Diagnosis and Treatment of Early-Stage Non-Small Cell Lung Cancer

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ABSTRACT

Current recommendations for the diagnostic workup and treatment of early-stage non-small cell lung cancer are presented, and the rationale behind these recommendations is reviewed. Early-stage disease is found in approximately 30% of patients at initial presentation. Surgeons continue to be uncertain with regard to how extensively they should look for metastatic disease, especially in asymptomatic patients with newly diagnosed lung cancer. While it is generally agreed that surgery is an important component of treatment for stage I and II non-small cell lung cancer, the role of adjuvant therapies in early-stage disease merits further study. Stage IIIa lung cancer is evolving as a disease for which multimodality therapy is likely to play a role, but the timing and sequence of treatment is an area of intense investigation. The recommendations made in this article are based upon the results of randomized clinical trials whenever possible. The Oncologist 1996;1:201-209

INTRODUCTION

In 1995, approximately 170,000 new cases of lung cancer were diagnosed in the United States; non-small cell lung cancer (NSCLC) represents approximately 75%-80% of these cases [1]. When diagnosed, only 30% of patients are found to have early-stage disease (stage I or II), while another 15%-20% are found to have more advanced locoregional disease (stage IIIa). It is these groups of patients who have been found to benefit from surgery as either the only treatment modality or as part of a multimodality approach to their disease. This paper will review the currently accepted approach to the diagnosis and treatment of early-stage NSCLC.

DIAGNOSIS – GENERAL

History and Physical Exam

The history and physical examination direct further diagnostic testing, the aim of which is to stage the lung cancer as accurately as possible. Presenting symptoms in a review of 7,539 lung cancer patients included cough (45%-75%), weight loss (8%-68%), dyspnea (37%-58%), hemoptysis (27%-57%), chest pain (27%-49%), and hoarseness (2%-18%) [2]. Local symptoms are found more commonly with squamous cell lung cancers, whereas large-cell carcinomas and adenocarcinomas more commonly cause symptoms due to distant metastasis and are more often responsible for symptoms related to paraneoplastic syndromes. The presence of symptoms portends a less-favorable prognosis. Shimizu reported five-year survival to be 25% for symptomatic patients with lung cancer, compared to 56% for asymptomatic patients [3].

Despite efforts to rule out distant disease in patients offered surgery with curative intent, distant metastatic disease goes unrecognized in a significant number. In one series of 103 patients who died in the perioperative period after lung resection, autopsy found 19 (18%) to have asymptomatic distant metastatic disease [4]. Furthermore, the Lung Cancer Study Group (LCSG) has reported that following complete resection of stage I NSCLC, over 60% of patients first recur at either distant site(s) alone or in combination with locoregional recurrence and that most of the recurrences were within two years of lung resection [5].

DIAGNOSIS – LOCOREGIONAL DISEASE

Chest Roentgenogram

Plain chest roentgenograms rarely detect a tumor <1 cm in diameter. Once a tumor is identified, however, the workup of either a solitary pulmonary nodule (SPN) (<4 cm) or
mass (>4 cm) presumed to be a lung cancer is aimed at determining its clinical stage. It is only after clinical staging has been completed that decisions regarding treatment can be made.

A solitary pulmonary nodule, often referred to as a “coin lesion,” is a single asymptomatic ovoid or rounded lesion seen on chest x-ray. The maximum size implied by the term SPN is 4 cm. It should be surrounded by normal lung parenchyma without evidence of pneumonia, atelectasis, or adenopathy. The immediate challenge is to determine whether it is benign or malignant, and whether to observe it or remove it.

The incidence of malignancy in surgical series of SPNs is between 30% and 50% [6]. When evaluating an SPN, information regarding the patient’s age, history of smoking, previous cancer, recent or remote pulmonary infection, including exposure to tuberculosis or asbestos, as well as residency in an area endemic for histoplasmosis or coccidiomycosis, should be obtained. All available prior chest x-rays should be carefully reviewed for comparison. If there has been no change in the lesion for one or more years, observation at three- to six-month intervals for two years and yearly thereafter is warranted. If the lesion has grown, an estimate of the doubling time can be made. Extremely long and short doubling times suggest benign disease, whereas most malignant nodules or masses have an estimated doubling time between 40 and 280 days [7]. If the lesion is considered indeterminate, a tissue diagnosis should be pursued.

