Treatment of Stage IIIA Non-small Cell Lung Cancer*

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Stage IIIA non-small cell lung cancer represents a relatively heterogeneous group of patients with metastatic disease to the ipsilateral mediastinal (N2) lymph nodes and also includes T3N1 patients. Presentations of disease range from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky multistation nodal disease. Controversy abounds as to the optimal treatment of the various stage IIIA subsets, which is fueled by a lack of meaningful, large randomized trials. Multimodality therapy of some type appears to be preferable in stage IIIA patients.

(CHEST 2003; 123:202S–220S)

Key words: adjuvant chemotherapy; adjuvant radiotherapy; chemotherapy; guidelines; lung carcinoma; neoadjuvant therapy; non-small cell lung cancer; pulmonary surgical procedures; radiation therapy

Abbreviations: CALGB = Cancer and Leukemia Group B; CAP = cyclophosphamide-doxorubicin-cisplatin; CHART = continuous hyperfractionated accelerated radiation therapy; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; HART = hyperfractionated accelerated radiation therapy; LCSG = Lung Cancer Study Group; MRC = Medical Research Council; NSCLC = non-small cell lung cancer; NSCLCCG = Non-Small Cell Lung Cancer Collaborative Group; PET = positron emission tomography; PS = performance status; SWOG = Southwest Oncology Group; UFT = uracil-tegafur

The evidence-based guidelines that follow are written primarily to provide a succinct synthesis of the medical literature and provide specific treatment guidelines that can serve as a useful tool for the clinician who deals directly with locally advanced non-small cell lung cancer (NSCLC). Exhaustive detail about published trials will be avoided in order to make this a more readable and usable guide. In order to develop the following guidelines for stage IIIA disease, the authors reviewed 15 other published guidelines, 9 meta-analyses, 12 systematic reviews, and 80 primary articles on this topic, focusing on the most well-designed, peer-reviewed reports. Selected key references are included in the bibliography.

Based on the collected series of 5,230 patients with NSCLC seen in the period from 1975 to 1988 at the M.D. Anderson Cancer Center reported by Clifton Mountain in the 1997 revision of lung cancer staging criteria,1 30% of all patients have locally advanced disease at initial presentation. Of those, one third (10% of the total) have stage IIIA with ipsilateral N2 lymph node metastases, which in the United States would then encompass approximately 17,000 new patients yearly. This group forms perhaps the most therapeutically challenging and controversial subset of patients with lung cancer, with a published 5-year survival of only 23%.

This border-zone subset of stage IIIA patients, which lies between the generally resectable stage I and II tumors and unresectable stage IIIB patients, has been the subject of a wide variety of clinical trials incorporating various combinations of chemotherapy, radiotherapy, and surgery. Unfortunately, most published studies have significant limitations since they are not randomized, lack rigorous pretreatment staging, or involve a significant lack of homogeneity in the study population, making interpretation of the results difficult. There are a few more rigorous randomized trials, which will be discussed subsequently, that suggest a combined modality approach may be beneficial in stage IIIA disease. The approach showing the greatest promise in selected patients employs initial treatment (induction or neoadjuvant therapy) with chemotherapy or chemoradiotherapy followed by surgery. Nevertheless, more widespread use of induction therapy followed by surgery for lung cancer has been used for only 7 years, and as a result there is little reliable data with larger patient groups. This lack of meaningful, larger,
randomized data underscores the importance of enrolling patients in clinical trials whenever possible.

Since staging and treatment are so very interdependent, intraoperative staging with systematic mediastinal node sampling or dissection is critically important. Unless histologic confirmation of mediastinal node status is obtained at the time of surgery, postoperative pathologic staging will be inaccurate, as will further treatment recommendations and the discussion of prognosis. Therefore, the standard of care in modern thoracic surgery dictates that mediastinal node sampling or dissection must be performed at the time of every lung resection for lung cancer.

Under the 1997 revised lung cancer staging system,1 stage IIIA encompasses all tumors with ipsilateral mediastinal lymph node metastases (T1–3, N2). Also included in this stage are tumors with resectable chest wall involvement and hilar node metastases (T3N1), added primarily because of similar survival rates. However, the treatment recommendations and applicable clinical trials for T3N1 are the same as for stage II. Therefore, for the purposes of these current guidelines, T3N1 tumors are discussed in the preceding chapter on stage II. Therefore, for the purposes of these current guidelines, T3N1 tumors are discussed in the preceding chapter on stage II tumors. The present chapter will deal only with N2 disease.

Nevertheless, the patients with stage IIIA (N2) tumors present substantial heterogeneity in clinical presentation, treatment, and prognosis. Therefore, for the purposes of generating rational treatment guidelines, we have chosen to classify N2 tumors into four subsets (Table 1), which have been published previously.2 The subsequent discussion of the literature and treatment guidelines will be broken down into these subsets.

PREVIOUSLY PUBLISHED GUIDELINES

In drafting these evidence-based guidelines for stage IIIA NSCLC, the authors not only reviewed the literature of clinical trials and reviews, but also 15 sets of recently published, major lung cancer guidelines were considered.3–15 In general, there were few real differences in the actual recommendations between guidelines in this area of lung cancer. Some of the previously published guidelines were consensus based entirely, while others (such as the current guidelines) followed the evidence-based format. Among the latter group of guidelines, there were only some minor differences, primarily in determining the strength of the evidence supporting the specific recommendations.

TREATMENT OF SPECIFIC PATIENT GROUPS

Incidental N2 Disease (Stage IIIA1–2)

Despite careful preoperative staging including CT scan, positron emission tomography (PET), and mediastinoscopy, some patients will be found to have metastases to mediastinal N2 lymph nodes at thoracotomy. In some, metastatic nodal disease will be found as a surprise a number of days postoperatively on the final pathologic examination of the surgical specimen (stage IIIA1). In others, metastases will be found intraoperatively as an unexpected finding at thoracotomy with a frozen-section pathologic examination of mediastinal nodes (stage IIIA2). Unexpected nodal metastases in this setting are not that unusual. In the pre-PET scan era, one surgical series of 102 patients from the Brompton Hospital in London with no clinical evidence of mediastinal adenopathy at thoracotomy found 24% of patients had pathologically positive nodes.16,19

Surgery: Despite negative preoperative staging studies including mediastinoscopy, as many as one fourth of patients will be found at surgery to have occult N2 metastatic disease.18,19 If only one nodal station is unexpectedly found to be involved with metastatic lung cancer at open thoracotomy, and all of the involved nodes are technically resectable and the primary tumor is also technically resectable, then the surgeon should proceed at that time with the planned lung resection along with a mediastinal lymphadenectomy. If a complete resection is not possible or there is multistation or bulky, unresectable extracapsular nodal disease, then the planned lung resection should be aborted. Although incomplete resection rarely results in long-term survival, collected results of surgery alone in stage IIIA (N2 disease) provides a 14 to 30% 5-year survival, with the best survival seen in cases with minimal N2 disease and complete resection.20–27

At least 27 to 36% of patients with metastatic disease to the mediastinal N2 nodes will not have

<table>
<thead>
<tr>
<th>Subset</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>IIIA1</td>
<td>Incidental nodal metastases found on final pathologic examination of the resection specimen</td>
</tr>
<tr>
<td>IIIA2</td>
<td>Nodal (single station) metastases recognized intraoperatively</td>
</tr>
<tr>
<td>IIIA3</td>
<td>Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)</td>
</tr>
<tr>
<td>IIIA4</td>
<td>Bulky or fixed multistation N2 disease</td>
</tr>
</tbody>
</table>

*Adapted from Ruckdeschel.2
involvement of the hilar or lobar lymph nodes. If resection of clinically negative mediastinal lymph nodes is not performed at the time of lung resection, it is possible that occult, subclinical metastatic disease to the N2 nodes will be missed, which will provide inaccurate pathologic staging and may alter the clinical course.

