Treatment of Non-small Cell Lung Cancer-Stage IIIA*

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

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Study objectives: **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. This review explores the published clinical trials to make treatment recommendations in this controversial subset of lung cancer.**

Design, setting, and participants: **Systematic searches were made of MEDLINE, HealthStar, and Cochrane Library databases up to May 2006, focusing primarily on randomized trials, with inclusion of selected metaanalyses, practice guidelines, and reviews. Study designs and results are summarized in evidence tables.**

Measurement and results: **The evidence derived from the literature now appears to support routine adjuvant chemotherapy after complete resection of stage IIIA lung cancer encountered unexpectedly at surgery. However, using neoadjuvant therapy followed by surgery for known stage IIIA lung cancer as a routine therapeutic option is not supported by current published randomized trials. Combination chemoradiotherapy, especially delivered concurrently, is still the preferred treatment for prospectively recognized stage IIIA lung cancer with all degrees of mediastinal lymph node involvement. Current and future trials may modify these recommendations.**

Conclusions: **Multimodality therapy of some type appears to be preferable in all subsets of stage IIIA patients. However, because of the relative lack of consistent randomized trial data in this subset, the following evidence-based treatment guidelines lack compelling evidence in most scenarios.** ***(CHEST 2007; 132:243S–265S)***

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

Abbreviations: ALPI = Adjuvant Lung Project Italy; CALGB = Cancer and Leukemia Group B; CAP = cyclophosphamide-doxorubicin-cisplatin; CHART = continuous hyperfractionated accelerated radiation therapy; ECOG = Eastern Cooperative Oncology Group; HART = hyperfractionated accelerated radiation therapy; MaxSUV = percentage change in the standardized uptake value; NSCLC = non-small cell lung cancer; PET = positron emission tomography; RTOG = Radiation Therapy Oncology Group; SUV = standardized uptake value

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 are avoided to make this a more readable and useable guide. To develop the following guidelines for stage IIIA disease, the authors conducted a systematic search of MEDLINE, HealthStar, and Cochrane Library databases up to May 2006, reviewing 15 other published clinical guidelines, 10 metaanalyses, 12 systematic reviews, and 91 primary articles with clinical trials on this topic, focusing on the

most well-designed, largest peer-reviewed reports. Selected key references are included in the bibliography.

Based on the collected series of 5,230 NSCLC patients seen in the period from 1975 to 1988 at the MD Anderson Cancer Center reported by Dr. Clifford 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 lung cancer patients, with a published 5-year survival rate of only 23%.[1]

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 because they are not randomized, lack rigorous pretreatment staging, or involve significant inhomogeneity in the study population, making interpretation of the results difficult. There are a few more rigorous randomized trials, which are discussed subsequently, that strongly suggest a combined modality approach is beneficial in stage IIIA disease. The approach showing promise in selected patients uses 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 12 years, and as a result there are limited reliable data with larger patient groups. In addition, the few larger randomized trials show conflicting data that further confounds our attempts to propose specific guidelines. Therefore, treatment recommendations for stage IIIA in this chapter are generally weak in many recommendations. This lack of consistent, larger, randomized data underscores the importance of enrolling patients in clinical trials whenever possible.

Because staging and treatment are so interdependent, intraoperative staging with systematic mediastinal node sampling or dissection is critically important. Unless histologic conformation 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 or mediastinal 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 I and II tumors. The present chapter will deal only with N2 disease. Furthermore, in patients with resectable T3 tumors (chest wall involvement, but not superior sulcus Pancoast tumors) who are found at surgery or preoperatively to have N2 mediastinal lymph node involvement, the following treatment recommendations apply in every respect.

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

Table 1—*Subsets of Stage IIIA(N_2)**

Subset	Description
$IIIA_1$	Incidental nodal metastases found on final pathology examination of the resection specimen
$IIIA_2$	Nodal (single station) metastases recognized intraoperatively
$IIIA_3$	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
$IIIA_4$	Bulky or fixed multistation N2 disease

*Adapted from Ruckdeschel.[2]

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previously.[2] The subsequent discussion of the literature and treatment guidelines will be broken down into these four subsets.

Treatment of Specific Patient Groups

Incidental N2 Disease (Stage IIIA$_{1-2}$)

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 IIIA$_1$). In others, metastases will be found intraoperatively as an unexpected finding at thoracotomy with a frozen section pathologic examination of mediastinal nodes (stage IIIA$_2$). Unexpected nodal metastases in this setting are not that unusual. In the era before PET scanning, one surgical series of 102 patients in 1990 from the Brompton Hospital in London who had no clinical evidence of mediastinal adenopathy at thoracotomy, 24% of patients had pathologically positive nodes.[3,4] With current preoperative staging including PET scans, finding unexpected N2 involvement at surgery is an uncommon event.

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.[3,4] 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 rate, with the best survivals seen in minimal N2 disease and complete resection.[5–12]

At least 27 to 36% of patients with metastatic disease to the mediastinal N2 nodes will not have involvement of the hilar or lobar lymph nodes.[13,14] In other words, in approximately one third of patients, metastatic tumor cells bypass the N1 hilar lymph nodes and spread directly to the mediastinal N2 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 versus dissection question. In a prospective randomized trial, Izbicki et al[15] found no survival benefit of an *en bloc* mediastinal lymph node dissection compared to systematic lymph node sampling in NSCLC. However, data from the North American Intergroup trial[16] comparing adjuvant postoperative radiotherapy with chemoradiotherapy 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[17] of lymph node harvesting techniques and results from this Intergroup trial, mediastinal lymph node dissection resulted in a significantly longer median survival than systematic lymph node sampling, but interestingly the survival advantage was limited to patients with right lung tumors (66.4 mo vs 24.5 mo; $p < 0.001$). 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 metastatic disease is found in the N2 nodes at mediastinoscopy before thoracotomy, for example, then further surgery at that time should be avoided based on the poor results of primary resection for stage IIIA disease. 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 if possible. This topic is discussed in a subsequent section.

Recommendations

1. *Surgical Considerations*: In patients with NSCLC who have incidental (occult) N2 disease (IIIA$_2$) found at surgical resection and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of

the planned lung resection and mediastinal lymphadenectomy is recommended. Grade of recommendation, 2C

2. In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended. Grade of recommendation, 1B

Adjuvant Radiotherapy

Although 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, 45 to 55 Gy, to eradicate microscopic residual disease and reduce rates of local recurrence was strongly suggested in several early single-institution trials.[18–20] What has remained controversial is whether 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. First, 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 radiation therapy might be curative? Second, what is the morbidity and mortality of adjuvant mediastinal radiotherapy with modern treatment planning techniques?

