Multidisciplinary Care of Lung Cancer Patients, Part I

THE MULTIMODALITY TREATMENT OF STAGE III A/B NON-SMALL CELL LUNG CANCER
The Role of Surgery, Radiation, and Chemotherapy

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The optimal treatment of stage III a/b non-small cell lung cancer continues to evolve. Depending on the specific clinical situation, surgical resection and/or radiation therapy may be utilized with or without concomitant chemotherapy. Because of the heterogeneity of this disease, there can be no one uniform approach to treatment. Approximately 10 years ago, the American Joint Committee on Cancer Staging (AJCC) and International Union Against Cancer (UICC) divided stage III lung cancer into two distinct divisions (14): one potentially surgically approachable (stage IIIa), and the other usually treated by nonoperative means (stage IIIb).

In this international classification, stage IIIa included those patients with tumors designated T3 by virtue of involvement of potentially resectable structures, such as the adjacent chest wall, diaphragm, pericardium, or proximal airways. The presence of involved ipsilateral mediastinal or subcarinal lymph nodes (N2) also placed tumors into this category.

Stage IIIb are those tumors designated T4 by virtue of involvement of usually unresectable structures, such as the trachea, great vessels, and
vertebral body, or with a malignant pleural effusion. Additionally, tumors with involvement of contralateral mediastinal or supraclavicular lymph nodes (N3) are included in this subgroup.

Although improved prognostic ability was gained by this subdivision of stage III disease, with stage IIIa associated with a better prognosis than stage IIIb, heterogeneity within these subdivisions remains. For example, a small peripheral lesion with isolated chest wall involvement (T3N0), and a larger lesion with chest wall and mediastinal nodal involvement (T3N2), are both grouped under stage IIIa. Despite having the same stage of disease, a patient with the former should fare better than a patient with the latter, more advanced lesion. Thus, careful consideration of the specific tumor (T), node (N), and metastatic (M) characteristics of a given patient are essential. In the new (1997) consideration of the staging system, T3N0-1 will be classified as stage IIb to indicate its more favorable prognosis.

Accurate staging of lung cancer is essential, because the selection of treatment approach is T and N dependent. Traditionally, with the exception of T3N0 tumors, most stage IIIa and IIIb lesions have been treated with external beam radiation therapy, with 5-year survival rates of less than 10%. Multimodality treatment approaches, however, have shown definite promise, especially for N2 and T3 disease, and they are the subject of this treatise.

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PRETREATMENT STAGING IN LOCALLY ADVANCED DISEASE

In conjunction with standard noninvasive staging methods, accurate staging of lung cancer currently requires invasive surgical techniques. Originally described by Carlens in 1959, cervical mediastinoscopy has become a mainstay of staging efforts with regard to nodal status. It requires only a small cervical incision and can be performed on an outpatient basis or immediately prior to a definitive resection. The information gained from this procedure is invaluable and determines the appropriate treatment course.

Our indications for cervical mediastinoscopy are thus broad. Based on experience that tumors with mediastinal nodal involvement are managed poorly by primary surgical resection, we utilize this technique prior to thoracotomy in nearly all patients being considered for resection.
We recently extended the staging accuracy of standard cervical mediastinoscopy. At the Memorial Sloan-Kettering Cancer Center (MSKCC), in 81 patients seen with non-small cell lung carcinoma, after completion of a standard cervical mediastinoscopy, ipsilateral scalene lymph node biopsies were performed through the same cervical incision. We used the mediastinoscope to reach the scalene fat pad. Of those with N2 disease (n=39) at standard mediastinoscopy, six (15.4%) had occult nonpalpable involvement of scalene nodes (N3). Of those with contralateral mediastinal disease (n=19), the majority (n=13, 68.4%) also harbored metastatic scalene nodes. No patient with a negative standard mediastinoscopy (n=23) had scalene nodes involved. Interestingly, every patient with occult scalene nodes had a centrally located, nonsquamous primary. Because of these results, we believe that this technique, or an open scalene biopsy in conjunction with standard cervical mediastinoscopy, should be considered in the complete staging of locally advanced lesions, especially those central in location and nonsquamous in origin.