The optimal intraoperative approach to deal with the mediastinal lymph nodes remains unsettled. There is general agreement that systematic invasive harvesting of nodes from all possible lymph node stations is essential for accurate staging, but controversy arises as to whether complete mediastinal lymph node dissection is of therapeutic benefit in improving long-term survival rates. Theoretically, mediastinal lymph node dissection will harvest more nodes and thereby provide more accurate staging. Few published randomized studies have addressed the sampling vs dissection question. In a prospective randomized trial, Izbicki and associates found no survival benefit of an en bloc mediastinal lymph node dissection compared to systematic lymph node sampling in NSCLC. However, data from the recent North American Intergroup trial comparing adjuvant postoperative radiotherapy with radiochemotherapy in N1 and N2 node-positive patients shows a mild significant benefit for mediastinal dissection, although this analysis was retrospective and the choice of the approach to nodes in the mediastinum was left to the surgeon. In a companion analysis of lymph node harvesting techniques and results from this North American Intergroup trial, mediastinal lymph node dissection resulted in a significantly longer median survival than systematic lymph node sampling, but the survival advantage was limited to patients with right lung tumors (66.4 months vs 24.5 months, p < 0.001). Realistically, the distinction between what constitutes a mediastinal lymphadenectomy as opposed to systematic mediastinal lymph node sampling is technically somewhat blurred and is quite surgeon dependent.

However, if prior to thoracotomy, metastatic disease is found in the N2 nodes at mediastinoscopy, for example, then further surgery at that time should be avoided. If appropriate, induction therapy first is more advantageous, followed later in selected patients by definitive surgical resection of the primary lung cancer along with as complete a mediastinal lymphadenectomy as possible. This topic will be discussed in a subsequent section.

Recommendations

1. In patients with an occult single-station mediastinal node metastasis that is recognized at thoracotomy and when a complete resection of the nodes and primary tumor is technically possible, then proceed with the planned lung resection and a mediastinal lymphadenectomy. Level of evidence: poor; benefit, small; grade of recommendation: C

2. In every patient undergoing a lung resection for lung cancer, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection must be performed. Level of evidence: good; benefit, substantial; grade of recommendation: A

Adjuvant Radiotherapy: While it is recognized that the finding of regional metastatic N2 disease at surgery is a poor prognostic feature, there is little consensus as to the appropriate postthoracotomy management of these patients. Despite the great frequency of lung cancer, there have been relatively few patients entered into prospective trials evaluating the role of adjuvant postoperative radiation therapy, chemotherapy, or both.

The role of postoperative radiation therapy in patients with NSCLC has been debated for many years. The ability of postoperative radiation therapy in moderate doses, 4,500 to 5,500 cGy, to eradicate microscopic residual disease and reduce rates of local recurrence was established in several early single-institution trials. What has remained controversial is whether or not the reduction in locoregional recurrence also leads to an improvement in overall survival. While the nonrandomized, single institution trials suggested that this was the case, data from the prospective trials have been less supportive. Two separate issues are likely involved: (1) How large is the group of patients who have residual disease locally in the chest without occult distant metastatic disease, the subgroup for whom adjuvant mediastinal irradiation therapy might be curative? (2) What is the morbidity and mortality of adjuvant mediastinal radiotherapy with modern treatment planning techniques?

The Lung Cancer Study Group (LCSG) conducted a phase III trial in which patients with resected squamous cell carcinoma of the lung were randomized between observation and mediastinal irradiation to 50 Gy in 5 weeks. Entry into the study was restricted to patients with squamous cell carcinoma because of the greater tendency of this tumor to fail locally rather than distantly, compared with adenocarcinoma and large cell carcinoma. The majority of patients had N1 disease, but smaller proportions had N2 or T3N0 disease. The results of the trial were striking. Local failure as a first site of relapse was seen in 20% of patients on the observation arm but was seen in only 1% of those randomized to adjuvant nodal irradiation. The LCSG and
other trials of adjuvant postoperative radiation have been criticized for their small sample size, their mixture of N1 and N2 patients, and for the reliance on data on the site of first failure. It should be remembered that these deficiencies did not prevent the demonstration of a striking effect of radiotherapy on local control. What was lacking was the efficacy of good local control to result in long-term freedom from disease.

Several other randomized trials have addressed the same issue in patients with resected NSCLC of all histologies and have consistently failed to demonstrate a significant survival advantage (Table 2). In some trials there have been poorer survivals for irradiated patients, most likely due to increased cardiopulmonary toxicity. In both the LCSG and Medical Research Council (MRC) trials there was a trend to improved survival for the irradiated N2 but not N1 patients, but these survival differences did not reach statistical significance.

The meta-analysis by the Postoperative Radiation Therapy Meta-analysis Trialist Group of 2,128 patients treated in nine randomized trials (six previously published series and three unpublished series) of postoperative irradiation therapy concluded that this treatment was associated with a highly significant increase in the risk of death.44 Overall, the risk ratio was 1.21 (p = 0.001). The authors concluded that postoperative radiotherapy as used in these studies was detrimental and should not be used. It is important to recognize that there are several significant differences between the treatment administered in a number of the trials included in this meta-analysis and current practice patterns in the United States. First, a substantial portion of the patients included in this study, 562 of 2,128 patients (26.4%), had stage I disease without demonstrated nodal metastases. There has never been a strong case that postoperative radiation therapy as used in these studies was detrimental and should not be used. It is important to recognize that there are several significant differences between the treatment administered in a number of the trials included in this meta-analysis and current practice patterns in the United States. First, a substantial portion of the patients included in this study, 562 of 2,128 patients (26.4%), had stage I disease without demonstrated nodal metastases. There has never been a strong case favoring the postoperative irradiation of these stage I patients, and there is little suggestion from patterns of their failure after surgery that such treatment would be beneficial. Thus, one fourth of the patients in this analysis stood to gain little from treatment. Second, the details of treatment, including preoperative staging, surgical technique, and radiation dose and dose delivery, differed substantially from current practice. Several of the trials required or allowed very large daily fraction sizes in excess of 2.0 Gy, with the MRC trial using 2.6 Gy/d and the Slovenian trial using 3.0 Gy/d. Such larger fraction sizes would be expected to have an increase in acute and late complications compared to slower fractionation.

Seven of the nine trials also allowed the use of 60Co treatment beams, with their poorer depth-dose characteristics than higher-energy linear accelerator beams, and only one study included CT scan-based treatment planning. Therefore, compared with present standards of treatment, the likelihood is great that postoperative radiation therapy would lead to excess deaths from cardiac and pulmonary damage.

In such a meta-analysis that included patients with little chance of benefit of treatment, this would likely result in an overall survival detriment. It is notable that in this meta-analysis, the increased risk of death was most marked in those patients with stage I disease and was not significant for patients with N2 disease. This is consistent with, although it does not prove, a potential benefit for properly delivered radiotherapy for resected N2 patients.

At present, postoperative radiation therapy cannot be recommended on the basis of any proof of improved survival, but it should be considered in selected patients to reduce the risk of local recurrence, particularly when there is involvement of multiple nodal stations, extracapsular tumor spread, or close or microscopically positive resection margins. While adjuvant mediastinal radiotherapy has often been viewed as routine, it can be associated with significant cardiac and pulmonary toxicity, and care in treatment planning and delivery is essential.

Table 2—Randomized Controlled Trials of Surgery Plus Adjuvant Radiotherapy vs Surgery Alone*

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Radiotherapy Dose, Gy</th>
<th>Stage</th>
<th>Survival</th>
<th>Local Recurrence Surgery Plus Radiotherapy/Surgery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paterson and Russe97</td>
<td>1962</td>
<td>202</td>
<td>45</td>
<td>Any</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Bagnas98</td>
<td>1971</td>
<td>73</td>
<td>45</td>
<td>Any</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Van Houte et al99</td>
<td>1980</td>
<td>224</td>
<td>60</td>
<td>I, II</td>
<td>ND</td>
<td>4.8/20.7 (p = 0.002)</td>
</tr>
<tr>
<td>Weisenberger (LCSG 773)</td>
<td>1985</td>
<td>210</td>
<td>50</td>
<td>II, IIIA</td>
<td>ND</td>
<td>1/19 (p = 0.02)</td>
</tr>
<tr>
<td>Stephens et al (MRC)41</td>
<td>1996</td>
<td>308</td>
<td>40</td>
<td>II, IIIA</td>
<td>ND</td>
<td>18/29 (p = 0.003)</td>
</tr>
<tr>
<td>Debevec et al42</td>
<td>1996</td>
<td>74</td>
<td>30</td>
<td>IIIA</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Dautzenberg et al43</td>
<td>1999</td>
<td>728</td>
<td>60</td>
<td>II, IIIA</td>
<td>Worse for radiotherapy group (p = 0.002)</td>
<td></td>
</tr>
</tbody>
</table>

*ND = no significant difference.
Adjuvant Chemotherapy: Since the predominant pattern of failure is systemic recurrence of metastatic disease in patients with fully resected stage IIIA lung cancer, numerous trials of adjuvant postoperative chemotherapy have been carried out over the last 3 decades. These trials have been hampered by a number of problems, including inconsistent staging especially in the earlier trials, lack of effective chemotherapeutic agents until recently, and the poor tolerance of postthoracotomy patients to chemotherapy due to GI toxicity in an era lacking strong antiemetic agents.