Chest Computed Tomography

The clinical stage of a tumor is determined by assessment of its size, the presence or absence of hilar or mediastinal lymphadenopathy or satellite lesion(s), as well as the likelihood that the tumor has invaded contiguous structures (chest wall, vertebral body, diaphragm, great vessels, etc.). The best means of ascertaining many of these tumor characteristics is by performing a contrast-enhanced chest CT scan. A chest radiologist who is cognizant that lung cancer is suspected will not only recommend intravenous contrast administration for optimal assessment of the mediastinum in this setting, but also will scan through the upper abdomen to obtain images of the liver and adrenal glands. In addition, if there is any suggestion of thoracic bone metastasis, bone windows can be generated to better assess the suspicious region(s), and plain films of the area can be obtained for comparison.

Few computed tomographic features provide assurance that an SPN is benign. Certain patterns of calcification, specifically a central nidus or a laminated onion-skin pattern of calcification on plain radiograph or on high-resolution CT scan are, except in rare circumstances, reliable for benignancy. A popcorn style of calcification is pathognomonic of hamartoma. Lesions meeting the above criteria may be observed with interval chest radiographs. Other patterns of calcification are of little use in determining the benign or malignant nature of a lesion.

A number of authors have recommended using CT density criteria to aid in the determination of the benign or malignant nature of a lesion. Benign nodules with their associated microcalcifications have higher densities. Zerhouni and associates have suggested the use of a phantom reference nodule for comparison. After thin sections are taken through the nodule, a printout is compared to a reference phantom nodule of 185 Hounsfield units. If the nodule is as dense or denser than the phantom, it is considered benign and is observed [8]. The validity of such an approach is supported by Ward who, using the phantom reference, determined that 20 nodules were benign when only one had had standard plain radiographic evidence of its benign nature [9]. Swensen, however, noted that 10/85 nodules initially deemed benign by the criteria outlined by Zerhouni proved to be malignant on subsequent follow-up [10]. Caution is urged, therefore, in the use of CT density measurements alone to rule out malignancy.

Other CT characteristics such as the absence or presence of margin spiculation, air bronchograms within lesions, nonhomogeneous attenuation, and lobulation have proved to be unreliable determinants of the benign or malignant nature of a nodule.

Tissue Diagnosis

While a tissue diagnosis is not always required prior to proceeding to thoracotomy, when the suspicion of malignancy is high, there are four commonly accepted methods of obtaining one. Sputum cytology; bronchoscopy with washings, brushings, and biopsies; transthoracic needle aspiration biopsy (TNAB); and excisional biopsy may all play a role in selected cases when a tissue diagnosis is required.

Early-morning sputum samples should be obtained and assessed for the presence of malignant cells as well as infectious organisms, if the situation dictates. Sputum cytology has a low diagnostic yield. Ten to twenty percent of malignant lesions are associated with positive cytology. Sputum cytology is positive most often with squamous cell carcinoma, owing to its tendency to be centrally located and to produce endobronchial disease. Sputum cytology contributes little to the diagnosis of malignancies of histology other than squamous cell [11].

Bronchoscopy with washings, brushings, and endobronchial or transbronchial biopsies can establish the diagnosis in up to one-third of patients with lung cancer. The
yield increases in proportion to the size and proximity of the lesion to a central airway (so-called "positive bronchus sign") and in proportion to the ability to directly visualize an endobronchial lesion [12]. Bronchoscopy is also useful for determining the resectability of central lesions and for defining tracheobronchial anatomy.

Transthoracic needle aspiration biopsy is a direct and simple procedure which, when properly performed, may establish the diagnosis of a pulmonary nodule. Khouri obtained a malignant diagnosis by TNAB in 449/486 (92%) surgically confirmed cases of malignancy and a specific benign diagnosis in 93/137 (68%) surgically confirmed benign diagnoses [13]. These results have been difficult to duplicate and were only achieved by close collaboration between interventional radiologists and experienced cytopathologists, along with the routine use of needles able to provide core tissue samples, and CT or preferably fluoroscopic-directed biopsies. In this series, approximately 12% of patients required a repeat TNAB. Complications included a 10%-20% incidence of pneumothorax (of which about one-half required chest-tube placement and one-half observation only) and a 10% incidence of hemoptysis. Needle tract seeding by carcinoma is a recognized but exceedingly uncommon complication. Contraindications to its use include uncorrectable coagulopathy, pulmonary hypertension, and inability of the patient to cooperate. Emphysema is a relative contraindication. The major drawback of TNAB is its limited ability to diagnose benign disease.