The Lung Cancer Study Group conducted a phase III trial[21] 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 Lung Cancer Study Group 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 patients who have undergone irradiation, most likely attributable to increased cardiopulmonary toxicity. In both the Lung Cancer Study Group and Medical Research Council 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 recently published postoperative radiation therapy meta-analysis[29] (PORT Meta-analysis Trialist Group) of 2,128 patients treated in nine randomized trials (six previously published series and three unpublished series) of postoperative radiation therapy concluded that this treatment was associated with a highly significant increase in the risk of death. Overall, the risk ratio was 1.21 ($p = 0.001$). The

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

Source	Year	Patients, No.	XRT Dose, Gy	Stage	Survival	Local Recurrence, Surgery Plus XRT/Surgery, %
Paterson and Russel[22]	1962	202	45	Any	NS	
Bagma[23]	1971	73	46	Any	NS	
Van Houtte et al[24]	1980	224	60	I, II	NS	4.8/20.7 ($p = 0.002$)
Weisenberger, LCSG 773[25]	1985	210	50	II, IIIA	NS	1/19 ($p = 0.02$)
Stephens et al[26]	1996	308	40	II, IIIA	NS	18/29 ($p = 0.003$)
Debevec et al[27]	1996	74	30	IIIA	NS	
Dautzenberg et al[28]	1999	728	60	II, IIIA	Worse for XRT group ($p = 0.002$)	

*NS = no significant difference; XRT = radiotherapy.

authors[29] 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 metaanalysis 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 > 2.0 Gy, with the Medical Research Council 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 ^{60}Co treatment beams, with their poorer depth-dose characteristics than higher energy 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 metaanalysis 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 metaanalysis, 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.

A later review and practice guidelines on postoperative radiotherapy in stage II and IIIA were developed and published in 2004 by the Lung Cancer Disease Site Group of Cancer Care Ontario Program of Evidence-Based Care.[30] After their review of the literature including metaanalyses, they concluded also that no survival benefit was found with postoperative radiotherapy in completely resected stage IIIA disease and that the data for improved local control were conflicting. They therefore recommended that the decision regarding postoperative radiotherapy be assessed in an individual case basis.

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, especially as assessed by the surgeon performing the resection. 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.

Adjuvant Chemotherapy

Because 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 performed over the past 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 because of 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, and in fact in most there was a detrimental effect resulting in a relative 15% increase in death in patients receiving adjuvant chemotherapy.[31]

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 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 et al[32] 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 metaanalysis by the Nonsmall Cell Lung Cancer Collaborative Group in 1995 analyzed the results of five non-cisplatin-based adjuvant chemotherapy regimens and found no survival benefit.[31] The Nonsmall Cell Lung Cancer Collaborative Group also

Table 3—*Randomized Controlled Trials of Surgery Plus Adjuvant Cisplatin-Based Chemotherapy vs Surgery Alone (With or Without Adjuvant Radiotherapy)

Source	Year	Patients, No.	Adjuvant Chemotherapy	Stage	Disease-Free Survival	Long-Term Survival (5 yr) in Surgery-Chemo/ Surgery, %
Niiranen et al[32]	1992	110	CAP	I–III (I, 90%)	NS	67/56 (p = 0.05 for stage I)
Ohta et al[33]	1993	181	CDDP/Vd	III	NS	35/41 (p = 0.86)
Feld et al[34]	1993	269	CAP	I–II (I, 84%)	NS	53/57 (p = 0.92)
Figlin and Piantodosi[35]	1994	188	CAP	II–III	NS	NS
SGACLC[36]	1995	333	CDDP/A/UFT	I–III (I, 61%)	NS	68.7/58.1 (p = 0.35)
Wada et al[37]	1996	323	CDDP/Vd/UFT vs UFT alone vs Surg alone	I–III		60.6/64.1/49 (p = 0.1)
Scagliotti et al[38]	2003	1209	Surg/MVP/RT vs Surg/RT	I–III (IIIA, 29%)	NS; HR, 0.89 (p = 0.13)	NS; HR, 0.96 (p = 0.59)
Waller et al[39]	2003	381	CV, MIC, MVP or NP for 3 cycles	I–III (IIIA, 34%)	54% both arms (p = 0.98)	NS
Arriagada et al[40]	2004	1867	CDDP + Et, Vn, or Vb 3–4 cycles	I–IIIA (IIIA, 39%)	39.4% (chemo) vs 34.3% at 5 yr; HR, 0.83 (p < 0.003)	44.5% (chemo) vs 40.4% at 5 yr; HR, 0.86 (p < 0.03)
Douillard et al[41] ANITA	2005	840	NP 4 cycles	I–IIIA (IIIA, 35%)		42% (chemo) vs 26% (p = 0.013)

*SGACLC = Study Group of Adjuvant Chemotherapy for Lung Cancer. A = doxorubicin; CAP = cyclophosphamide-doxorubicin-cisplatin; CDDP = cisplatin; Chemo = chemotherapy; CV = cisplatin, vindesine; Et = etoposide; HR = hazard ratio; MIC = mitomycin C, ifosphamide, cisplatin; MVP = mitomycin C, vindesine, cisplatin; NP = vinorelbine, cisplatin; RT = radiotherapy; Surg = surgery; Vb = vinblastine; UFT = uracil-tegafur; Vd = vindesine; Vn = vinorelbine. See Table 2 for expansion of abbreviations not used in the text.

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 et al[42] 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 of 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 positive Japanese experience in 1996 with low-dose, minimally toxic, prolonged adjuvant therapy with uracil-tegafur suggests that the "standard" short-term, dose-intense adjuvant therapy may not be the best or only approach to consider.[37]

In the 2000s, a number of larger randomized trials of cisplatin-based adjuvant chemotherapy trials have matured providing data to review. All compared surgery with postoperative chemotherapy (some with adjuvant radiotherapy) to surgery (with or without adjuvant radiotherapy) in resected stages IB-IIIA. The Adjuvant Lung Project Italy (ALPI) trial[38] published in 2003 enlisted the enrollment of 1,209 patients (28.5% stage IIIA) from 66 Italian centers and 5 other European centers outside of Italy who were randomized within 42 days after surgery to three cycles of adjuvant chemotherapy with mitomycin C, vindesine, and cisplatin versus no chemotherapy. Adjuvant radiotherapy was given to 65% of patients in the mitomycin C, vindesine, and cisplatin arm and 82% of patients in the control arm. Sixty-nine percent of patients in the mitomycin C, vindesine, and cisplatin arm completed all chemotherapy doses. After a median 64.5-month follow-up, the combined results showed no significant improvement in overall survival (hazard ratio, 0.96) or progression-free survival (hazard ratio, 0.89). Similarly negative results were also presented in 2003 with the much smaller Big Lung Trial (Medical Research Council), in which 381 patients (34% stage IIIA) underwent surgical resection with randomization to adjuvant chemotherapy with three cycles of one of four cisplatin-based regimens vs no chemotherapy.[39] Of the chemotherapy arm, only 64% received all planned cycles. On analysis

of results, there was no survival benefit with adjuvant chemotherapy (hazard ratio, 1.00; p = 0.98), confirming the ALPI findings.[38]