In the 1970s and 1980s, a number of adjuvant chemotherapy trials used drug combinations that predated cisplatin-containing regimens. Most of these trials used alkylating agents and provided no survival advantage to patients; in fact, in most there was a detrimental effect result in a relative 15% increase in death in patients receiving adjuvant chemotherapy.\(^45\)

In the 1990s, a number of controlled, randomized trials were published using a variety of cisplatin-based chemotherapy regimens, commonly using cyclophosphamide-doxorubicin-cisplatin (CAP). Most of these trials (Table 3) of adjuvant chemotherapy after lung resection had a mixture of stages. Common to most trials was significant GI toxicity (studies predated the availability of serotonin-receptor antagonist antiemetics), and few patients received the full planned course of chemotherapy. Almost all trials showed no advantage in disease-free survival or overall survival with postoperative adjuvant chemotherapy. Niiranen and associates\(^46\) did find a significant increase in survival in resected T1–3N0 patients with adjuvant CAP chemotherapy. However, the surgery-only control arm had a high proportion of pneumonectomy cases, and when the pneumonectomy cases were excluded from analysis the survival advantage disappeared.

A meta-analysis by the Non-Small Cell Lung Cancer Collaborative Group (NSCLCCG) in 1995 analyzed the results of five non-cisplatin-based adjuvant chemotherapy regimens and found no survival benefit.\(^45\) The NSCLCCG also analyzed eight cisplatin-based adjuvant chemotherapy trials and found a 13% decrease in the relative risk of death with chemotherapy and an absolute survival benefit of 3% at 3 years and 5% at 5 years, but all of the differences were not statistically significant. A later meta-analysis by Le Chevalier\(^52\) in 1998, of all randomized, controlled adjuvant chemotherapy trials, also suggested a small 5% survival benefit with cisplatin-based regimens.

A persistent problem with postoperative chemotherapy has been administering the planned doses and cycles of chemotherapy. However, with the elimination of drugs such as doxorubicin and the introduction of better supportive care drugs such as improved antiemetics and cytokine support for hematologic toxicity, there would theoretically be improved chemotherapy dose compliance. Unfortunately, the experience of ongoing trials shows that the problem has not resolved and only approximately 65% of the planned dose of chemotherapy is actually received. The recent positive Japanese experience with low-dose, minimally toxic, prolonged adjuvant therapy with uracil-tegafur (UFT) suggests that the “standard” short-term, dose-intense adjuvant therapy may not be the best or only approach to consider.\(^51\)

Adjuvant Combination Chemoradiotherapy: With the lack of any apparent survival advantage in adjuvant chemotherapy or radiotherapy in resected N2 lung cancer, attention turned to exploration of the potential benefit of combination chemoradiotherapy postoperatively. Adjuvant radiotherapy appears to decrease local recurrence, but failure with distant metastases is a predominant pattern that theoretically should be amenable to the addition of adjuvant systemic chemotherapy.

To date, there have been five published randomized controlled trials involving N2 disease patients (Table 4) with adjuvant chemotherapy and radiotherapy, beginning with LCSG 791.\(^53\) This trial involved patients who had incomplete resections (positive

### Table 3—Randomized Controlled Trials of Surgery Plus Adjuvant Cisplatin-Based Chemotherapy vs Surgery Alone*

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, Year</th>
<th>Adjuvant Chemotherapy</th>
<th>Stage</th>
<th>Disease-Free Survival</th>
<th>Surgery-Chemotherapy/Surgery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niiranen et al(^46)</td>
<td>1992</td>
<td>CAP</td>
<td>I–III (1, 90%)</td>
<td>ND</td>
<td>67.56 (p = 0.05 for stage I)</td>
</tr>
<tr>
<td>Ohta et al(^47)</td>
<td>1993</td>
<td>Cisplatin/vindesine</td>
<td>III</td>
<td>ND</td>
<td>35/41 (p = 0.86)</td>
</tr>
<tr>
<td>Feld et al (LCSG)(^48)</td>
<td>1993</td>
<td>CAP</td>
<td>I–II (1, 84%)</td>
<td>ND</td>
<td>53/57 (p = 0.92)</td>
</tr>
<tr>
<td>Figlin and Piantadosi(^49)</td>
<td>1994</td>
<td>CAP</td>
<td>II–III</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>SGALC(^50)</td>
<td>1995</td>
<td>Cisplatin/doxorubicin/UFT</td>
<td>I–III (1, 61%)</td>
<td>ND</td>
<td>68.7/58.1 (p = 0.35)</td>
</tr>
<tr>
<td>Wada et al(^51)</td>
<td>1996</td>
<td>Cisplatin/vindesine/UFT vs UFT</td>
<td>I–III</td>
<td>ND</td>
<td>60.6/64.1/49 (p = 0.1)</td>
</tr>
</tbody>
</table>

*See Table 2 and abbreviation list for expansion of abbreviations.
margins or involvement of the most proximal lymph node in the mediastinum) and compared postoperative split course radiotherapy with the same radiotherapy plus CAP chemotherapy. There was an increase in the recurrence-free survival favoring the chemotherapy arm (p = 0.004), but overall survival was not increased.

Later trials failed to demonstrate any improvement in disease-free survival or overall survival with the addition of adjuvant chemotherapy to radiotherapy. The most recently published report is the 488 patient North American Intergroup trial (E3590), which also failed to demonstrate any increase in median survival or disease-free survival. In a companion laboratory subset analysis, Schiller and associates found a nonsignificant trend toward improved median survival in adjuvant chemoradiotherapy patients who had normal (wild-type) K-ras expression compared to mutant K-ras patients (median survival, 42 months vs 25 months; p = 0.09). Nevertheless, evidence is yet to be established substantiating the benefit of the routine addition of adjuvant chemotherapy to postoperative radiotherapy in stage IIIA lung cancer.

Recommendations

3. Adjuvant Radiotherapy: In the patient with fully resected stage IIIA lung cancer, there is no definite improvement in survival with adjuvant postoperative radiotherapy, but it significantly reduces local recurrence and should be considered in selected patients. Level of evidence: fair; benefit: small; grade of recommendation: C

4. Adjuvant Chemotherapy: In the patient with fully resected stage IIIA lung cancer, adjuvant chemotherapy administered alone might offer a very modest survival advantage, but this modality should not be routinely utilized outside of a clinical trial. Level of evidence: poor; benefit: small; grade of recommendation: I

5. Adjuvant Chemoradiotherapy: In the patient with fully resected stage IIIA lung cancer, based on randomized clinical trials to date, there is no survival benefit appreciated by adding postoperative adjuvant chemotherapy to adjuvant radiotherapy. Therefore, the routine use of combined postoperative chemotherapy and radiotherapy is not recommended and should not be employed outside of a clinical trial. Level of evidence: fair; benefit: none; grade of recommendation: D

Potentially Resectable N2 Disease (Stage IIIA)

Traditionally, the finding of any metastasis whatsoever to the mediastinal N2 nodes deemed that patient to have an unresectable lung cancer. With the development of chemotherapeutic agents with significant activity against lung cancer, beginning with cisplatin in the early 1980s, and with the development of modern radiotherapy techniques, studies have appeared suggesting that combining chemotherapy and/or radiotherapy followed by surgery in selected stage IIIA patients may offer therapeutic benefit. The poor survival rates with surgery alone in N2 disease, even with adjuvant postoperative chemotherapy or radiotherapy, has led to efforts at giving initial nonsurgical (radiotherapy and/or chemotherapy) therapy first, often to convert the unresectable tumor to resectable and, as well, to improve long-term survival. After a number of initial phase II trials with various drugs and radiotherapy doses administered prior to surgery in the neoadjuvant or induction setting, there were enough positive