**T3 Tumors**

*Tumors Involving Chest Wall (Fig. 1)*

Most of these tumors can be effectively managed with complete surgical resection. The primary determinant of a successful long-term outcome, however, is the status of the mediastinal lymph nodes. Even with complete surgical extirpation, it is a rare patient with both chest wall and mediastinal nodal involvement who will survive in the long term.

At MSKCC, of 125 patients who underwent resection for lesions invading the chest wall, the operative mortality was 4%. Of these 125, 48 (38%) had tumors that were incompletely resected or unresectable at thoracotomy. Not one of these 48 survived beyond 2.5 years. Seventy-seven patients had tumors that were completely resectable and had a 5-year actuarial survival of 40%. Nodal status was a significant prognostic indicator. Patients without nodal involvement (T3N0, n=45) had a 5-year survival of 56%, whereas N1 or N2 involvement (T3N1, n=10; T3N2, n=22) was associated with a survival rate of 21% overall.

**Figure 1.** A T3 tumor involving chest wall is best resected en-bloc. A variety of prostheses may be used to replace the defect.
Other reports of surgery alone for this stage of disease suggest up to a 50% 5-year survival in patients with completely resected T3N0 disease. At our institution, McCaughan et al. identified the depth of tumor invasion as a negative prognostic factor. Histologic involvement of the parietal pleura (n=54) was associated with a 5-year survival of 48%. In contrast, muscle or rib involvement (n=23) was associated with a survival of only 16% (P=0.02). In evaluation of only T3N0 lesions, this trend persisted, although statistical significance was lost. Parietal pleural involvement (n=31) was associated with a 5-year survival of 62%, whereas deeper chest wall invasion (n=14) had a survival of 35% (P=0.1).

Extrapleural resection without en-bloc chest wall resection was performed in 48 (62%) of the 77 patients undergoing complete resection. Of those with T3N0 disease, 5-year survival was 62%. A selective approach to these lesions was thus advocated. For lesions with only parietal pleural involvement, extrapleural resection may be appropriate. En-bloc chest wall resection was reserved for lesions with deeper chest wall involvement. A selective approach is not recommended by all, however. Albertucci and colleagues at Creighton and USC treated 37 patients over 10 years with peripheral T3 (chest wall) tumors. Extrapleural resection was performed in 16, and en-bloc resection was done in 21. Operative mortality was similar for the two techniques. Examination of the resected specimens, however, uncovered histologic evidence of tumor cell involvement at the deep surgical margin in 11 of the 16 (69%) extrapleurally resected specimens. Conversely, all en-bloc resection specimens had negative deep surgical margins. As might be expected, a higher local recurrence rate was experienced by the extrapleural resection group (37.5%) as compared with the en-bloc resection group (9.5%). Additionally, in evaluation of only those with T3N0 disease, long-term survival was 50% with en-bloc resection (n=15) and 33% with extrapleural resection (n=6) (P<0.05). Because en-bloc chest wall resection ensures a negative deep margin, it is prudent to advise this as standard treatment, especially because the accompanying morbidity is low.

Reconstruction of the chest wall is performed selectively for large defects anteriorly or laterally. Most posterior chest wall defects do not require reconstruction if they are covered by the scapula. Our preference for large bony defects is a Marlex methylmethacrylate sandwich, customized and shaped for the specific defect. Selective use of a double layer of Marlex (Pavol Inc., Cranston, RI) mesh or Gore-tex (W. Gore and Assoc., Flagstaff, RI) is appropriate, but it lacks the same rigidity and cosmetic result for large defects. Whenever stability of the chest wall is questioned, reconstruction should be performed.