However, 2004 saw the publication of the larger International Adjuvant Lung Cancer Trial of 1,867 patients with stages IB to IIIA (39% stage IIIA),[40] which randomized patients to three to four cycles of postoperative cisplatin-based chemotherapy versus the control group of surgery alone (with adjuvant 60 Gy radiotherapy given in both arms of stage IIIA patients). After a median 56-month follow-up, the overall survival rate was significantly higher in the chemotherapy group (hazard ratio, 0.86), with a 5-year survival rate of 44.5% in the chemotherapy group versus 40.4% in the control arm, with the strongest benefit in patients with stage III disease. The disease-free survival rate was likewise significantly higher in the chemotherapy group (hazard ratio, 0.83).

The most recently presented adjuvant chemotherapy trial is the Adjuvant Navelbine International Trialist Association study that randomized 840 completely resected patients with stages I to IIIA (35% stage IIIA) to four postoperative cycles of cisplatin and navelbine vs observation (patients received postoperative radiotherapy per preference of each participating center).[41] After a median follow-up of > 70 months, the long-term 5-year survival of stage IIIA patients in the chemotherapy arm was significantly greater at 42% vs 26% in the observation arm (p = 0.013). The benefit of adjuvant chemotherapy was also seen in stage II patients but not in stage I.

The most recent metaanalysis of adjuvant chemotherapy published in 2005 by Berghmans et al[43] involved 19 trials totaling 7,644 patients (12 studies included some stage IIIA patients). Their analysis did include the International Adjuvant Lung Cancer Trial and ALPI trial but not the strongly positive Adjuvant Navelbine International Trialist Association trial. Although the combined results for all stages of disease significantly favored adjuvant chemotherapy over observation alone (hazard ratio, 0.85; 95% confidence interval, 0.79 to 0.91), the subgroup analysis with stage III (N2 positive) patients showed a trend favoring adjuvant treatment but it did not quite reach statistical significance (combined hazard ratio with fixed-effects, 0.84; 95% confidence interval, 0.74 to 0.95; p = 0.07). The authors suggest that future trials consider clearly separating resected stage III from the earlier stages to better address the role of adjuvant chemotherapy in this controversial advanced stage.

Adjuvant Combination Chemoradiotherapy

With the lack of any clear-cut survival advantage in adjuvant radiotherapy and the possible positive benefit of adjuvant chemotherapy in resected N2 lung cancer, attention turned to question the potential benefit of combination chemoradiotherapy postoperatively. Adjuvant radiotherapy appears to decrease local recurrence but failure with distant metastases is a predominant pattern, which theoretically should be complementary to the addition of adjuvant systemic chemotherapy.

To date there have been five published randomized controlled trials involving patients with N2 disease (Table 4) with adjuvant combined chemotherapy and radiotherapy, beginning in 1988 with the Lung Cancer Study group 791.[44] This trial involved patients who had incomplete resections (positive 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 in 2000 is

Table 4—*Randomized Controlled Trials of Surgery Plus Adjuvant Chemoradiotherapy vs Surgery Plus Adjuvant Radiotherapy

Source	Year	Patients, No.	Stage	Chemotherapy Radiotherapy Regimens	Disease-Free Survival	Long-term Survival Surgery-XRT vs Surgery-XRT/Chemotherapy, %
Lad et al[44]	1988	164	II–III	CAP40 Gy (split course)	Chemo favored (p = 0.004)	54/68 (p = 0.1); 1 yr
Sawamura et al[45]	1988	52	II–III	Tegafur-CDDP 50 Gy	NS	NS
Pisters et al[46]	1994	72	III	Vd-CDDP 40 Gy	NS	44/31 (p = 0.42); 2 yr
Dautzenberg et al[47]	1995	267	I–III	A-C-CCNU-CDDP-V 60 Gy	NS	12/13 (p = 0.68); 10 yr
Keller et al[16] (Intergroup E3590)	2000	488	II–IIIA	CDDP-VP-16 50.4 Gy	NS	39 mo/38 mo (p = 0.56 median)

*CCNU = lomustine; V = vincristine; VP-16 = etoposide; see Tables 2 and 3 for other abbreviations.

the Intergroup trial (E3590), which included 488 patient and failed to demonstrate any increase in median survival or disease-free survival. In a companion laboratory subset analysis, Schiller et al[48] 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 mo vs 25 mo; $p = 0.09$). 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.

Looking from the other direction, little data are available addressing the question of the survival advantage of adding adjuvant radiotherapy to adjuvant chemotherapy in fully resected stage IIIA patient. The only recent randomized study designed to answer this question was the Phase III Cancer and Leukemia Group B (CALGB) 9734 trial presented in 2003.[49] This small study of 40 patients (closed early because of poor accrual) with resected stage IIIA disease compared four cycles of adjuvant carboplatin and paclitaxel with or without 50-Gy adjuvant radiotherapy. One-year survival rates were not significantly different at 70% in the chemotherapy arm, vs 72% in the chemotherapy/radiotherapy arm. The authors concluded that there was no benefit to adding adjuvant radiotherapy to adjuvant chemotherapy in completely resected stage IIIA NSCLC.

RECOMMENDATION

3. *Adjuvant Chemotherapy*: In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1-2}$) and who have good performance status, adjuvant platinum-based chemotherapy is recommended. Grade of recommendation, 1A

RECOMMENDATION

4. *Adjuvant Radiotherapy*: In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1-2}$), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence. Grade of recommendation, 2C

RECOMMENDATION

5. *Adjuvant Chemoradiotherapy*: In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1-2}$), combined postoperative concurrent chemotherapy and radiotherapy is not recommended except as part of a clinical trial. Grade of recommendation, 1B

Potentially Resectable N2 Disease (Stage $IIIA_3$)

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, with hopes 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 given before surgery in the neoadjuvant or induction setting, there were enough positive results to persuade even the most pessimistic that this approach may have value, warranting randomized trials.