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>Radiotherapy Regimens</th>
<th>Disease-Free Survival</th>
<th>Long-term Survival Surgery-Radiotherapy vs Surgery-Radiotherapy/Chemotherapy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lad et al (LCSG)</td>
<td>1988</td>
<td>164</td>
<td>II–III</td>
<td>CAP 40 Gy (split course)</td>
<td>Chemo. favored (p = 0.004)</td>
<td>54/68 (p = 0.1) 1 yr</td>
<td></td>
</tr>
<tr>
<td>Sawamura et al</td>
<td>1988</td>
<td>52</td>
<td>II–III</td>
<td>Tegafur-cisplatin 50 Gy</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Pisters et al</td>
<td>1994</td>
<td>72</td>
<td>III</td>
<td>Vindesine-cisplatin 40 Gy</td>
<td>ND</td>
<td>44/31 (p = 0.42) 2 yr</td>
<td></td>
</tr>
<tr>
<td>Dautzenberg et al</td>
<td>1995</td>
<td>207</td>
<td>I–III</td>
<td>Doxorubicin-cyclophosphamide-lomustine-cisplatin-vincristine</td>
<td>60 Gy</td>
<td>12/13 (p = 0.68) 10 yr</td>
<td></td>
</tr>
<tr>
<td>Keller et al (North American Intergroup E3590)</td>
<td>2000</td>
<td>488</td>
<td>II–IIIA</td>
<td>Cisplatin-etoposide 50.4 Gy</td>
<td>ND</td>
<td>39 mo/38 mo (p = 0.56) median</td>
<td></td>
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</tbody>
</table>

*See Table 2 for expansion of abbreviation.
results to persuade even the most pessimistic that this approach may have value.

Induction (Neoadjuvant) Therapy: The majority of stage IIIA patients have enlarged (> 1.0-cm short-axis diameter) N2 nodes (our stage IIIA2) on chest CT. Mediastinoscopy should generally be performed in this setting to document that these nodes actually contain metastatic tumor, since approximately 40% of moderately enlarged nodes may be benign, especially if there is an associated recent pneumonitis. Adverse prognostic factors associated with positive mediastinal nodes include extracapsular spread of tumor, multiple levels of involved lymph nodes, and bulky enlarged nodes.58 Of special note is the location of the N2 nodes, in that involvement of the higher, superior mediastinal nodes (nodes found positive that are generally available for biopsy at mediastinoscopy) portends a worse prognosis than patients with a negative mediastinoscopy result yet who are found to have positive nodes at thoracotomy.59 However, other studies contradict this finding. Naruke and colleagues60 found that metastatic disease to the subcarinal lymph nodes adversely affected prognosis compared to other lymph node locations. The LCSG retrospectively analyzed 163 patients with stage III disease from their postoperative treatment protocols and found that the survival rate was worse for patients with subcarinal lymph node metastases plus nodes from other sites, than for subgroups of patients with mediastinal nodal metastases in other locations.61 Miller and associates62 analyzed their lung-term survival rates in 167 patients who at thoracotomy were found to have N2 nodal metastases, not suspected preoperatively. The 5-year survival was worse when there was metastatic disease in the subcarinal or lower lymph nodes (stations 8 or 9). Also, survival was worse when multiple lymph node stations were involved.62 Finally, Okada and colleagues63 reviewed their long-term survival rates in 141 patients with N2 nodal metastatic disease and found that the survival rate depended on the location of the lung cancer (upper or lower lobes) in relationship to the location of the nodal metastases. For example, upper-lobe lung cancer patients with metastases limited to upper mediastinal nodal stations did better than when the lower mediastinum (subcarinal nodes) was involved in the upper-lobe cancers.60 The only conclusion that can be realistically drawn from the somewhat conflicting information from these and other studies is that multistation nodal disease has a somewhat worse prognosis that single-station disease, but the location of metastatic disease to a single nodal station probably has no significant effect.

There are theoretical advantages of the neoadjuvant approach including decreasing tumor size to allow more ready resection, decreased micrometastases, decreased surgical seeding, and increased patient acceptance. However, neoadjuvant therapy also has the potential disadvantages of a delay in primary tumor control and increased surgical morbidity and mortality. The literature is replete with numerous phase II nonrandomized clinical trials of neoadjuvant chemotherapy with or without radiotherapy followed by lung resection in highly selected patients.

As summarized by Rusch,58 results of these phase II trials suggest that the neoadjuvant approach may offer improved resectability with acceptable surgical morbidity and mortality and is associated with an improved survival benefit over single-modality therapy. Martini and colleagues64 gave induction chemotherapy with mitomycin, vindesine or vinblastine, and cisplatin to stage IIIA patients with bulky mediastinal nodal metastases or multilevel nodal disease and found a 65% complete resection rate, a 15% treatment-related mortality, and a 28% 3-year survival, which was far better than historical control subjects (8% 3-year survival). Other phase II induction chemotherapy trials have generally confirmed this trial.

Eight small, randomized phase III trials of neoadjuvant therapy in stage IIIA patients have been published over the last decade (Table 5). Many concerns have been raised about these phase III as well as the phase II neoadjuvant trials: (1) there was no consistent surgical (pathologic) staging of the mediastinal lymph nodes; (2) variable numbers of patients with a much better prognosis (T3N0 and T3N1) were included in these trials, which might have influenced the outcome of the trials; (3) some patients with a poorer prognosis (stage IIIB) were mixed in with patients with a better prognosis, thereby worsening results; and (4) many trials have small numbers of patients due to poor accrual with resultant low statistical power. With these caveats in mind, the results of the largest trials from Barcelona, Spain67,68 and the M.D. Anderson Cancer Center69,70 provide promising results. Both of these trials were closed early to further accrual after the interim analyses demonstrated significant survival advantages for the induction chemotherapy arm.

Rosell and associates67,68 in Barcelona, Spain, randomized 60 stage IIIA patients to either surgery alone or three cycles of induction chemotherapy with mitomycin, ifosfamide, and cisplatin followed by surgery. All patients received postoperative radiation therapy. Lymph nodes were pathologically staged initially by mediastinoscopy in only 73% of patients. Twenty-seven percent of patients had more favorable T3N0 or T3N1 tumors. A significant survival advantage was seen in the induction chemotherapy-
surgery arm with a 22-month median survival, compared to 10 months in the surgery-only arm (p < 0.005). Two-year and 5-year survivals were 29% and 17% for the chemotherapy-surgery arm vs 5% and 0% in the surgery-only arms, respectively. Although encouraging, this study has been criticized not only for the small number of patients but also for the significant imbalance of patients with poor prognosis K-ras mutations and aneuploid tumors in the surgery-only arm, which may have adversely biased the outcome in this arm. Also, there were no 5-year survivors in the surgery-only arm, which is surprising since 27% of the patients had favorable T3N0 or T3N1 tumors.

Roth and colleagues,69,70 at the M.D. Anderson Cancer Center, also randomized 60 stage IIIA patients to surgical resection alone or three cycles of induction chemotherapy with cyclophosphamide, etoposide, and cisplatin followed by surgery and then three cycles postoperatively. Postoperative radiation therapy was administered only to incompletely resected patients. Only 83% of patients were invasively staged prior to treatment. Also, 26% of patients had more favorable T3N0 or T3N1 tumors. The median survivals were 21 months for the chemotherapy-surgery arm vs 14 months for the surgery-only arm (p < 0.048). The 3-year and 5-year survival rates likewise favored the chemotherapy-surgery arm at 46% and 36% compared to 19% and 15% in the surgery-only arms, respectively. This study has also been criticized for its small patient numbers as well as a significant postoperative stage imbalance, with 40% stage IIIB and IV patients in the surgery-only arm compared with 11% in the chemotherapy-surgery arm. However, this imbalance potentially could have been the result of downstaging in the chemotherapy-surgery arm due to the induction therapy. Although encouraging, the results of these small randomized trials are unclear but strongly argue for the completion of the current larger trials in progress.