In a small retrospective analysis at the University of Toronto, adjuvant radiotherapy had shown some early promise. Over 12 years, 35 patients underwent resection of a peripheral T3 chest wall tumor, the majority performed en bloc. Adjunctive radiotherapy was given to 13 patients either pre- or postoperatively. Twenty-two patients did not receive adjuvant radiotherapy. Overall, the radiation therapy group had
a better overall survival than did the nonirradiated group (56% versus 30%, respectively). Of those with T3N0 disease, those irradiated (n=9) had a 78% long-term survival, whereas those not irradiated (n=14) had only a 21% survival. Local recurrence (27%) was limited to the nonirradiated group. Conversely, a review of the Mayo Clinic experience demonstrated no difference in long-term survival with the use of radiotherapy. Accordingly, we reserve adjuvant chest wall radiotherapy for the very rare individual with positive microscopic surgical margins.

**Tumors Involving the Mediastinum**

One of the largest series in the literature was reported from our institution by Burt et al. From 1974 to 1984, 225 patients were explored for tumors with primary mediastinal invasion. This series included patients with tumors that would be considered T4 today, with 47% of the patients having direct invasion of the aorta, superior vena cava, esophagus, or atrium. Additionally, 68% also had N2 mediastinal nodal disease. Not surprisingly, the percentage of patients able to have complete resection was only 22%, with a 5-year survival of 7%.

More recently, we reanalyzed this experience, excluding those with N2 mediastinal nodal involvement. Of 102 patients, 58 had T3 lesions and 44 had T4 involvement. Complete resection was possible in 45% overall, with an operative mortality of 6%. Overall 5-year survival was 19%; however, it improved to 30% for those with complete resections.

Based on this experience, we believe that all lesions with mediastinal invasion should be evaluated by cervical mediastinoscopy. At least 68% of the series reported by Burt et al had mediastinal nodal involvement, and because of poor long-term outcome, this is considered a contraindication to primary surgical resection; however, if N2 or N3 disease can be excluded and the patient is otherwise a suitable operative candidate, primary surgical resection may be appropriate if the lesion can be completely resected.

**Tumors Involving the Main Stem Bronchus (Figs. 2 and 3)**

Tumors with endobronchial extension to within 2 cm of the main carina are also classified as T3 and often require innovative surgical management. Although pneumonectomy remains the procedure most commonly employed, for some lesions a sleeve lobectomy may be an appropriate alternative. This involves resection of a sleeve of main stem bronchus with adjacent lobar bronchi.

As with most other locally advanced lesions, we believe a cervical mediastinoscopy is an essential procedure prior to resection. Although N2 or N3 mediastinal nodal involvement distinct from the tumor mass is a contraindication to surgical resection, direct invasion of these nodes (versus metastasis) may still allow a complete resection. In addition to the primary tumor, multiple biopsies of the main carina, distal lateral tracheal walls, and
distal uninvolved airways must be performed preoperatively to assess tumor extent (T3 versus T4).

Figure 2. C & D technique of right upper lobe sleeve lobectomy.

In properly selected patients, it is likely that resection of a proximal lung carcinoma by sleeve lobectomy will, by preservation of functioning lung parenchyma, enable a better quality of life. Also, patients who could not tolerate a pneumonectomy may survive a more limited bronchoplastic procedure.

In the good-risk patient who can tolerate a pneumonectomy, however, a more limited resection would be reasonable only if postoperative morbidity, mortality, and survival were not compromised. In experienced hands, these procedures can yield comparable results. In an early series from 1961-1987, Faber reported a 33% 5-year survival rate for 110 sleeve lobectomy patients. Perioperative mortality was 1.7%.

The negative prognostic effect of nodal status was also demonstrated in this T3 subset. Node-negative patients had a 50% 5-year survival (n=11) as compared with 9.7% survival for those node-positive (N1 or N2) (n=8, P<0.05).

Figure 3. Sleeve pneumoectomy for a T4 tumor of right hilum.