Induction (Neoadjuvant) Therapy

The majority of stage IIIA patients have enlarged (> 1.0 cm short axis diameter) N2 nodes (our stage $IIIA_3$) on chest CT. Mediastinoscopy should generally be performed in this setting to document that these nodes actually contain metastatic tumor, because 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.[50] Of special note is the location of the N_2 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 yet who are found to have positive nodes at thoracotomy.[51] However, other studies contradict this finding. Naruke et al[52] found that metastatic disease to the subcarinal lymph nodes adversely affected prognosis compared to other lymph node locations. The Lung Cancer Study Group[53] 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 medi-

astinal nodal metastases in other locations. Miller et al[54] analyzed their long-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. Finally, Okada et al[55] 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. 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 with potential nodal clearance of tumor with down-staging, decreased surgical seeding, *in vivo* chemosensitivity testing of the chemotherapy regimen, and increased patient acceptance and compliance. However, neoadjuvant therapy also has the potential disadvantages of a delay in primary tumor control (resection) 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,[50] 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 et al[56] gave induction chemotherapy with mitomycin C, vindesine or vinblastine, and cisplatin to patients with stage IIIA disease with bulky mediastinal nodal metastases or multilevel nodal disease and found a 65% complete resection rate, 15% treatment-related mortality, and a 28% 3-year survival, which was far better than historical controls (8% 3-year survival). Other phase II induction chemotherapy trials have generally confirmed this trial.

Eight randomized phase III trials of neoadjuvant therapy in stage IIIA patients have been published over the past decade (Table 5) comparing neoadjuvant therapy followed by surgery vs surgery alone. Many concerns have been raised about these phase III as well as the phase II neoadjuvant trials. First, there was no consistent surgical (pathologic) staging of the mediastinal lymph nodes. Second, variable numbers of much better prognosis patients (T3N0 and T3N1) were included in these trials that might have influenced the outcome of the trials. Third, some poorer prognosis patients (stage IIIB) were mixed in with better-prognosis patients, thereby worsening results. Fourth, most trials have small numbers of patients because of poor accrual with resultant low statistical power. With these caveats in mind, the results of the trials from Barcelona[57,58] and MD Anderson[59,60] provide promising results. Both of these trials were closed early to further accrual after the interim analyses

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

Study	Year	Patients, No.	Induction, Study Arm 1/Study Arm 2	Median Survival, Study Arm 1/Study Arm 2, mo	Survival Rate, Study Arm 1/Study Arm 2, %
Pass et al[61]†	1992	27	Cis, Et/none	29/16 (p = 0.095)	42 (3 yr)/12 (3 yr)
Rosell et al[57,58]‡	1994/1999	60	Ifos, MIC, Cis/none	22/10 (p < 0.005)	29 (2 yr), 17(5 yr)/5(2 yr), 0 (5 yr)
Roth et al[59,60]‡	1994/1998	60	Cis, Et, Cyclo/none	21/14 (p = 0.048)	46 (3 yr), 36 (5 yr)/19 (3 yr), 15 (5 yr)
Wagner et al[62]	1994	57	Mito, Vb, Cis/ XRT 44 Gy	12/12	27% at 4 yr for both arms
Elias et al[63]	1997	57	XRT 40 Gy/ Cis, Et	23/19 (p = 0.64)	NR/NR
DePierre et al[64]§	2002	167 with IIIA	Mito, Cis, Ifos/none	NR	28 (5 yr, chemo)/20 (5 yr, estimated); p = NS
Nagai et al[65]†	2003	62	Cis, Vd none	17/16	10 (5 yr, chemo)/22 (5 yr, estimated); p = 0.5274

*Adapted from Garland et al.[66] > Cis = cisplatin; Cyclo = cyclophosphamide; Ifos = ifosfamide; Mito = mitomycin C; NR = not reported. See Tables 2 and 3 for abbreviation not used in the text.

†Study closed early because of poor accrual.

‡Study closed early due to large, significant differences between treatment arms.

§Study combined patients with stages IB, II, and IIIA disease.

demonstrated significant survival advantages for the induction chemotherapy arm.

Rosell et al[57,58] in Barcelona randomized 60 stage IIIA patients to either surgery alone or three cycles of induction chemotherapy with mitomycin C, 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 ($p < 0.005$). The 2- and 5-year survival rates 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 because 27% of the patients had more favorable T3N0 or T3N1 tumors.

Roth et al[59,60] at MD Anderson 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 given only to incompletely resected patients. Only 83% of patients had disease invasively staged before treatment. Also, 26% of patients had more favorable T3N0 or T3N1 tumors. The median survivals were 21 months for the chemotherapy-surgery arm versus 14 months for the surgery-only arm ($p = 0.048$). The 3- 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 down-staging in the chemotherapy-surgery arm because of the induction therapy. Although encouraging, the clinical implications of the results of these small randomized trials are unclear.

The most recent neoadjuvant chemotherapy trial with all stages is from Depierre et al[64] 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: primary surgery vs two cycles preoperative chemotherapy with mitomycin C, ifosfamide, and cisplatin followed by surgical resection and then two cycles postoperatively. Patients in both 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 had 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 chemotherapy-surgery arm; 75 patients in 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 invasive histologic verification of nodal stage before 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 theses 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 stage IIIA NSCLC.

The small recent Japanese Clinical Oncology Group 9202 trial[65] randomized 62 histologically proven stage IIIA (N2) patients to either three cycles of induction chemotherapy with cisplatin and vindesine vs surgery alone. Unfortunately, this well-designed study terminated prematurely because of poor accrual lowering the statistical power. After a median 6.2-year follow-up, there were no significant differences in the survival rates of the two arms (median survival, 17 mo in the chemotherapy group, vs 16 mo with surgery alone; $p = 0.5274$).

The 2005 metaanalysis of Berghmans et al[43] evaluating neoadjuvant chemotherapy in the four randomized trials (including the French Cooperative Trial) involving stage III patients found only a very marginal benefit in favor of induction chemotherapy

Table 6—*Randomized Controlled Trials of Preoperative Neoadjuvant (Induction) Therapy and Surgery vs Chemotherapy/Radiotherapy Alone (No Surgery) in Stage IIIA NSCLC

Source	Year	Patients, No.	Chemo/Radiotherapy/Surgery	Chemo-Radiotherapy	Median Survival, mo	Survival, %
Johnstone et al[66]	2002	73	Cis/Vb/Mito, no XRT	Cis/Vb/Mito + 64 Gy XRT	19.4(surgery) vs 17.4 (p = NS)	70 (surgery) vs 66 at 1 yr (p = NS)
Taylor et al[68]	2004	107	Cis-based, 2–4 cycles, no XRT	Cis-based 3 cycles + 69.9 Gy concurrent XRT	31 (surgery) vs 27 (p = NS)	33 (surgery) vs 30 at 5 yr (p = NS)
van Meerbeeck et al[69]	2005	333	Cis-based 3 cycles, no XRT	Cis-based 3 cycles + 60 Gy concurrent XRT	16.4 (surgery) vs 17.5 (p = NS)	16 (surgery) vs 13 at 5 yr (p = NS)
Albain et al[70]	2005	396	Cis/Et 2 cycles + 45 Gy XRT then Surg (26% oper mortality in pneumo)	Cis/Et 2 cycles + 61 Gy concurrent XRT	12.8 (surgery) vs 10.5 (progression-free) [p = 0.017]	27.2 (surgery) vs 20.3 at 5 yr (p = 0.10)

*Oper = operative; Pneumo = pneumonectomy; see other tables for expansion of abbreviations.