Our approach is to reserve TNAB for patients with either indeterminate nodules or suspicious nodules who are medically unable or unwilling to undergo resection without prior tissue diagnosis. Unless TNAB is able to render a definitive benign diagnosis, patients with indeterminate nodules are likely to require thoracoscopy or limited thoracotomy and resection for diagnosis and definitive management.

Thoracotomy with excisional biopsy is the gold standard for the determination of the nature of an SPN. Traditionally, this has involved either a limited, muscle-sparing or standard thoracotomy with complete excision of the nodule, a two- to five-day hospitalization, and the discomfort and morbidity of a thoracotomy incision. More recently, video-assisted thoroscopic surgery (VATS) has modified our approach in many patients [14]. Small (<3 cm) peripheral lesions may be removed with VATS. If the nodules or lesions are benign, patients are generally discharged within 24 hours of the procedure. It is still standard practice to proceed directly to thoracotomy for definitive treatment of a lung cancer diagnosed by VATS. Deep-seated lesions may be amenable to localization with percutaneous hooked wires with or without injection of methylene blue and then removal by VATS [15, 16]. It is recommended that all specimens be removed from the chest cavity in a plastic pouch, as there have been at least 20 reports of tumor implantation in port tracts by unprotected specimens.

In the uncommon instance when a nodule cannot be accessed or completely removed by a wedge resection, or when core-needle biopsy at the time of thoracotomy fails to provide a definitive diagnosis, segmentectomy or lobectomy is an acceptable procedure.

**Mediastinoscopy/Anterior Mediastinotomy**

There is wide variation in the extent to which surgeons use mediastinoscopy and anterior mediastinotomy (Chamberlain procedure) to stage patients with lung cancer. While most use it only when pathological mediastinal lymphadenopathy (lymph node >1 cm in shortest transverse axis) is present on chest CT scan, others use it on virtually every patient. A meta-analysis of 42 studies examining the ability of CT to detect pathologically enlarged mediastinal nodes reported an overall sensitivity of 0.79 and a specificity of 0.78 [17]. In single studies, its sensitivity has been reported to be lower for adenocarcinoma (61%) compared to squamous cell carcinoma (86%), whereas the specificity is the same (93%-94%) [18]. The explanation offered is that adenocarcinoma produces microscopic metastasis without nodal enlargement more often than other cell types. Mediastinoscopy, on the other hand, has a sensitivity of 87% and a specificity of 100%. In addition, its positive predictive value is 100%, negative predictive value is 93%, and overall accuracy is 95% [19].

In an effort to better define the role of mediastinoscopy in staging lung cancer, the Canadian Lung Oncology Group recently completed a randomized trial of mediastinoscopy following a positive chest CT (one which demonstrated lymphadenopathy >1 cm in shortest transverse axis) versus mediastinoscopy alone in 685 patients. The primary endpoint was thoracotomy without cure. They found that the chest CT strategy was likely to produce the same or fewer unnecessary thoracotomies than doing a mediastinoscopy on all patients, and that it was likely to be as or less expensive [20].

Based upon the best evidence published to date, mediastinoscopy should be performed on all patients with clinically operable lung cancer whose chest CT scan demonstrates pathologically enlarged (>1 cm) mediastinal lymph nodes. In addition, it should be considered for patients in whom thoracotomy poses more than the usual risks.
DIAGNOSIS — METASTATIC DISEASE

The optimal way to investigate a patient for metastatic disease was the subject of a recently completed phase III trial by the Canadian Lung Oncology Group. The trial, entitled “Investigation of Metastatic Disease in Operable Lung Cancer,” randomized patients with suspected lung cancer to an evaluation for metastatic disease based upon their history, physical examination, and the results of routine blood tests versus a complete evaluation for metastatic disease regardless of signs, symptoms, or blood test results. This trial accrued 634 patients between January 1, 1992, and September 30, 1995, 318 of whom had a complete evaluation and 316 of whom had a minimal evaluation. Final follow-up will be completed in September, 1996, and the results will be reported in early 1997.