In a review of modern bronchoplasty series, Tedder et al reviewed 1915 bronchoplasty procedures for lung carcinoma to determine morbidity, mortality, and survival. Although 30-day mortality for sleeve lobectomy was an acceptable 5.5%, there was a surprisingly high local recurrence rate (12.5%). Nevertheless, long-term survival following sleeve lobectomy was stage-dependent and comparable to pneumonectomy. Five-year survival following sleeve lobectomy was 63% for stage I, 37% for stage II, and 21% for stage III. In comparison, survival rates of 58%, 37%, and 22% for stages I, II, and III, respectively, have been reported with conventional pulmonary resections.

When properly selected and meticulously applied, sleeve lobectomy is an appropriate and desired alternative to standard pneumonectomy. Perioperative morbidity and mortality
are comparable, with similar long-term results. Meticulous utilization of intraoperative frozen sectioning of all resection margins will minimize the chances of local recurrence. As with other T3 tumors, nodal involvement (N1 or N2) is an adverse prognostic factor.

Occasionally, sleeve pneumoectomy may be required if the tumor is extremely proximal. This procedure is more likely to be required for T4 tumors involving the carina. This procedure carries a much higher perioperative risk.

**N2 Disease**

**Primary Surgical Resection**

This subset of stage IIIa disease remains the most controversial with regard to treatment. Therapeutic approaches have included radiation therapy alone, primary surgical resection alone, chemotherapy plus radiation therapy given either sequentially or concurrently, or chemoradiotherapy followed by surgical resection. The numerous phase II and phase III trials in the literature give an indication of the lack of one single best regimen or approach to this stage of disease and of the poor overall prognosis.

Aggressive primary surgical resection has been attempted. The report by Martini et al. provides perspective on the true number of patients who would benefit from an aggressive surgical approach alone. From 1974 to 1981, the group at MSKCC saw 1598 patients with non-small cell lung cancer. Of these, 706 had evidence of N2 disease. Ultimately, however, only 151 (21% of those with N2 disease) were able to have a complete resection, with a 5-year survival of 29%. Of those 151, only 33 (22%) had clinical evidence of N2 disease preoperatively, the rest having microscopic, subclinical N2 disease, discovered only at thoracotomy. Those with clinical N2 involvement had a 3-year survival of 8%, and none survived 5 years disease-free. Conversely, subclinical N2 involvement was associated with a 3-year survival of 50%.

Goldstraw et al. and Watanabe et al. also reported their experience with aggressive primary surgical resection for N2 non-small cell lung cancer. Goldstraw identified 149 patients without clinical evidence of N2 disease preoperatively, who were ultimately found at thoracotomy to have N2 disease. Of those undergoing complete resection (85%), a 5-year survival of 20.1% was experienced. Watanabe et al performed aggressive surgical resection for both clinical N2 disease (n=190) and subclinical N2 disease (n=47). Complete resection was possible in only 53 (28%) of the clinical N2 patients, with a 5-year survival of 20% in those having complete resection. Of those with subclinical disease, 31 (66%) were able to have complete resections, with a 5-year survival of 33%. Interestingly, Watanabe et al noted the marked limitations of using the CT scanner alone to stage the mediastinum. Of 203 patients identified to have clinical N2 disease by
preoperative CT scan and who were subsequently explored, only 115 (57%) actually possessed N2 disease. The rest were true pathologic N0 (n=50, 25%), N1 (n=26, 13%), or N3 (n=12, 6%).

The inherent inaccuracy of noninvasive clinical staging leaves much to be desired. Peritumoral inflammation or other inflammatory or granulomatous processes can result in significant mediastinal lymph node enlargement, quite unrelated to tumor involvement. Over-reliance on such staging techniques may falsely upstage an early stage tumor to a higher stage, denying an appropriate curative resection. Conversely, occult N2 or N3 disease needs to be ruled out. Unfortunately, most nonoperative treatment protocols do not require invasive surgical staging, and therefore comparison with trials that require this type of definitive staging is impossible.