The most recently reported neoadjuvant trial is from Depierre and associates74 with the French Thoracic Cooperative Group. From 1991 through 1997, they randomized 373 patients with stages IB, II, and IIIA together into two treatment arms:

### Table 5—Randomized Controlled Trials of Preoperative Neoadjuvant (Induction) Therapy and Surgery vs Surgery Alone in Stage IIIA (NSCLS)*

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Induction Arms</th>
<th>Median Survival, mo</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass et al [NCI]65†</td>
<td>1992</td>
<td>27</td>
<td>1. Cisplatin, etoposide</td>
<td>29 (3 yr)</td>
<td>42 (3 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. None</td>
<td>16 (3 yr)</td>
<td>(p = 0.095)</td>
</tr>
<tr>
<td>Fleck et al66</td>
<td>1993</td>
<td>96</td>
<td>1. 5-FU, cisplatin/radiotherapy 30 Gy</td>
<td>NR</td>
<td>NR (arm 1 reported better resection rate and freedom from progression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Cisplatin, vinblastine, mitomycin, cisplatin</td>
<td>22 (2 yr), 17 (5 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. None</td>
<td>10 (2 yr), 0 (5 yr)</td>
<td>(p &lt; 0.005)</td>
</tr>
<tr>
<td>Rosell et al67,68‡</td>
<td>1994</td>
<td>60</td>
<td>1. Ifosfamide, mitomycin, cisplatin</td>
<td>22 (2 yr), 17 (5 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. None</td>
<td>10 (2 yr), 0 (5 yr)</td>
<td>(p &lt; 0.005)</td>
</tr>
<tr>
<td>Roth et al69,70‡</td>
<td>1994</td>
<td>60</td>
<td>1. Cisplatin, etoposide, cyclophosphamide</td>
<td>21 (3 yr), 36 (5 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. None</td>
<td>14 (3 yr), 15 (5 yr)</td>
<td>(p = 0.048)</td>
</tr>
<tr>
<td>Wagner et al (LCSG)71</td>
<td>1994</td>
<td>57</td>
<td>1. Mitomycin, vinblastine, cisplatin</td>
<td>12</td>
<td>27 at 4 yr for both arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Radiotherapy, 44 Gy</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Elias et al (CALGB)72</td>
<td>1997</td>
<td>57</td>
<td>1. Radiotherapy, 40 Gy</td>
<td>23</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Cisplatin, etoposide</td>
<td>19</td>
<td>NR</td>
</tr>
<tr>
<td>Ichinose et al (JCOG)73</td>
<td>2000</td>
<td>62</td>
<td>1. Cisplatin vindesine</td>
<td>18</td>
<td>8 (5 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. None</td>
<td>16</td>
<td>25 (5 yr)</td>
</tr>
<tr>
<td>Depierre et al74§</td>
<td>2002</td>
<td>167 with IIIA</td>
<td>1. Mitomycin, cisplatin, ifosfamide</td>
<td>NR</td>
<td>28 (5 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. None</td>
<td>21 (5 yr)</td>
<td>(estimated) ND</td>
</tr>
</tbody>
</table>

*Adapted from Garland et al.75 NR = not reported; 5-FU = 5-fluouracil; ND = not done.
†Study closed early due to poor accrual.
‡Study closed early due to large, significant differences between treatment arms.
§Study combined stage IB, II, and IIIA.
(1) primary surgery, and (2) two cycles of preoperative chemotherapy with mitomycin, ifosfamide, and cisplatin, followed by surgical resection and then two cycles postoperatively. Patients in both treatment arms found postoperatively to have pathologic T3 or N2 disease received postoperative radiotherapy. The prerandomization stage was determined clinically based on chest CT, and any lymph node > 1 cm in short-axis diameter was considered positive for purposes of staging. The overall response to preoperative chemotherapy was 64%. The median survival overall with the combined stages was 37 months in the chemotherapy-surgery arm and 26 months in the surgery-only arm \( (p = 0.15) \). In a subset analysis, patients with N0 and N1 disease appreciated significant improvements in disease-free and overall survival in the chemotherapy-surgery arm compared to surgery only. For the subset of 167 patients with stage IIIA disease (92 patients in the chemotherapy-surgery arm, and 75 patients in the surgery-only arm), there was no significant difference in survival in the two treatment arms, with an estimated 5-year survival of approximately 29% in the chemotherapy-surgery group compared to 20% in the surgery-only group (survivals estimated from the published survival curves). Unfortunately, the subset analysis in the published report was not complete. This study may be criticized in a number of aspects, most notably for the lack of preoperative histologic verification of nodal stage prior to randomization, as well as the combination of diverse stages into the same study arm, thereby making the subset analysis of stages a retrospective exercise with potential imbalance of the patient groups. Despite the obvious deficiencies when evaluating these results for stage IIIA patients, this study still fails to demonstrate any significant survival benefit for induction chemotherapy followed by surgery compared to surgery alone in locally advanced NSCLC.

Until the larger, multi-institutional randomized phase III trials (such as the current North American Intergroup 0139 trial and European Organization for Research and Treatment of Cancer [EORTC]-08941) of neoadjuvant therapy designed specifically for stage IIIA lung cancer are completed, this approach with preoperative chemotherapy and possibly radiotherapy for N2 disease, which appears to be feasible, should not presently be considered the standard of care in the community. Ideally this approach should only be administered in the setting of an investigational protocol. For this reason, we recommend following the guidelines in this chapter for the different subsets of stage IIIA patients. Finally, the older patient or patient with poor performance status should still be approached with caution when considering these aggressive multimodality protocols.

**Recommendations**

6. Patients with stage IIIA (N2) lung cancer identified preoperatively have a relatively poor prognosis when treated with surgery as a single modality. Several small trials of induction chemotherapy have yielded conflicting results about its effect on survival. The relative roles of surgery and radiation therapy as the local treatment modality are also not clearly defined. Definitive treatment recommendations are difficult to make in this setting. Therefore, patients in this subset should be referred for multidisciplinary evaluation before embarking on definitive treatment. Level of evidence: poor; benefit: none; grade of recommendation: I

7. Whenever possible, induction (neoadjuvant) therapy followed by surgery for stage IIIA disease should be carried out in the setting of a clinical trial. Level of evidence: fair; benefit: moderate; grade of recommendation: B

8. Bimodality or trimodality therapy is better than surgery alone for locally advanced stage IIIA lung cancer. Level of evidence: good; benefit: substantial; grade of recommendation: A

**Surgical Considerations in Stage IIIA**

Although the use of neoadjuvant chemotherapy and/or radiotherapy appears to have potential advantages in the treatment of locally advanced lung cancer, concern has been raised in numerous publications about the perceived and real increase in morbidity and mortality of the subsequent lung resections. One of the most recent reports by Roberts and associates in 2001 found neoadjuvant chemotherapy increased the perioperative complications in their series of 34 patients. However, other groups, such as Sonett and colleagues in 1999, reported safe pulmonary resections after chemotherapy and high-dose thoracic radiation in 19 patients. Siegenthaler and associates at the M.D. Anderson Cancer Center in a larger group of patients found no increased surgical morbidity with preoperative chemotherapy in lung cancer when compared to their nonchemotherapy lung resection patients.

There is no doubt that patients with locally advanced lung cancer who undergo neoadjuvant therapy present more intraoperative, technical challenges to the thoracic surgeon and require more careful postoperative care. But with certain extra
precautions, safe lung resections are indeed possible, especially if the surgeon is experienced with this patient population and is performing a high volume of lung resections. As early as 1992, Romano and Mark\textsuperscript{76} reported that hospitals performing a high volume of lung resections experienced significantly better outcomes compared to lower volume hospitals. Using the Surveillance, Epidemiology, and End Results Cancer Registries that are linked to data on Medicare hospitalizations database, Bach and colleagues\textsuperscript{80} in 2001 reviewed 2,118 patients from 76 hospitals sampled from 22 states. They found that patients who undergo lung cancer resections at hospitals that perform large numbers of the procedures are more likely to survive longer than patients who undergo such surgery at hospitals performing a small number of lung resections.\textsuperscript{80} Finally, Silvestri and associates\textsuperscript{81} reviewed the South Carolina statewide results of lung cancer resections in all nonfederal acute care hospitals from 1991 to 1995. They found that the mortality for lung cancer resection was lower when the surgery was performed by a thoracic surgeon compared to a general surgeon.\textsuperscript{81}

The definition of what is meant by “resectable,” “marginal resectable,” and “unresectable” is not clear in most published studies. The problem is that this determination is subjective and highly dependent on the experience and expertise of the thoracic surgeon. For the best possible evaluation of an induction therapy candidate, the surgeon who ultimately may operate on the stage IIIA patient needs to be experienced in the handling of these more complex and technically challenging patients. Also, it is critically important that the surgeon also be involved initially in the beginning of the evaluation such that an informed estimate of the surgical resectability of the tumor can be made up front, so that appropriate candidates for induction therapy are chosen.