Current recommendations for the investigation of metastatic disease follow. The decision to perform a work-up for metastatic disease should be based upon symptoms and signs of disease as well as the T status of the lung primary since the propensity of a tumor to disseminate is known to increase with increasing T status.

Bone Scanning

It has been estimated that between 9% and 15% of patients with newly diagnosed NSCLC have bony metastasis at presentation [21, 22]. The vertebral bodies are most commonly affected by metastatic disease. Michel studied the bone scans of 110 patients with newly diagnosed NSCLC. While 37 (34%) scans were positive, only nine patients (8%) had confirmed metastatic disease. In addition, all patients who were proven to have metastatic disease had either pain, tenderness, an elevated alkaline phosphatase level, or an elevated serum calcium level [21]. There is evidence, however, that as many as 14% of patients with bone metastases are asymptomatic, and that between 41% and 90% of positive bone scans in asymptomatic patients are false-positive scans [22]. Because a bone scan costs about $400 to perform and interpret, and an unnecessary thoracotomy may cost as much as $40,000, many negative scans can be performed and still be potentially cost-effective. If a scan-all strategy is adopted, however, asymptomatic patients with a solitary lesion on bone scan will often be required to undergo additional testing (plain films, MRI, bone biopsy) because of the high false-positive rate reported [22]. This will, in turn, decrease the cost-effectiveness of a scan-all strategy.

Algorithms have emerged which recommend that a bone scan be performed in patients who complain of A) bone pain or B) chest pain, or who have C) an elevated serum calcium level, or D) an elevated serum alkaline phosphatase level.

Head Computed Tomographic Scanning

While a head CT scan should be obtained in any patient who complains of the onset of new central nervous system (CNS) symptoms, whether to perform a head CT scan on an asymptomatic lung cancer patient is a more difficult problem to resolve. Routine head CT scanning yields evidence of asymptomatic metastatic disease in 3%-8% of patients [23, 24]. In contrast with bone scans, false-positive results are obtained in fewer than 1% of patients. In 1976, Butler et al. reported that scanning all patients would result in a substantial cost savings [24]. A decision analysis performed by Colice et al. in 1995, however, reported that if every American diagnosed with lung cancer that year (estimated 170,000) had a head CT scan ($500-$700 per scan), the total annual cost would be $100 million [25]. Justification for adopting a strategy to scan all patients versus a strategy of scanning selected patients depends on the negative predictive value of the clinical examination for brain metastasis—that is, how good is a negative CNS examination in ruling out brain metastasis? A meta-analysis indicated that the negative predictive value was at least 0.95 [26]. The marginal cost per quality adjusted year of life expectancy for the scan-all strategy was $70,000. This is an expensive strategy when compared to many other medical interventions considered to be cost-effective; thus the strategy was not endorsed by the authors of the decision analysis [25].

In general, a patient who has no CNS signs or symptoms and who has resectable lung cancer (T1 > T2, T3) does not require a preoperative head CT scan. A possible exception is the patient who is known to have an adenocarcinoma by virtue of a fine-needle aspiration biopsy. The propensity of this tumor to cause asymptomatic brain metastasis is greater than with squamous cell tumors, and such patients might merit a head CT scan regardless of the T status of the primary tumor [26]. Finally, patients who have substantial medical comorbidity in whom surgery poses more than usual risks might benefit from a maximal approach to ruling out metastatic disease, although it should be understood that the yield of these additional investigations will be low.

Adrenal and Hepatic Imaging

Adrenal. NSCLC metastasizes to the adrenal glands in 18%-38% of cases. The widespread availability of computed tomography has disclosed a higher-than-expected incidence of unilateral adrenal masses in the
diagnosis and treatment of early-stage nsclc

general population. Approximately two-thirds of adrenal masses in NSCLC patients are benign adenomas. In two studies of 330 and 246 patients with clinically resectable NSCLC, 7.5% and 4.1%, respectively, were found to have unilateral adrenal masses detected by computed tomography. Only 2.4% and 1.6% of these masses, respectively, were found to be malignant when biopsied [27, 28]. A third study of 546 patients, 124 of whom had lung cancer, found that 22 (4%) had one or more adrenal masses. Seventeen of those patients underwent adrenal biopsy, which revealed metastatic disease in five (29%) and benign disease in 12 (71%). Needle biopsy of the adrenal gland had a 96% accuracy rating in a study of 72 patients [29]. A study of 28 patients with known cancer and adrenal masses used nuclear gamma images after the injection of an iodocholesterol analog (131-I NP-59) to determine benignancy versus malignancy. All 14 of the cases with intense tracer update were confirmed to be adenomas on biopsy, while carcinoma was confirmed in 10/14 of the cases where there was decreased or symmetric uptake of tracer [30]. To date, no noninvasive study has been identified which can replace adrenal biopsy.