For these reasons we believe that invasive staging of the mediastinum is essential. Pearson et al demonstrated the ability of this technique to select patients for surgical resection. Over 17 years at the

Toronto General Hospital, 141 patients were explored who on final pathologic analysis had N2 involvement. Cervical mediastinoscopy was performed preoperatively on all of these patients. Seventy-nine were mediastinoscopy "positive," and 62 were mediastinoscopy "negative." Of those mediastinoscopy "positive," actuarial 5-year survival was 9%. Those mediastinoscopy "negative" had a 5-year survival of 24% overall. Complete resection was possible in 25 of these mediastinoscopy "negative" patients (n=62), with a 5-year survival of 41%.

The pattern of mediastinal nodal involvement also has prognostic implications. The Lung Cancer Study Group (LCSG) used the results of three randomized adjuvant treatment trials to evaluate the prognostic consequences of the pattern of mediastinal nodal involvement. Multistation nodal disease that is, subcarinal plus paratracheal--was associated with the poorest outcome as compared with single-station disease (P<0.02). Higher levels of paratracheal involvement were a poorer prognostic indicator than was lower level disease. Extracapsular nodal spread is also a negative prognostic factor as compared with microscopic nodal disease.

Fortunately, not all mediastinal nodal disease is associated with a dismal prognosis. Patterson et al identified the subaortic nodal station as a relatively favorable nodal location, with a prognosis paralleling that of hilar nodal (N1) involvement. Of 35 patients with a left upper lobe tumor and isolated subaortic nodal disease, postresection 5-year survival was 28%. For those able to have complete resections (n=23, 66%), 5-year survival was 42%.

Primary Radiotherapy
It has been estimated that only 15% to 20% of those with N2 disease, have subclinical N2 involvement. Only these patients will benefit from primary surgical resection, whereas the rest have more extensive disease and are not candidates for this approach. Although a recent trial by the Radiation Therapy Oncology Group demonstrated improved survival with a regimen of hyperfractionated high dose radiation therapy, to a dose of 69.6 Gy, previous experience with standard radiation regimens have documented 5 year survivals of < 10%.

Adjuvant Therapy Following Primary Surgical Resection

Chemotherapy.

Following primary surgical resection, the dominant form of recurrence has been at distant sites. In 151 patients with N2 disease, Martini et al noted an overall recurrence rate of 68%. Of these recurrences, 86% involved distant sites (82% distant sites alone, 4% local plus distant sites), locations not usually addressed by either surgical resection or radiation therapy. Theoretically, chemotherapy would address these sites of metastatic involvement, preferrably when microscopic and most susceptible; however, previous trials of chemotherapy given in the postoperative adjuvant setting have been conflicting and disappointing. In an early trial performed by the LCSG, 141 patients with completely resected stage II and stage III adeno- and large cell carcinoma were randomized to receive postoperative adjuvant cyclophosphamide, doxorubicin, and cisplatin (CAP) for 6 months, or 4 weeks of immunotherapy (intrapleural bCG and oral levamisole). Both disease-free and overall survival were prolonged in the chemotherapy group, although only the improvement in disease-free survival reached statistical significance. Actual clinical benefit was small, with only a 7-month interval increase in disease-free survival for these patients.

In another trial, the LCSG prospectively randomized 172 patients with incompletely resected (positive surgical margins or highest paratracheal lymph node positive) non-small cell lung carcinoma to postoperative radiation therapy with or without CAP chemotherapy. The combined modality group had a statistically significant longer median time to disease recurrence of 6 months (P=0.004), with a trend toward improved overall survival (P=0.13).