(hazard ratio with a random effect, 0.66; 95% confidence interval, 0.48 to 0.93).

The most recent phase III trials (Table 6) of neoadjuvant therapy that were designed specifically for stage IIIA lung cancer took a slightly different approach, comparing induction chemotherapy followed by surgery versus chemoradiotherapy alone (no surgery). This strategy was intended to test which local treatment modality (surgery or radiotherapy) is most efficacious. The Radiation Therapy Oncology Group (RTOG) 8901 trial[67] published in 2002 treated 73 patients with histologically proven N2 disease with cisplatin, vinblastine, and mitomycin C (mitomycin C was eliminated later) then randomized the patients to surgery or 64 Gy radiotherapy, followed by consolidation chemotherapy with cisplatin and vinblastine. Local control and survival rates were essentially equal between the two arms, although low accrual rates to the study lowered the statistical power of the study.

Taylor et al[68] at MD Anderson in 2004 published their trial of 107 patients with "clinical" stage IIIA NSCLC who were randomized to receive either two to four cycles of cisplatin-based chemotherapy followed by surgery and postoperative radiotherapy (64% of patients) vs the concurrent chemotherapy/radiotherapy arm (three cycles of cisplatin-based chemotherapy plus 69.9-Gy radiotherapy). After a mean 20-month follow-up, there was no significant difference in the two treatment groups for local control and survival rates. Of interest, surgical patients whose disease responded to induction chemotherapy had a significantly improved 5-year survival rate over those with stable or progressive disease (50% vs 16%; p = 0.0001).

The large European Organization for Research and Treatment of Cancer 08941 trial[69] presented at the American Society of Clinical Oncology meeting in 2005 treated 333 histologically proven stage IIIA (N2) patients with three cycles of cisplatin-based chemotherapy, then randomized them to surgery (with optional postoperative radiotherapy in 39%) vs sequential 60-Gy thoracic radiotherapy. Complete resection was performed in only 51% patients in the surgical arm, but there was pathologic down-staging in 42%. After a median 72-month follow-up, there was no significant difference in overall survival (35% surgery vs 41% at 2 years; hazard ratio, 0.95) or progression-free survival (2-year progression-free survival 27% surgery vs 24%; p = 0.6).

The more recent of the North American Intergroup 0196 trial[70] presented in 2005 had 396 patients with histologically proven stage IIIA NSCLC that were technically resectable and who were randomized to either chemotherapy (two cycles cisplatin/etoposide) and concurrent 45-Gy radiotherapy followed by surgery (with two cycles postoperative

chemotherapy) vs two cycles cisplatin/etoposide and 61 Gy radiotherapy. Treatment-related mortality was higher in the surgery group (7.9%) vs the nonsurgical arm (2.1%). Surgical mortality was particularly high in pneumonectomies (26%). In the surgical arm, there was a complete pathologic response in 18%, and down-staging with nodal clearance in 46%. Progression-free survival was significantly better in the surgical arm but the overall 5-year survival was similar in the two arms (27.2% surgical vs 20.3%; $p = 0.10$). However the 5-year survival in the surgical arm with complete pathologic clearing of lymph node disease was significantly greater at 41% ($p < 0.0001$).

As is apparent from Tables 5 and 6, the evidence favoring induction chemotherapy followed by surgery in stage IIIA NSCLC is marginal at best, even in the larger trials in which there is pretreatment histologic confirmation of accurate staging. Although the use of induction chemotherapy (with or without radiotherapy with N2 disease) followed by surgery in stage IIIA lung cancer appears feasible, published data do not support this treatment as the standard of care in the community. Ideally, this approach should only be administered in the setting of an investigational protocol. Finally, the older patient or the poor performance status patient should still be approached with caution when considering these aggressive multimodality protocols.

Recommendations

6. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), referral for multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment. Grade of recommendation, 1C

7. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), induction therapy followed by surgery is not recommended except as part of a clinical trial. Grade of recommendation, 1C

8. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who do receive induction chemoradiotherapy as part of a clinical trial, pneumonectomy is not recommended. The subsequent surgical resection in this setting should be limited to a lobectomy. If after induction chemoradiotherapy it appears that a pneumonectomy will be needed, it is recommended that pneumonectomy not be performed and treatment should be continued with full-dose radiotherapy. Grade of recommendation, 1B

9. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), primary surgical resection followed by adjuvant therapy is not recommended except as part of a clinical trial. Grade of recommendation, 1C

10. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgery alone is not recommended. Grade of recommendation, 1A

11. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), platinum-based combination chemoradiotherapy is recommended as primary treatment. Grade of recommendation, 1B

Surgical Considerations in Stage $IIIA_3$

Although the use of neoadjuvant chemotherapy with or without radiotherapy may have potential advantages in the treatment of locally advanced lung cancer, concern has been raised in numerous publications about the possible increase in morbidity and mortality of the subsequent lung resections. One of the reports by Roberts et al[71] in 2001 found neoadjuvant chemotherapy increased the perioperative complications in their series of 34 patients. However, other groups such as Sonett et al[72] in 1999 reported safe pulmonary resections after chemotherapy and high-dose thoracic radiation in 19 patients. Siegenthaler et al[73] at MD Anderson in a larger group of 380 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[74] 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 et al[75] 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 low volume of lung resections. Finally, Silvestri et al[76] 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.