Hepatic. A series of 84 patients with potentially operable NSCLC revealed that 5% were found to have liver metastasis [31]. Hepatic hemangiomas and cysts, however, confound the interpretation of CT scans in patients with lung cancer. At least 30% of hepatic hemangiomas have an atypical appearance. A biopsy is indicated when a liver metastasis is suspected.

TREATMENT

Stage I Lobectomy is the surgical treatment of choice for patients with stage I lung cancer. Less often, a bilobectomy or pneumonectomy is required. Lesser resections should be reserved for high-risk patients who would not tolerate lobectomy. These statements are based on evidence from a recently reported LCSG clinical trial. The LCSG completed a multi-institutional randomized trial comparing limited resection (wedge or segmentectomy) to lobectomy in patients with peripheral T1N0 NSCLC which was confirmed by intraoperative hilar and mediastinal lymph node frozen section analysis (LCSG-821). There were 276 patients randomized, 247 of whom were eligible for analysis. Patients in the limited resection group experienced a 75% increase in locoregional recurrence rate (21 versus 8, p = 0.008) and 30% increase in overall death rate (48 versus 38, p = 0.008) compared to patients in the lobectomy group [32]. While the study demonstrated an early difference in pulmonary function in favor of the limited resection group, this did not translate into lower morbidity or operative mortality for the group, and the difference was no longer significant at one year.

Patients who have T1N0M0 lesions but who are considered of high operative risk due to cardiac or pulmonary dysfunction may be eligible for a feasibility study developed by the Cancer and Leukemia Group B (CALGB) entitled, “Video-Assisted Wedge Resection (VAR) and Radiotherapy for High-Risk T1 NSCLC: A Phase II Study” [33]. The primary objective is to determine the feasibility of this as-yet-unproved approach (limited resection and local adjuvant radiation therapy) in the treatment of patients with T1N0M0 NSCLC. Secondary objectives include the determination of local recurrence rates, patterns of survival and disease-free survival, the feasibility of ipsilateral thoracoscopic lymph node sampling, the conversion rate to thoracotomy, the operative complication rate, and radiation toxicity. This study was recently opened to the Thoracic Intergroup, which includes the Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group, and Southwestern Oncology Group. It has accrued eight of a projected 60 patients to date.

While the five-year survival rate following complete resection of T1N0M0 NSCLC approximates 75%-80%, five-year survival for patients with T2N0M0 tumors is 60% [34-37]. Distant metastatic disease is the first site of recurrence in 65%-75% of patients following complete resection of stage I NSCLC [4]. To date, this high distant failure rate has prompted performance of two randomized studies of adjuvant chemotherapy for resected stage I NSCLC. Both studies employed CAP (cyclophosphamide, doxorubicin, cisplatin) chemotherapy which has inferior activity against NSCLC than newer agents. In addition, both studies were methodologically flawed. In the study by Niiranen et al., only 90% of patients had stage I disease, and the treatment groups were dissimilar in that there was an overabundance of pneumonectomy patients in the control arm [38]. Significantly, only 57% [38] and 53% [39] of the patients, respectively, completed their assigned chemotherapy, most often due to its toxicity. The study by Niiranen et al. suggested improved survival in the chemotherapy group; this was not corroborated by the larger study completed by the LCSG [38, 39]. Because of the high systemic failure rate in patients with early-stage NSCLC and the relative inactivity of adjuvant CAP chemotherapy, clinical trials testing new agents continue to be appropriate. Two such trials are currently being developed by members of the Thoracic Intergroup.
Radiation therapy plays a role in the definitive treatment of stage I NSCLC patients who either refuse surgery or who by virtue of medical illness are inoperable. It is recommended that a dose of 65 Gy be delivered to the primary tumor in fractions of 1.8-2.0 Gy per day. A 30% local failure rate has been reported for T1 tumors, which increases to 70% for T2 tumors. Five-year survival has been reported to be between 6% and 42%. The wide variation seen has been attributed to differences in the rigor with which patients were staged as well as to technical differences in the way radiation therapy was delivered. In an effort to improve local control, the use of accelerated fractions, hyperfractionation, and 3-D conformal therapy are new approaches currently being investigated.