The decision to proceed with surgery after induction therapy should not be automatic. While there is evidence that 60 to 75% of patients will respond to induction regimens, nonresponders should not undergo surgery. In the phase II Southwestern Oncology Group trial of induction chemoradiotherapy followed by surgery in stage IIIA and IIIB disease, there was complete pathologic clearance of tumor in 22% of resection specimens with an overall 27% 3-year survival.\textsuperscript{82} But of particular interest, the patients with a complete pathologic clearing of residual disease had a 30-month median survival compared to 10 months for those with residual tumor in the lymph nodes (p = 0.0005). A more recent study by Bueno and associates\textsuperscript{83} emphasized the importance of residual nodal disease after induction therapy in stage IIIA tumors. In their study, the long-term survival stratified by nodal status after induction therapy and lung resection found that 28% of patients downsized to pathologic N0 had a 35.8% 5-year survival, whereas the remainder of patients with residual nodal disease at surgery had only a 9% 5-year survival. These and other studies suggest that surgical resection should be avoided in patients after induction therapy who have definite, biopsy-proven residual tumor in the mediastinal nodes.

Clinical restaging with standard chest CT scans is not accurate enough to predict pathologic response in the lymph nodes, as recently reported by Margsitora and colleagues.\textsuperscript{84} The use of PET after induction therapy to determine response to therapy looks promising, with 100% accuracy in one small preliminary trial.\textsuperscript{85,86} In a retrospective review of the accuracy of PET scans after induction chemotherapy, radiotherapy, or both in 56 patients who underwent subsequent surgery, Akhurst and colleagues\textsuperscript{87} found that PET had a 98% positive predictive value for detecting residual viable disease in the primary tumor. However, PET overstaged the nodal status in 33%, understaged it in 15%, and was correct in only 52%. Therefore, until further studies are available, it is premature to routinely employ postinduction therapy PET scans for restaging in order to make decisions about surgical resectability and nodal involvement. Finally, careful re-evaluation for surgery after induction therapy is necessary since incomplete resection or thoracotomy with no resection results in a poor survival in the stage IIIA patient. And if after a thoracotomy and resection in the stage IIIA patient there is known residual nodal disease or there was an incomplete resection of the primary tumor, postoperative radiotherapy should be considered to aid in local control.

**Recommendations**

9. **Surgical Consideration**: Patients with incomplete resections have poor survivals, and debulking procedures should be avoided. Level of evidence: fair; benefit: negative; grade of recommendation: D

10. **Surgical Consideration**: Patients with incomplete resections and those with residual nodal disease found at surgery should be considered for postoperative radiotherapy. Level of evidence: poor; benefit: moderate; grade of recommendation: B

**Unresectable, Bulky N2 Disease (Stage IIIA\textsubscript{4})**

Many patients with stage IIIA lung cancer have less favorable presentations of their disease because they have bulky nodal involvement and/or unresectable primary tumors. Evaluation of various trials in
this subset of patients is complicated by a lack of definition of what constitutes "bulky" nodal disease as well as what is "unresectable." It is generally agreed that mediastinal lymph nodes > 1 cm in short-axis diameter are suspicious. We then would define bulky nodal disease as those involving lymph nodes > 2 cm in short-axis diameter measured by CT, especially with extranodal involvement, multistation nodal disease, and/or groupings of multiple, positive smaller lymph nodes. Nevertheless, this determination is somewhat subjective, much like the definition of resectability, which falls back to the experience and judgment of the thoracic surgeon.

However, aside from the relatively few question-able presentations, most experienced lung cancer clinicians can agree on what constitutes unresectable, bulky N2 stage IIIA disease that warrants only nonsurgical therapy. Traditionally, these patients with locally advanced disease were treated with conventional radiotherapy alone with relatively poor long-term survivals, but in the last decade combination chemoradiotherapy appears to offer improved results, as discussed in the following sections.

Radiotherapy Alone: Early attempts to use nonsurgical treatment modalities for unresectable locally advanced disease (our stage IIIA) involved single-modality chest radiotherapy, yielding poor survivals at 5 years of 5 to 10% with traditional dose and fractionation schedules (1.8 to 2.0 Gy per fraction per day to 60 to 70 Gy in 6 to 7 weeks). Patterns of failure for patients treated with radiotherapy alone included both locoregional and distant failures. Attempts to improve on locoregional control tested alternative radiotherapy doses and schedules, applying radiotherapy at escalating doses at shortened intervals (hyperfractionation) that, in theory, would maximize cell killing in lung cancers with relatively short doubling times. A hyperfractionated, higher-dose radiotherapy trial utilized from 60.0 to 79.2 Gy, delivered in smaller-than-standard fractions administered in two fractions per day rather than one. Hyperfractionation of radiotherapy yielded an improved but still poor 2-year survival of 20%, with an apparent benefit for patients treated at 60.6 Gy. There appeared to be acceptable acute or late toxicity using the hyperfractionated schedule.88

Further alterations of standard dose and fractionation led to testing accelerated hyperfractionation. In the United Kingdom, three radiotherapy fractions were delivered per day in a continuous schedule (7 days rather than 5 days per week) over 12 days to a total dose of 50.4 Gy or 54 Gy. This continuous hyperfractionated accelerated radiation therapy (CHART) regimen yielded good radiographic responses in tumors with an acceptable early and late toxicity profile. In a randomized trial comparing CHART with a standard dose and fractionation radiotherapy regimen in locally advanced NSCLC, there was a survival advantage for CHART.89 American groups have utilized versions of CHART that eliminate the weekend doses and deliver multiple daily fractions within an 8-h time period, referred to as hyperfractionated accelerated radiation therapy (HART). A recent Eastern Cooperative Oncology Group (ECOG) pilot study (ECOG 4593) utilized this schedule and obtained a preliminary median survival of 13 months with acceptable toxicities, primarily esophagitis, at the completion of radiotherapy.90 In a subsequent companion quality-of-life assessment of patients undergoing the accelerated HART regimen in ECOG 4593, Auchter and associates91 found that the decrement in physical and functional quality of life during treatment returned to baseline within 4 weeks of completing treatment. However, the emotional well-being of patients improved at all time points.91

Recently, the ECOG conducted a multicenter trial for unresectable, locally advanced NSCLC in which patients were randomized after induction chemotherapy to standard fractionation radiotherapy to a total dose of 64 Gy or HART to a total dose of 57.6 Gy in a randomized design. One hundred thirty patients were entered into the trial that is now closed, and the analysis is pending. An important trial end point was the local failure rate, as it is hoped that HART will yield improved local control of disease and thereby impact favorably on survival.

Combined Chemotherapy With Radiotherapy: Although patients have gained symptomatic benefit with radiotherapy for unresectable, bulky locally advanced stage IIIA disease, their outcome has generally been poor, usually as a result of systemic, not local, failure. With the development of more effective platinum-based chemotherapy, attempts to improve outcome of treatment by decreasing relapse from distant disease have prompted the addition of systemic chemotherapy to definitive radiotherapy. Chemotherapy has been combined with radiotherapy in different fashions (chemotherapy followed by radiotherapy, chemotherapy with closely sequenced radiotherapy, chemotherapy concurrent with radiotherapy, or induction chemotherapy followed by concurrent chemotherapy/radiotherapy) in multiple phase II trials involving heterogeneous and often poorly staged groups of patients with locally advanced disease.

In general, trials using platinum-containing chemotherapy regimens in combination with radiotherapy have shown good tumor response rates and have suggested an improvement in survival. One promis-
ing pilot trial showed significantly improved median and 2-year survivals of 16 months and 30%, respectively, using four cycles of etoposide and cisplatin with concurrent radiotherapy to 60 Gy.\textsuperscript{92} Looking at collective data from multiple phase II trials, acute and late toxicities associated with combined chemotherapy and radiotherapy have included mild-to-severe esophagitis, pneumonitis, and also treatment-related deaths. Overall, however, these trials showed the feasibility of combined modality therapy and suggested that chemotherapy plus radiotherapy would yield improved outcomes compared to radiotherapy alone.