The definition of what is meant by "resectable," "marginally 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 is also involved initially in the beginning of the evaluation, such that an informed estimate of the surgical resectability of the tumor can be made initially, 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 necessarily undergo surgery. Although the data are not conclusive, a combination of anatomic (CT scan) and physiologic (PET scan) imaging may be useful in this decision-making process. In the phase II Southwestern Oncology Group trial[77] of induction chemoradiotherapy followed by surgery in stages IIIA and IIIB disease, there was complete pathologic clearance of tumor in 22% of resection specimens with an overall 27% 3-year survival rate. 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 et al[78] 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 down-staged to pathologic N0 had a 35.8% 5-year survival rate, whereas the remainder of patients with residual nodal disease at surgery had only a 9% 5-year survival rate. These and other studies suggest that surgical resection should be avoided after induction therapy in patients 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 Margaritora et al.[79] The use of PET after induction therapy to determine response to therapy looks somewhat promising with current studies summarized in Table 7. Early small studies found up to 100% accuracy with PET restaging after induction chemotherapy (100% in one small preliminary trial).[80] In a retrospective review of the accuracy of PET scans after induction chemotherapy, radiotherapy, or both in 56 patients who underwent subsequent surgery, Akhurst et al[81] found that PET had a 98% positive predictive value for detecting residual viable disease in the primary tumor. However, PET overstaged the

Table 7—*Accuracy of ^{18}F Fluorodeoxyglucose-PET for Diagnosis of Residual Tumor or Mediastinal Disease After Induction Chemotherapy or Chemoradiotherapy in Surgically Treated Patients With Stage IIIA NSCLC

Source	Year	Patients, No.	Primary Tumor				Mediastinal Lymph Nodes (Calculated per Nodal Station)				Median Survival
			Se	Sp	PPV	NPV	Se	Sp	PPV	NPV	
Vansteenkiste et al[80]	1998	15 (9 surgical)					100	100	100	100	Better with mediastinal clearance of > 50% decrease in SUV of primary tumor after IC
Akhurst et al[81]	2002	56	90	67	98	29	77	57	63	27	NR
Hellwig et al[82]‖	2004	47	81	64	84	58	50†, 64‡, 64§	88, 79, 96	57, 33, 70	85, 93, 94	After resection > 56 mo with SUV < 4; 19 mo with SUV ≥ 4 ($p < 0.001$)
Cerfolio et al[83]‖	2006	93					68	88	75	80	NR

*IC = induction chemotherapy; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Sp = specificity. See Table 5 for expansion of abbreviation not used in the text.

†Calculated per patient.

‡Quantitative reading.

§Visual (qualitative) reading.

‖Induction chemoradiotherapy used.

nodal status in 33%, understaged it in 15%, and was correct in only 52%. They concluded that after induction therapy, PET accurately detects residual viable primary tumor but not the involvement of mediastinal nodes.

In a subsequent study, Hellwig et al[82] reevaluated 47 patients with FDG-PET after induction chemoradiotherapy in stage IIIA disease, finding unexpected metastases in nine patients. The standardized uptake value (SUV) was higher with viable residual primary tumor than those with no viable tumor, with an SUV > 5.8 indicating viability of the tumor after chemotherapy. Median survival after resection was significantly greater when the tumor SUV was < 4 (56 mo with SUV < 4 vs 19 mo with SUV > 4; $p < 0.001$). The reevaluation of the mediastinal lymph nodes in this study was more accurate. There was a high negative predictive value of PET in mediastinal restaging especially with visual reading of the PET scan, which the authors concluded allows omission of repeat invasive mediastinal restaging.

The most recent trial by Cerfolio et al[83] prospectively evaluated the accuracy of fusion PET/CT and conventional CT in restaging 93 patients after induction chemoradiotherapy. They found that the percentage change in the SUV (MaxSUV) when restaging the primary tumor was an accurate predictor of pathologic response, such that a decrease of $> 75\%$ of MaxSUV suggested no viable malignant cells in the primary tumor. A decrease of $> 50\%$ in the MaxSUV in mediastinal lymph nodes suggested complete tumor clearing. Still, the 20% false-negative rate and 25% false-positive rate in lymph nodes strongly argues for rebiopsy of nodes in question. Although the authors found integrated PET/CT to be more accurate than standard CT in reevaluation of staging after induction therapy especially in stage 0 and I disease, results are not accurate enough to make firm treatment decisions without histologic confirmation.

Therefore, until further refinements in imaging techniques are available, it is premature to routinely use postinduction therapy PET scans for restaging to make decisions about surgical resectability and particularly whether there is residual nodal involvement with viable tumor. Finally, careful reevaluation for surgery after induction therapy is necessary because incomplete resection or thoracotomy with no resection results in a poor survival in the stage IIIA patient.

Recommendations

12. *Surgical Considerations*: In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgical debulking procedures are not recommended. Grade of recommendation, 1A

13. *Surgical Considerations*: In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who have incomplete resections, postoperative platinum-based chemoradiotherapy is recommended. Grade of recommendation, 1C

Unresectable Bulky N2 Disease (Stage $IIIA_4$)

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 diameter in short axis are suspicious. We then would define bulky nodal disease as those involving lymph nodes > 2 cm in short-axis diameter measured by chest 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 relies on the experience and judgment of the thoracic surgeon.

However, aside from the relatively few questionable 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 past decade combination chemoradiotherapy appears to offer improved results, as discussed in the next sections.

Radiotherapy Alone

Early attempts to use nonsurgical treatment modalities for unresectable locally advanced disease (our stage $IIIA_4$) involved single modality chest radiotherapy, yielding poor survival rates 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[84] used 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 rate of 20%, with an apparent benefit for patients treated at 69.6 Gy. There appeared to be acceptable acute or late toxicity using the hyperfractionated schedule.[84]

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) for > 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[85] comparing CHART with a standard dose and fractionation radiotherapy regimen in locally advanced NSCLC, there was a survival advantage for CHART. American groups have used versions of CHART that eliminate the weekend doses and deliver multiple daily fractions within an 8-hour time period, referred to as hyperfractionated accelerated radiation therapy (HART). A recent Eastern Cooperative Oncology Group (ECOG) pilot study (ECOG 4593) used this schedule and obtained a preliminary median survival of 13 months with acceptable toxicities, primarily esophagitis, at the completion of radiotherapy.[86] In a subsequent companion quality of life assessment of patients undergoing the accelerated HART regimen in EGOG 4593, Auchter et al[87] 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.

Recently, the ECOG conducted a multicenter trial for unresectable locally advanced stage IIIA and IIIB NSCLC (ECOG 2597) in which patients were randomized after induction chemotherapy with two cycles carboplatin and paclitaxel to standard fractionation radiotherapy to a total dose of 64 Gy vs HART to a total dose of 57.6 Gy in a randomized design.[88] The trial entered 141 patients into the trial (only 42% of the target), but it closed early because of slow accrual, mucosal toxicity, and logistics of administering HART. Although statistical significance was not reached (possibly because it was underpowered), the median survival rates were 20.3 months for the HART arm vs 14.9 months for standard fractionation radiotherapy ($p = 0.28$). There was a nonsignificant trend for improved 3-year survival with 34% (HART) vs 14% for standard radiotherapy. The findings in this study suggest that this technique of accelerated radiotherapy may work by altering tumor cell kinetics resulting in adverse affects on tumor repopulation and improved patient survival, all arguing for additional future exploration of the HART treatment strategy.