The role that retinoids play in the prevention of second primary lung cancers has been the subject of one published [41] and two ongoing randomized clinical trials. Pastorino et al. evaluated the role of retinyl palmitate (Vitamin A, 300,000 IU/day) × 12 months versus no treatment in 307 resected stage I NSCLC patients. While 18 of the patients (12%) taking Vitamin A developed a second primary tumor, which was not significantly different. The incidence of tobacco-related tumors was significantly different between the two groups (13 in Vitamin A-treated patients versus 25 in patients receiving no treatment). The two groups had similar survival rates. These results were explained in part by low event rates and, therefore, low probability of detecting a difference (if any), as well as by the close follow-up which both groups received, enabling prompt treatment of second primary tumors. The Euroscan trial includes 2,000 patients with either head and neck or lung primaries, and randomizes patients to retinyl palmitate, N-acetylcysteine, both, or placebo in a 2 × 2 factorial design. The Thoracic Intergroup trial randomizes 1,260 patients with resected stage I NSCLC to receive 13-cRA versus placebo and follows patients for three years. Both studies are nearing completion, and results are anticipated within 12 to 18 months [42].

Stage II

Ten percent of patients with lung cancer have stage II disease (T1N1M0, T2N1M0). Five-year survival following complete surgical resection of stage II lung cancer is 30%-60% [43, 44]. Because it has been difficult to identify patients who have stage II disease preoperatively, clinical trials have focused on adjuvant therapies for this group of patients. Several trials (only one of which was randomized) [45] have studied the effect of adjuvant radiation therapy in patients after complete resection of stage II and IIIa disease, and most have demonstrated a decrease in the locoregional recurrence rates with this approach. This has not, however, translated into a statistically significant survival benefit for patients so treated [45]. These results are not surprising in view of the fact that, as with stage I disease, most failures with stage II disease are at distant sites [37, 43]. Several combined modality studies have addressed stage II disease, usually in conjunction with stage IIIa disease. An LCSG trial randomized patients with incompletely resected stage II or IIIa NSCLC (either highest mediastinal lymph node positive or positive resection margin) to radiation therapy alone or chemotherapy plus radiation. While median survival and one-year survival were prolonged in the chemotherapy arm (20 versus 15 months and 68% versus 51%), these differences did not reach statistical significance. The number of deaths due to cancer in the first year, however, was significantly lower in the group receiving combined modality therapy (0.309/person versus 0.556/person; p = 0.02) [46]. Other studies have reported similar results, but all were flawed due to low percentages of patients completing their assigned treatments, and they were confounded by the use of different methods of staging patients. The failure to complete assigned treatment regimens emphasizes the difficulty in administering chemotherapy to patients in the postoperative period, especially in combination with radiation therapy. Whether or not this continues to be problematic despite advances in the care of oncology patients awaits the completion of current studies.

At present, an ECOG-based phase III clinical trial is open to the Thoracic Intergroup. It compares the role of adjuvant radiation therapy (50.4 Gy) to concurrent chemotherapy (cisplatinum 60 mg/M2 + etoposide 120 mg/M2 × 4 cycles) plus radiation (50.4 Gy) in completely resected stage II and IIIa NSCLC patients. The study has accrued 375 patients out of a total of 462 to date, and has a projected closing date of April, 1997. Recommendations with respect to the use of platinum-based adjuvant chemotherapy in stage II disease await the results of this trial.

Stage IIIa

Treatment for stage IIIa NSCLC is the most controversial. While most oncologists approach patients with stage IIIa NSCLC with more than one treatment modality, the sequence (neoadjuvant versus adjuvant, concurrent versus sequential) and types of treatment (chemotherapy, radiation therapy, surgery) offered to patients vary widely. There is general agreement that patients with good performance status and weight loss <5% should be offered systemic therapy in addition to a locoregional therapy (radiation or surgery). The overall incidence of distant metastasis has been decreased by at least 15% when chemotherapy is added to locoregional therapy.
The results of randomized trials of radiation therapy alone compared with radiation therapy plus chemotherapy are summarized in Table 1. In trials of appropriate size, combined modality therapy has generally been associated with an improvement in both median and two-year survival. After cisplatin-based chemotherapy alone, approximately 20% of patients are rendered pathologically free of disease. Small sample sizes and the use of nonplatinum-based chemotherapy regimens might explain why some trials have been negative. Locoregional control remains problematic. The role that surgery may play in improving locoregional control is being assessed in an Intergroup trial entitled, “A Phase III Comparison between Concurrent Chemotherapy plus Radiotherapy, and Concurrent Chemotherapy Plus Radiotherapy followed by Surgical Resection for Stage IIIa (N2) Non-Small Cell Lung Cancer.”