Multiple phase III trials using platinum chemotherapy plus radiotherapy have confirmed improved survivals for chemotherapy plus radiotherapy compared to radiotherapy alone. Selected key trials are outlined in Table 6, with some trials discussed below. Of note, the earliest trial results were negative, showing no survival benefit with chemotherapy but the regimens used had either low-dose cisplatin or non-platinum-based chemotherapy, which might be expected to be ineffective. Later trials using more appropriate dose chemotherapy all had positive results.

A pivotal Cancer and Leukemia Group B (CALGB) randomized trial initially presented in 1990 showed the benefit of adding chemotherapy in a sequential fashion to radiotherapy in the setting of locally advanced disease.\textsuperscript{102} The CALGB study compared two cycles of cisplatin and vinblastine added to standard fractionation radiotherapy to 60 Gy with radiotherapy alone in patients with favorable prognostic characteristics (good performance status and minimal weight loss). Objective tumor response rate was improved for the chemotherapy-plus-radiotherapy group compared to radiotherapy alone (56% vs 43%, \(p = 0.012\)), and survival at 2 years and 5 years was also improved (26% and 13% vs 13% and 6%, respectively).

The superiority of combined-modality chemotherapy plus radiotherapy in a sequential fashion compared to radiotherapy alone has been shown in several other large randomized trials including a Radiation Therapy Oncology Group trial showing an improved 1-year and median survival with chemotherapy plus conventional radiotherapy compared to both conventional radiotherapy and hyperfractionated radiotherapy alone.\textsuperscript{101} A multicenter French study reported by Le Chevalier and associates\textsuperscript{105} also confirmed improved survival for the chemotherapy-plus-radiotherapy arm compared to radiotherapy alone (11% vs 5% 3-year survival, respectively) with an improved distant failure rate for chemotherapy plus radiotherapy (22% vs 46% at 1 year, respectively). Unfortunately, both treatment groups showed similarly high locoregional failure with 1-year local control rates of only 15% and 17%, illustrating the vexing problem of obtaining good locoregional control of disease in the locally advanced setting. Three meta-analyses reviewing > 50 trials have confirmed the survival benefit of combined platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced, unresectable lung cancer.\textsuperscript{45,106,107}

The most recently published study was a large British trial randomizing 446 patients with localized, unresectable disease to two arms: (1) chemotherapy (mitomycin, ifosfamide, and cisplatin) followed by radical radiotherapy (median, 50 Gy; range, 40 to 60 Gy), or (2) radical radiotherapy alone (median, 50 Gy; range, 40 to 64 Gy).\textsuperscript{104} This trial allowed performance status (PS)-2 patients, and 15% of the chemoradiotherapy arm and 11% of the radiotherapy-only arm were PS-2 patients. The median survival and 2-year survival were not significantly different (\(p = 0.14\)) between the two arms: 11.7 months and 20% in the chemoradiotherapy arm, and 9.7 months and 16% in the radiotherapy arm. Inclusion of patients with poorer PS in this trial, unlike most other trials, is believed to have possibly influenced the results, particularly in the chemoradiotherapy arm.

**Concurrent Chemotherapy and Radiotherapy:**
Concurrent chemotherapy with radiotherapy has been studied in the locally advanced setting through randomized trials that have attempted to capitalize on the radiosensitizing properties of chemotherapy. An EORTC three-arm trial published in 1992 compared radiotherapy (split course) concurrent with daily or weekly concurrent cisplatin to radiotherapy alone.\textsuperscript{96} There were improved 2-year and 3-year survivals for daily chemotherapy concurrent with radiotherapy compared with radiotherapy alone (26% and 16% vs 13% and 2%, respectively). There was no significant advantage for the weekly chemotherapy-plus-radiotherapy arm, with an intermediate survival compared to the other arms.

Whether concurrent chemotherapy plus radiotherapy yields an improvement in survival over sequential chemotherapy plus radiotherapy has been addressed by a few trials, including a large Japanese randomized trial of 320 patients that compared chemotherapy (mitomycin, vindesine, and cisplatin for two cycles) concurrent with split-course daily radiotherapy to 56 Gy compared to chemotherapy followed by continuous daily radiotherapy to 56 Gy.\textsuperscript{108} Esophagitis rates were low with concurrent therapy. At 5-year median follow-up, 2-year and 5-year survival was improved for concurrent chemotherapy over sequential chemotherapy with radiotherapy (34.6% and 15.8% vs 27.4% and 8.8%, respectively). Myelosuppression was greater among
<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Timing Chemotherapy/Radiotherapy</th>
<th>Regimens</th>
<th>Study Result</th>
<th>Acute Toxicity Chemotherapy Plus Radiotherapy, %</th>
<th>2-year Survival Chemotherapy Plus Radiotherapy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soresi et al</td>
<td>1988</td>
<td>95</td>
<td>Concurrent</td>
<td>Cisplatin/50 Gy</td>
<td>Negative</td>
<td>40/25</td>
<td></td>
</tr>
<tr>
<td>Mattson et al</td>
<td>1988</td>
<td>238</td>
<td>Sequential plus concurrent</td>
<td>Cyclophosphamide doxorubicin-cisplatin/55 Gy</td>
<td>Negative</td>
<td>19/17</td>
<td></td>
</tr>
<tr>
<td>Ansari et al</td>
<td>1991</td>
<td>183</td>
<td>Concurrent</td>
<td>Cisplatin/60 Gy</td>
<td>Negative</td>
<td>15/9</td>
<td></td>
</tr>
<tr>
<td>Morton et al</td>
<td>1991</td>
<td>114</td>
<td>Sequential</td>
<td>MACC/60 Gy</td>
<td>Negative</td>
<td>21/9</td>
<td>21/16</td>
</tr>
<tr>
<td>Trovo et al</td>
<td>1992</td>
<td>173</td>
<td>Concurrent</td>
<td>Cisplatin/45 Gy</td>
<td>Negative</td>
<td>15/7</td>
<td>13/13</td>
</tr>
<tr>
<td>Schaake-Koning et al</td>
<td>1992</td>
<td>308</td>
<td>Concurrent</td>
<td>Cisplatin/55 Gy (split course)</td>
<td>Positive</td>
<td>41/11</td>
<td>26/13</td>
</tr>
<tr>
<td>Wolf et al</td>
<td>1994</td>
<td>85</td>
<td>Sequential plus concurrent</td>
<td>Vindesine-ifosphamide-cisplatin/50 Gy</td>
<td>Positive</td>
<td>8.2/11</td>
<td>24/12</td>
</tr>
<tr>
<td>Le Chevalier et al</td>
<td>1994</td>
<td>353</td>
<td>Sequential</td>
<td>Vindesine-lomustine-cisplatin-cyclophosphamide/65 Gy</td>
<td>Positive</td>
<td>21/14</td>
<td></td>
</tr>
<tr>
<td>Sause et al</td>
<td>1995</td>
<td>452</td>
<td>Sequential</td>
<td>Cisplatin-vinblastine/60 Gy</td>
<td>Positive</td>
<td>26/22</td>
<td>30/19</td>
</tr>
<tr>
<td>Dillman et al</td>
<td>1996</td>
<td>155</td>
<td>Sequential</td>
<td>Cisplatin-vinblastine/60 Gy</td>
<td>Positive</td>
<td>14/6</td>
<td>26/13</td>
</tr>
<tr>
<td>Jeremic et al</td>
<td>1996</td>
<td>131</td>
<td>Concurrent</td>
<td>Carboplatin-etoposide/60.9 Gy bid</td>
<td>Positive</td>
<td>52/38</td>
<td></td>
</tr>
<tr>
<td>Callen et al</td>
<td>1999</td>
<td>446</td>
<td>Sequential</td>
<td>Mitomycin-ifosphamide-cisplatin/median 50 Gy</td>
<td>Negative</td>
<td>20/16</td>
<td>(p = 0.14)</td>
</tr>
</tbody>
</table>

*MACC = methotrexate-doxorubicin-cyclophosphamide-CCNU.
patients in the concurrent arm, but the mortality rate was low (<1%) and not significantly different in both groups. Further evaluation through randomized trials addressing this issue are required, with an emphasis on the toxicity profiles of concurrent strategies vs sequential strategies.