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 sequentially by radiotherapy, concurrent chemotherapy/radiotherapy, induction chemotherapy followed by concurrent chemotherapy/radiotherapy, or concurrent chemotherapy/radiotherapy followed by consolidation chemotherapy) 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 promising pilot trial[89] showed significantly improved median and 2-year survival rates of 16 months and 30%, respectively, using four cycles of etoposide and cisplatin with concurrent radiotherapy to 60 Gy. 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 8, with some trials discussed in this article. Of note, the earliest trials were negative showing no survival benefit with chemotherapy but the regimens used had either low-dose cisplatin or nonplatinum-based chemotherapy, which might be expected to be ineffective. Later trials using more appropriate dose chemotherapy all had positive results.

A pivotal CALGB randomized trial[98] initially presented in 1990 showed the benefit of adding chemotherapy in a sequential fashion to radiotherapy in the setting of locally advanced disease. The study com-

Table 8—*Randomized Controlled Trials of Sequential or Concurrent Chemoradiotherapy vs Radiotherapy Alone for Unresectable Stage III NSCLC**

Source	Year	Patients, No.	Timing CT/RT	Chemotherapy Radiotherapy Regimens, Gy	Study Result	Acute Toxicity CT+RT/RT, %	2-yr Survival CT+RT/RT, %
Soresi et al[90]	1988	95	Concurrent	Cis, 50	Neg		40/25
Mattson et al[91]	1988	238	Sequential plus concurrent	CAP, 55	Neg		19/17
Ansari et al[92]	1991	183	Concurrent	Cis, 60	Neg		15/9
Morton et al[93]	1991	114	Sequential	MACC, 60	Neg	21/9	21/16
Trovo et al[94]	1992	173	Concurrent	Cis, 45	Neg	15/7	13/13
Schaake-Koning et al[95]	1992	308	Concurrent	Cis, 55 (split course)	Pos	41/11	26/13
Wolf et al[96]	1994	85	Sequential plus concurrent	Vd/Ifos/Cis, 50	Pos	8.2/11	24/12
Le Chevalier et al[97]	1994	353	Sequential	Vd/Lo/Cis/Cyc, 65	Pos		21/14
Dillman et al[98]	1996	155	Sequential	Cis/Vinbl, 60	Pos	14/6	26/13
Jeremic et al[99]	1996	131	Concurrent	Carbo/Et, 69.9 bid	Pos		52/38
Cullen et al[100]	1999	446	Sequential	Mito/Ifos/Cis median, 50	Neg		20/16 (p = 0.14)
Sause et al[101]	2000	490	Sequential	Cis/Vb, + 60 vs standard RT vs Hyper	Pos	Chemo, 3.4; RT, 2.3; Hyper, 2.0	Chemo, 32; RT, 21; Hyper, 24 (p = 0.04)

*Carbo = carboplatin; Hyper = hyperfractionated radiotherapy; Lo = loumustine; MACC = methotrexate-doxorubicin-cyclophosphamide-lomustine; Mito = mitomycin; Neg = negative; Pos = positive. See other Tables for expansion of abbreviations.

pared two cycles of cisplatin and vinblastine added to standard fractionation radiotherapy (60 Gy) versus 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).

A multicenter French study reported by Le Chevalier et al[102] also confirmed improved survival for the chemotherapy plus radiotherapy arm compared to radiotherapy alone (3-year survival rates of 11% vs 5%, 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 metaanalyses[31,103,104] reviewing >50 trials have confirmed the survival benefit of combined platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced unresectable NSCLC.

A subsequent large British trial[100] randomized 446 patients with localized unresectable disease to two arms: (1) chemotherapy (mitomycin C, 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). This trial allowed lower performance status 2 (ECOG performance status 2) patients, and 15% of the chemoradiotherapy arm and 11% of the radiotherapy-only arm were ECOG performance status 2 patients. The median survival and 2-year survival rates 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. The inclusion of the poorer performance status patients in this trial, unlike most other trials, is thought to have influenced the results, particularly in the chemoradiotherapy arm.

However, when patients were selected with a good performance status (Karnofsky ≥ 70) and minimal weight loss ($<5\%$), the superiority of combined-modality chemotherapy plus radiotherapy in a sequential fashion compared to radiotherapy alone was readily demonstrated in a large randomized trial[101] of 458 patients with unresectable stages II, IIIA, and IIIB, performed by the Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and the Southwest Oncology Group. The final results showed improved 2-year, 5-year, and median survival rates with chemotherapy followed sequentially by conventional radiotherapy, which was significantly better than either conventional radiotherapy or hyperfractionated radiotherapy alone.

Concurrent Chemotherapy and Radiotherapy

With the combination of chemotherapy and radiotherapy demonstrating unequivocal improved survival over radiotherapy alone in locally advanced unresectable stage III NSCLC, this combination has become the standard of care worldwide. The remaining question now is, what is the optimal delivery strategy for treatment?

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. A European Organization for Research and Treatment of Cancer three-arm trial[95] published in 1992 compared radiotherapy (split course) concurrent with daily or weekly concurrent cisplatin to radiotherapy alone. There were improved 2-year and 3-year survival rates 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 subsequent trials including a large Japanese randomized trial[105] of 320 patients that compared chemotherapy (mitomycin C, 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. Esophagitis rates were low with concurrent therapy. At a 5-year median follow-up, 2-year and 5-year survival rates were 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 patients in the concurrent arm, but the mortality rate was low ($< 1\%$) and not significantly different in both groups.

A later RTOG trial[106] (RTOG 9410) randomized 610 patients with unresectable stage II and III to one of three arms: (1) sequential chemotherapy with cisplatin and vinblastine followed by 60-Gy radiotherapy; (2) concurrent chemotherapy with cisplatin and vinblastine with daily radiotherapy to 60 Gy; or (3) concurrent chemotherapy with cisplatin and vinblastine with twice-daily radiotherapy. The concurrent chemotherapy with daily radiotherapy significantly improved median and 4-year survival rates over sequential chemotherapy/radiotherapy, and the concurrent chemotherapy with twice-daily radiotherapy had intermediate rates. The 4-year survival rates were 12% sequential vs 21% concurrent chemotherapy/radiotherapy daily vs 17% concurrent chemotherapy/radiotherapy twice daily ($p = 0.46$). As expected, acute toxicity was somewhat higher in the concurrent arms, but late toxicity rates were similar.

