overall survival for resectable, non-small cell lung cancer (NSCLC). The reported cumulative 5-year survival for patients with primary lung cancer managed by resection has increased from 23% in 19601 to about 54% by 1990.2 However, this increase is not due to improved surgical technique, but to more accurate preoperative evaluation and selection of patients with completely resectable tumors. A considerable reduction in operative mortality has also been observed since the 1960s, when mortality varied from 10 to 25% for pulmonary resection.3 These rates decreased to approximately 4% in the early 1980s4 and slightly over 1% in 1994.4 Despite these improvements, lung cancer continues to be an extremely lethal disease, responsible for more cancer deaths than any other solid tumor.5 Resection remains the best treatment option for patients with localized NSCLC. Unfortunately, up to 70% of patients have disease that is too advanced for resection,6 highlighting the need for early diagnosis. The purpose of this article is to provide an overview of the role of surgery for NSCLC stages I-III, with a focus on optimizing long-term survival in those patients with completely resectable disease.

DIAGNOSIS AND STAGING

Accurate diagnosis and histologic classification are made with the assistance of imaging techniques (including CT, MRI, positron emission tomography [PET], and bone scans), sputum cytology, needle biopsy, bronchoscopy, thoracoscopy, mediastinoscopy, bone marrow biopsy, and blood tests. Video-assisted thoracoscopic surgery is also becoming popular due to demonstrated diagnostic accuracy and the ability of the surgeon to visualize the entire lung, pleura, and mediastinum.

In 1997, the International Staging System for Lung Cancer was revised (Table 1)7 to address the heterogeneity of end results within stage groups and the lack of specificity in stage classification. Changes from the previous system include the division of stage I into two categories (IA and IB) based on tumor size, and the division of stage II into two categories (IIA and IIB) based on tumor size and nodal status. The category T3N0 has been moved from stage IIIA to stage IIB. Satellite tumor nodules in the same lobe as the primary tumor are now classified as T4, and separate metastatic tumor nodules in the ipsilateral, nonprimary tumor lobe are classified as M1.

Until recently, the accurate evaluation of nodal status has warranted wide application of invasive staging with mediastinoscopy, or a variant of this procedure. In the 1980s, CT came into use as a noninvasive method for mediastinal staging. However, the disappointing false-positive and false-negative rates associated with CT (approximately 50%5 and 20%,9 respectively) have resulted in the continued search for a more accurate noninvasive procedure. Investigators conducting nodal staging studies using PET scanning with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) have reported encouraging results, with FDG PET proving significantly more accurate than CT in the demonstration and staging of nodal involvement.10,11 These investigators reported correct diagnosis and staging with PET in 94% and 96% of cases, respectively, compared to 61% and 79% of cases evaluated by CT. Vansteenkiste et al12 evaluated the accuracy of FDG PET, visually correlated with CT in nodal staging, and concluded that a “negative mediastinum” on PET scan reduces the need for mediastinoscopy. The role of single-photon emission CT in the assessment of mediastinal involvement has also been evaluated, with results suggesting that single-photon emission CT is more accurate than CT13,14 but somewhat less accurate than PET15 in the detection of lymph node metastases.

Intraoperative Staging

Accurate and deliberate intraoperative staging with evaluation of lymph nodes is essential. The need for the precise assessment of lymph nodes cannot be overesti-

Table 1—Revised International Staging System for Lung Cancer*

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0 or T3N0M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-3N2M0 or T3N1M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4 any N M0 or any T N3M0</td>
</tr>
<tr>
<td>IV</td>
<td>any T any N M1</td>
</tr>
</tbody>
</table>

*TNM = tumor-node-metastasis; data from Mountain.7
mated, because the presence or absence of N2 disease profoundly affects both survival and the selection of patients for resection. The role of mediastinal lymph node dissection at the time of primary tumor resection is controversial. Although no survival advantage for dissection has been conclusively demonstrated, dissection is recommended over sampling, because it should increase the chance for a complete resection with minimal associated morbidity and add little operative time (approximately 20 to 30 min) to surgery.18–20

**INDICATIONS FOR RESECTION**

The goal of surgery in NSCLC is to provide complete resection of the primary tumor with no macroscopic tumor remaining and microscopically free margins. Only patients in whom a complete resection is anticipated are selected for surgery. These include patients with T1 to T4, N0 and N1 tumors and selected N2 cases. Multiple primary lung cancers can be resected with a reasonable prospect of survival if the tumors appear completely resectable. Survival following metastachonous cancer resection has been found to be higher than that following synchronous resection, with two studies reporting 5-year survivals of 20% and 37% in the former group and 0% in the latter group.21,22

In patients with hematogenous metastases, resection of metastases to the brain and adrenal gland can, in selected cases, result in significant survival benefit.23–26 The median survival of untreated brain metastasis is only one to two months.27 A review of > 230 patients who underwent surgical treatment for brain metastases from lung cancer reported survival rates of 46.3% and 14.7% at 1 year and 3 years, respectively, with a predicted 5-year survival rate of 12.5%.24 In a randomized study of 48 patients with solitary brain metastasis, surgery plus radiotherapy resulted in significantly better local control and longer survival than radiotherapy alone.25 In patients with clinically isolated adrenal metastasis, surgical treatment was associated with a 5-year survival rate of 24%.26 A significant advantage has been observed with the combination of surgery and chemotherapy compared to chemotherapy alone in patients with adrenal metastases.25

**TYPES OF RESECTION**

**Limited Resection**

Standard resections for primary lung cancer are pneumonectomy, lobectomy, and sleeve lobectomy in selected cases. Lesser or limited operations include wedge resection, segmental resection, nonanatomic limited resection, and sleeve lobectomy. Advantages for these lesser resections include preservation of pulmonary function, decreased perioperative mortality and morbidity, and the potential for future further pulmonary resection, if necessary. In patients with equivocal levels of pulmonary reserve, these advantages must be weighed against the potential for increased local recurrence and decreased survival.