Newer-generation chemotherapeutic agents, alone or in combination with the platinum agents, are being incorporated into combined modality chemotherapy plus radiotherapy for locally advanced disease. As an example, a recent phase II trial in locally advanced disease used induction paclitaxel with carboplatin followed by weekly doses concurrent with radiotherapy. This treatment yielded a good response rate (55%) in 38 evaluable patients, with a 1-year survival of 72% and a tolerable toxicity profile.109

Other phase I and II trials have reported the feasibility of combining docetaxel, gemcitabine, and irinotecan in concurrent design with radiotherapy but also do report a range of toxicity profiles. Phase III trials are needed that incorporate these newer, active agents in various dosing schedules with radiotherapy in standard and altered fractionation schedules to define the optimal role of these agents in treatment strategies for unresectable IIIA (N2) disease.

**Recommendations**

11. In patients with good PS, radiotherapy should not be used alone in treating unresectable stage IIIA lung cancer. Level of evidence: good; benefit: negative; grade of recommendation: D

12. In the patient with unresectable locally advanced lung cancer, platinum-based chemotherapy plus radiotherapy provides improved survival rates over radiotherapy alone and should be used for primary treatment. Level of evidence: good; benefit: substantial; grade of recommendation: A

13. Because in patients with stage IIIA lung cancer the optimal technique of combining chemotherapy and radiotherapy has not been determined, factors such as patient PS and age should be used to guide treatment planning. Level of evidence: poor; benefit: small; grade of recommendation: I

**Ongoing Clinical Trials**

Perhaps the greatest challenge to the clinician in the optimal management of stage IIIA disease is the lack of meaningful, definitive data from large randomized trials on which to base treatment decisions.

A large number of phase I and II trials are accruing involving locally advanced disease with newer chemotherapy agents, newer radiotherapy delivery techniques and fractionation schedules, and novel interventions such as vaccines and gene-based therapy. Fortunately, a number of large, multicenter phase III randomized trials are also ongoing, and on completion should provide results that serve as the basis for rationale treatment recommendations in the various clinical presentations of stage IIIA disease.

**A. Adjuvant Therapy Phase III Randomized Trials**

For fully resected minimal nodal disease patients (stage IIIA1–2), multiple randomized trials of postoperative chemotherapy are currently accruing, although recruitment is hampered by the reluctance of postsurgical patients to undergo chemotherapy and, particularly, to complete all planned cycles. Equally difficult is the reluctance of patients to be potentially randomized in phase III trials to the observation (no treatment) arm.

1. National Cancer Institute of Canada Clinical Trials Group/ECOG (JBR-10): This study compares adjuvant vinorelbine and cisplatin to no chemotherapy (completed accrual and now closed).
2. FRE-IALT/EU-96010: A European-based worldwide study comparing adjuvant combination chemotherapy with cisplatin plus vindesine, vinblastine, vinorelbine, or etoposide to no chemotherapy in resected stage I, II, and IIIA disease.
3. CNR-NICO-01/EU-97010: A European study of adjuvant cisplatin and etoposide after completely resected stage I, II, and IIIA disease.
4. LLCG-BLT/EU-98003/MRC-BLT: A study comparing adjuvant cisplatin-based chemotherapy to no chemotherapy.

**B. Neoadjuvant (Induction) Therapy Phase III Randomized Trials in Resectable Stage IIIA**

1. North American Intergroup 0139: This trial compares concurrent combination chemotherapy with cisplatin and etoposide plus radiotherapy followed by surgery or radiotherapy in stage IIIA (N2) disease (completed accrual and now closed).
2. EORTC 08941: A European study comparing platinum-based chemotherapy of choice followed (in responders only) by surgery or radiotherapy.

**C. Combination Chemotherapy and Radiotherapy in Unresectable Stage IIIA: Phase III Randomized Trials**

1. National Cancer Institute T99-0046: This study compares platinum-based combination chemotherapy and radiotherapy with or without shark cartilage extract (AE-941).
2. Southwest Oncology Group S0023: A study of cisplatin, etoposide, docetaxel, and radiotherapy with or without oral ZD-1839 in patients with unresectable stage III NSCLC.

3. CHNT-PC/MIC; EU-99046: A study of paclitaxel and carboplatin vs standard platinum (cisplatin plus mitomycin/ifosfamide or vinblastine/mitocyn) therapy in patients with inoperable stage IIIA, IIIB, or IV NSCLC.

4. ECOG-3598: A study of carboplatin, paclitaxel, and radiotherapy with or without thalidomide in patients with unresectable stage IIIA or IIIB NSCLC.


Despite many earlier studies, the optimal treatment recommendations in the various clinical presentations of stage IIIA (N2) disease are unclear. Hopefully, as the current phase III trials accrue and mature and the much-needed, subsequent randomized trials with newer chemotherapy agents and radiotherapy schemata are started and completed, more definitive treatment guidelines will emerge. Until that time, it is critically important that whenever possible the clinician who manages locally advanced NSCLC enroll their patients in every available clinical trial.

### SUMMARY OF RECOMMENDATIONS

#### A. Incidental (Occult) N2 Disease Found at Thoracotomy

1. **Surgical Consideration**: In patients with an occult single-station mediastinal node metastasis that is recognized at thoracotomy and when a complete resection of the nodes and primary tumor is technically possible, then proceed with the planned lung resection and a mediastinal lymphadenectomy. Level of evidence: poor; benefit: small; grade of recommendation: C

2. **Surgical Consideration**: In every patient undergoing a lung resection for lung cancer, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection must be performed. Level of evidence: good; benefit: substantial; grade of recommendation: A

3. **Adjuvant Radiotherapy**: In the patient with fully resected stage IIIA lung cancer, there is no definite improvement in survival with adjuvant postoperative radiotherapy, but it significantly reduces local recurrence and should be considered in selected patients. Level of evidence: fair; benefit: small; grade of recommendation: C

#### B. Potentially Resectable N2 Disease

6. **Induction (Neoadjuvant) Therapy**: Patients with stage IIIA (N2) lung cancer identified preoperatively have a relatively poor prognosis when treated with surgery as a single modality. Several small trials of induction chemotherapy have yielded conflicting results about its effect on survival. The relative roles of surgery and radiation therapy as the local treatment modality are also not clearly defined. Definitive treatment recommendations are difficult to make in this setting. Therefore, patients in this subset should be referred for multidisciplinary evaluation before embarking on definitive treatment. Level of evidence: poor; benefit: none; grade of recommendation: I

7. **Induction (Neoadjuvant) Therapy**: Whenever possible, induction (neoadjuvant) therapy followed by surgery for stage IIIA disease should be carried out in the setting of a clinical trial. Level of evidence: fair; benefit: moderate; grade of recommendation: B

8. **Induction (Neoadjuvant) Therapy**: Bimodality or trimodality therapy is better than surgery alone for locally advanced stage IIIA lung cancer. Level of evidence: good; benefit: substantial; grade of recommendation: A

9. **Surgical Consideration**: Incompletely resected patients have poor survival, and de-
bulking procedures should be avoided. Level of evidence: fair; benefit: negative; grade of recommendation: D

10. Surgical Consideration: Incompletely resected patients and those with residual nodal disease found at surgery should be considered for postoperative radiotherapy. Level of evidence: poor; benefit: moderate; grade of recommendation: B.

C. Unresectable, Bulky N2 Disease

11. Combination Chemotherapy and Radiotherapy: In patients with good PS, radiotherapy should not be administered alone in treating unresectable stage IIIA lung cancer. Level of evidence: good; benefit: negative; grade of recommendation: D

12. Combination Chemotherapy and Radiotherapy: In patients with unresectable locally advanced lung cancer, platinum-based chemotherapy plus radiotherapy provides improved survival rates over radiotherapy alone and should be used for primary treatment. Level of evidence: good; benefit: substantial; grade of recommendation: A

13. Combination Chemotherapy and Radiotherapy: Because in patients with stage IIIA lung cancer the optimal technique of combining chemotherapy and radiotherapy has not been determined, then factors such as patient performance status and age should be used to guide treatment planning. Level of evidence: poor; benefit: small; grade of recommendation: I

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