Concurrent chemoradiotherapy has several drawbacks, including the difficulty in maintaining full-dose chemotherapy to treat systemic disease, especially with some of the newer agents such as gemcitabine, docetaxel, and paclitaxel, all of which require dose reductions when given concurrently with radiotherapy. Concurrent chemotherapy/radiotherapy also has increased local adverse effects (esophagitis and pneumonitis). Finally, although concurrent is superior to sequential therapy, the long-term survival rates for patients remain low.

Another approach has been induction full-dose chemotherapy, which is intended to address micrometastases, before starting concurrent chemoradiotherapy. Three major randomized trials addressed this approach (CALGB/ECOG,[107] French Lung Cancer Study Group,[108] and CALGB 39801[109]); however, unfortunately, the results did not show any survival benefit for induction chemotherapy followed by concurrent chemotherapy/radiotherapy over concurrent chemoradiation alone.

More recently, interest has focused on the evaluation of concurrent chemoradiotherapy followed by consolidation chemotherapy. The Southwest Oncology Group began with a small phase II trial (Southwest Oncology Group 9019) enrolling 50 patients with stage IIIB NSCLC who received cisplatin/etoposide with concurrent radiotherapy (61 Gy) followed by two additional cycles of cisplatin/etoposide.[110] The 5-year survival rate of 15% was encouraging and led to the Southwest Oncology Group 9504 phase II trial[111,112] of 83 patients receiving concurrent chemotherapy/radiotherapy with cisplatin/etoposide and 61 Gy radiotherapy, but the follow-up consolidation was accomplished by docetaxel. The overall 5-year survival rate was 29% with docetaxel consolidation, which was much improved over the 15% rate with cisplatin/etoposide consolidation in the previous study. These highly encouraging results led to the larger ongoing phase III randomized trial Southwest Oncology Group 0023, which has accrued more than 500 patients. Patients with stage III NSCLC receive concurrent cisplatin/etoposide chemotherapy with radiotherapy followed by docetaxel consolidation chemotherapy, with subsequent randomization to maintenance gefitinib or placebo.[113] Preliminary results show a low incidence of pneumonitis (8%) and a median survival of 29 months (placebo) and 19 months (gefitinib) [$p = 0.09$]. Despite the lack of any favorable effect of gefitinib, this larger trial of concurrent chemotherapy/radiotherapy with docetaxel consolidation shows vary favorable survival rates compared to historical data. This technique of consolidation chemother-

apy is being investigated by the Hoosier Oncology Group LUN 01–24, currently undergoing accrual, which treats stage III patients with concurrent chemotherapy/radiotherapy then with randomization to docetaxel consolidation vs observation.

Although concurrent chemoradiotherapy (with its increased toxicity) in stage III NSCLC looks promising with its superior survival rates over sequential chemotherapy/radiotherapy treatment in good performance status patients, additional positive randomized trials will further cement this regimen in front as the preferred first-line treatment. Adding consolidation chemotherapy promises even greater survival gains, but awaits validation with larger randomized trials. The newer targeted therapies are theoretically attractive either in combination with concurrent therapy (perhaps functioning as radiosensitizers) or in the consolidation setting. Again, further clinical trials are needed to define the optimal role of these novel agents in treatment strategies for unresectable IIIA (N2) disease. The subsequent chapter on treatment of stage IIIB disease reviews chemoradiotherapy for unresectable locally advanced NSCLC in more depth.

Recommendations

14. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, radiotherapy alone is not recommended. Grade of recommendation, 1A

15. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, combination platinum-based chemotherapy and radiotherapy are recommended. Grade of recommendation, 1A

16. In patients with NSCLC who have bulky N2 disease ($IIIA_4$), good performance status and minimal weight loss, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy. Grade of recommendation, 1A

Conclusion

Despite many earlier studies, the optimal treatment recommendations in the various clinical presentations of stage IIIA (N2) disease are still evolving. Hopefully, as the current and future 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. Novel new agents including small peptides as well as molecular-directed chemotherapy and immunostimulating techniques may significantly change the future recommendations in stage IIIA disease. Until that time, it is critically important that, whenever possible, clinicians who manage locally advanced NSCLC enroll their patients in every available clinical trial.

Summary of Recommendations

1. *Surgical Considerations:* In patients with NSCLC who have incidental (occult) N2 disease ($IIIA_2$) found at surgical resection and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is recommended. Grade of recommendation, 2C

2. *Surgical Considerations:* In patients with NSCLC undergoing surgical resection, systematic mediastinal lymph node sampling or complete mediastinal lymph node dissection is recommended. Grade of recommendation, 1B

3. *Adjuvant Chemotherapy:* In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1–2}$) and who have good performance status, adjuvant platinum-based chemotherapy is recommended. Grade of recommendation, 1A

4. *Adjuvant Radiotherapy:* In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1–2}$), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence. Grade of recommendation, 2C

5. *Adjuvant Chemoradiotherpy:* In patients with resected NSCLC who were found to have incidental (occult) N2 disease ($IIIA_{1–2}$), combined postoperative concurrent chemotherapy and radiotherapy is not recommended except as part of a clinical trial. Grade of recommendation, 1B

6. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), referral for multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment. Grade of recommendation, 1C

7. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), induction therapy followed by surgery is not recommended except as part of a clinical trial. Grade of recommendation, 1C

8. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who do receive induction chemoradiotherapy as part of a clinical trial, pneumonectomy is not recommended. The subsequent surgical resection in this setting should be limited to a lobectomy. If after induction chemoradiotherapy it appears that a pneumonectomy will be needed, it is recommended that pneumonectomy not be performed and treatment should be continued with full-dose radiotherapy. Grade of recommendation, 1B

9. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), primary surgical resection followed by adjuvant therapy is not recommended except as part of a clinical trial. Grade of recommendation, 1C

10. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgery alone is not recommended. Grade of recommendation, 1A

11. In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), platinum-based combination chemoradiotherapy is recommended as primary treatment. Grade of recommendation, 1B

12. *Surgical Considerations:* In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$), surgical debulking procedures are not recommended. Grade of recommendation, 1A

13. *Surgical Considerations:* In NSCLC patients with N2 disease identified preoperatively ($IIIA_3$) who have incomplete resections, postoperative platinum-based chemoradiotherapy is recommended. Grade of recommendation, 1C

14. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, radiotherapy alone is not recommended. Grade of recommendation, 1A

15. In patients with NSCLC who have bulky N2 disease ($IIIA_4$) and good performance status, combination platinum-based chemotherapy and radiotherapy are recommended. Grade of recommendation, 1A

16. In patients with NSCLC who have bulky N2 disease ($IIIA_4$), good performance status, and minimal weight loss, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy. Grade of recommendation, 1A

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