It is generally accepted that sleeve lobectomy is an appropriate alternative to pneumonectomy in well-selected cases; survival data appear similar, although well-conducted randomized trials have yet to be reported.28,29

In 1982, the Lung Cancer Study Group initiated a randomized trial comparing limited resection (segmental or wedge) with standard lobectomy or pneumonectomy in patients with T1, N0 primary lung cancer. The results showed an unacceptably high local recurrence rate in patients managed by lesser resection.30 In addition, slightly less-favorable survival data were reported for the limited-resection group. These observations were recently confirmed by Landreneau et al, who reported a trend toward increased local recurrence and decreased survival in patients managed by wedge resection compared to lobectomy, using limited-access, video-assisted techniques for resection.

**Extended Resection**

Locally advanced lung cancer (stage IIIA) has a considerably less-favorable prognosis than earlier stages. If a complete resection is judged possible, two groups of patients with stage IIIA disease are potential surgical candidates: those with T3 tumors (primary tumors with direct extension beyond the lung into adjacent structures), and carefully selected cases with primary tumors with ipsilateral N2 involvement (ipsilateral mediastinal lymph node metastases).3 In patients whose tumors are completely resected, worthwhile survival may be obtained. Importantly, there is no alternative form of treatment that provides comparable results at this time.

**T3 Tumors:** If the primary tumor is locally advanced, radical surgery is recommended if the lesion is judged amenable to complete resection. Such resections include the main carina, chest wall, diaphragm, pericardium, lower roots of the brachial plexus in superior sulcus tumors, and the superior vena cava (in selected instances). Dartevelle et al described a technique for segmental resection of the superior vena cava with graft replacement in a small number of patients with primary lung cancer. Unfortunately, most cases of vena cava obstruction are due to metastatic disease in mediastinal nodes and are almost certainly incurable by such radical surgery. Graft replacement should only be considered when involvement is due to extension from the primary tumor itself. Favorable survival is reported following extended resection of the chest wall in cases without lymph node involvement. An actuarial 5-year survival rate of up to 54% has been found in patients undergoing chest wall resection for N0 disease.31,32 N1, and particularly N2, status in such patients confers a much less favorable outcome. The role of adjuvant radiotherapy in patients undergoing chest wall resection remains uncertain.33,34

Superior sulcus tumors are rare, accounting for 5% of all lung cancers.35 Treatment commonly includes preoperative brachytherapy and postoperative radiation. Most surgeons consider superior sulcus tumors with N2 disease to be inoperable. Dartevelle et al reported the innovation of an anterior approach for the resection of some superior sulcus tumors in 1993. Overall 5-year
survival of patients who underwent resection and radiation was 33% in one recent study.39 Optimal 5-year survival (60%) has been reported following combined lobectomy and en bloc chest wall resection.40

N2 Disease: Surgery in patients with N2 disease remains controversial, and the importance of selection in this setting cannot be overemphasized. The most carefully staged patients reported to date were those entered into the Lung Cancer Study Group trials between 1977 and 1989. In 1987, Mountain et al41 reported survival in this group of patients with N2 disease. All of these patients were completely resected using the criteria established by the Lung Cancer Study Group. In 37 patients with completely resected N2 squamous cell cancer and in 38 patients with completely resected N2 adenocarcinoma or large cell tumors, cumulative 5-year survival rates of 46% and 24% were reported, respectively.

The current criteria for operability in N2 disease includes non-small cell histology, ipsilateral metastases, and complete resectability anticipated by the surgeon. The involved nodes should be discrete, and not adherent to the trachea, subcarinal airway, or great vessels. If the most proximal nodal stations in the superior mediastinum (usually level 2) are involved, most surgeons consider the patient to be inoperable.1 En bloc lymphadenectomy is recommended, and the majority of practitioners add some form of adjuvant therapy in these locally advanced cases.

Although N3 tumors preclude a complete and potentially curative resection using standard techniques, Hata et al42 reported long-term survival in some patients with primary tumors of the left lung and nodal metastases on both sides of the superior mediastinum who underwent a mediasternotomy, left pneumonectomy, and bilateral radical lymphadenectomy. All patients received some form of adjuvant therapy. Since this report, other Japanese centers have adopted this approach, although most surgeons still consider this method of uncertain value.

INDICATIONS FOR ADJUVANT THERAPY

The current status of adjuvant and neoadjuvant trials in NSCLC were recently reviewed by Einhorn,43 who concluded that no survival benefit is observed following postoperative adjuvant radiotherapy, chemotherapy, or chemoradiation. At present, there is no clear indication for adjuvant therapy in surgically resected cases other than in the context of a clinical trial. In contrast, three studies have demonstrated improved survival following neoadjuvant therapy,44-46 although the case numbers are quite small (ie, a maximum of 30 patients per treatment arm). Never, more effective agents may provide hope for the future of chemotherapy in this setting.

SUMMARY

For patients with lung cancer, surgical resection provides the best possibility of cure in selected patients. It is again emphasized that surgical resection is only applicable for patients in whom a complete resection is deemed possible. Accurate diagnosis and staging maximizes this potential. Comprehensive evaluation of nodal status is imperative. Extended resection can be effective in locally advanced disease, with worthwhile survival possible in patients whose tumors are completely resected. To date, adjuvant therapy confers no significant survival benefit. At present, neoadjuvant therapy holds some promise in the quest for improved survival following surgical resection in patients with NSCLC.