The results of randomized trials of induction therapy in patients with stage III NSCLC are summarized in Table 2. Early stopping rules were invoked in two trials because of the survival advantage seen in their induction therapy arms at the time of interim analysis. Both pilot studies and randomized trials have demonstrated resectability rates averaging 60% and operative mortality rates between 0% and 20% in stage III NSCLC patients treated with induction therapies. The results of ongoing trials can be expected to shed substantial light on treatment recommendations for early-stage NSCLC, and are anxiously awaited by thoracic surgeons and oncologists.

### Table 1. Randomized trials of radiotherapy with or without chemotherapy in stage III non-small cell lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>XRT (Gy)</th>
<th>Chemotherapy</th>
<th>Median survival (months)</th>
<th>2-Year survival (%)</th>
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<tbody>
<tr>
<td>Mattson [47]</td>
<td>1988</td>
<td>238</td>
<td>55</td>
<td>–</td>
<td>10.2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55</td>
<td>CAP</td>
<td>10.9</td>
<td>20</td>
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<tr>
<td>Dillman [48]</td>
<td>1990</td>
<td>155</td>
<td>60</td>
<td>–</td>
<td>9.6</td>
<td>13</td>
</tr>
<tr>
<td>Trovo [49]</td>
<td>1990</td>
<td>101</td>
<td>45</td>
<td>–</td>
<td>11.7</td>
<td>–</td>
</tr>
<tr>
<td>Trovo [49]</td>
<td>1990</td>
<td>101</td>
<td>45</td>
<td>CAMPr</td>
<td>10.0</td>
<td>–</td>
</tr>
<tr>
<td>Morton [50]</td>
<td>1991</td>
<td>114</td>
<td>60</td>
<td>–</td>
<td>10.3</td>
<td>16</td>
</tr>
<tr>
<td>Morton [50]</td>
<td>1991</td>
<td>114</td>
<td>60</td>
<td>MACCe</td>
<td>10.4</td>
<td>21</td>
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<tr>
<td>Le Chevalier [51]</td>
<td>1994</td>
<td>353</td>
<td>65</td>
<td>VCPCe</td>
<td>12.0</td>
<td>21</td>
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<tr>
<td>Sause [52]</td>
<td>1994</td>
<td>452</td>
<td>60</td>
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<td>19</td>
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<tr>
<td>Sause [52]</td>
<td>1994</td>
<td>452</td>
<td>60</td>
<td>VlbP</td>
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<td></td>
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<td></td>
<td>69.6</td>
<td>–</td>
<td>12.3</td>
<td>24</td>
</tr>
</tbody>
</table>

C = cyclophosphamide; A = doxorubicin (Adriamycin); P = cisplatin; Vlb = vinblastine; M = methotrexate; Pr = procarbazine; Ce = lomustine; V = vindesine.

### Table 2. Randomized trials of induction therapy and surgery versus surgery alone in stage III non-small cell lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Chemotherapy</th>
<th>Median survival (months)</th>
<th>3-Year survival (%)</th>
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<td>Roth [54]</td>
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<td>60</td>
<td>EP x 2 cycles</td>
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</tr>
<tr>
<td>Rosell [55]</td>
<td>1994</td>
<td>59</td>
<td>–</td>
<td>11.0</td>
<td>15</td>
</tr>
<tr>
<td>Rosell [55]</td>
<td>1994</td>
<td>59</td>
<td>CEP x 6 cycles</td>
<td>64.0</td>
<td>56</td>
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<td></td>
<td>MIP x 3 cycles</td>
<td>8.0</td>
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</tr>
</tbody>
</table>

C = cyclophosphamide; E = etoposide; P = cisplatin; M = mitomycin; I = ifosfamide.
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