In a third phase III trial, the LCSG randomly assigned 188 patients with completely resected stage II and III non-small cell lung cancer (squamous 53%, nonsquamous 47%) to receive either immediate or delayed CAP chemotherapy (at the time of first systemic relapse). Despite the prior suggestion of some beneficial effect of CAP chemotherapy,
both the median time to recurrence and overall survival did not differ significantly between the two groups.

Ohta and colleagues prospectively randomized 209 patients with stage III non-small cell lung carcinoma to three monthly cycles of cisplatin and vindesine chemotherapy or to no further treatment. With a mean follow-up of 2.6 years, there were no differences in disease-free survival (37% chemotherapy versus 42% control) or overall survival (35% chemotherapy versus 41% control).

Wada et al, using patients with stages I, II, IIIa, and IIIb non-small cell lung carcinoma, randomized patients into one of three different treatment arms: surgical resection alone, resection followed by three courses of cisplatin and vindesine with 1 year of oral tegafur and uracil (CVUf), or resection followed by 1 year of oral uracil (Uf). Apparently, tegafur given orally is gradually converted to 5-fluorouracil (5-FU). Uracil inhibits 5-FU degradation and has antitumor activity as well. Both chemotherapy treatment groups enjoyed improved 5-year survival (60.6% CVUf, \( P = .08 \)) (64.1% Uf, \( P = .02 \)) as compared with the surgery-alone group (49.0%). Unfortunately, because only 62 of the 310 patients (20%) in this study had locally advanced disease (stages IIIa, IIIb), and the results of this subset were not presented individually, the utility of this adjuvant regimen for the locally advanced lesion remains unclear.

The decidedly limited success of the adjuvant therapy trials published to date are probably the result of multiple factors. The use of relatively ineffective drugs at ineffective dosages and the limited tolerance of patients to intensive chemotherapy after resection may be partially to blame. For example, in one LCSG adjuvant trial, because of treatment-related toxicity and poor patient compliance, only 53% of the patients received all prescribed courses of chemotherapy, and only 57% of these were received on time.

Thus, the published literature does not support the use of adjuvant chemotherapy in locally advanced lung carcinoma. The results of a recently published meta-analysis analyzing only studies using cisplatin-based chemotherapeutic regimens support this view. The cumulative survival benefit of chemotherapy overall was small, estimated to be only 3% at 2 years.

Radiotherapy.

The LCSG performed an important phase III trial evaluating postoperative radiation therapy in completely resected stage II and III epidermoid carcinoma. Historically, this stage of disease can experience a high local recurrence rate. What effect postoperative radiation would have on survival as well as the pattern of recurrence was assessed. From 1978 to 1985, after complete resection and staging, 210 patients were randomly assigned
to receive either 50 Gy of postoperative radiotherapy or no further treatment. There were no differences in disease-free or overall survival between the two groups; however, the pattern of first recurrence was altered significantly. Of the no-further-treatment group (n=108), 21 (19%) developed a first recurrence at a local site. Conversely, the radiation therapy group (n=102) had only one (1%) first local recurrence (P<0.001). Accordingly, following complete or incomplete resection of locally advanced lesions with N2 involvement, we refer most patients for postoperative radiotherapy. We have found this therapeutic combination to maximize local control with an acceptable morbidity. A recent North American trial, not yet reported, has compared post-operative radiotherapy to chemoradiotherapy using platinum and etoposide as the chemotherapeutic agents in this stage of disease.

**Primary Chemoradiotherapy Without Surgical Resection**

Locally advanced lesions fare poorly with primary radiotherapy or surgery alone. Recent nonsurgical approaches have employed induction or concurrent chemotherapy combined with radiotherapy with promising results.

The results of several recent randomized phase III trials for locally advanced (clinical stages IIIa and IIIb) non-small cell lung cancer have been reported. Of these eight trials, four showed a statistically significant positive effect of combining chemotherapy with radiation therapy as compared with the use of radiation therapy alone. (See Table 3.)

Dillman and colleagues have now reported the mature 7-year results of a Cancer and Leukemia Group B (CALGB) phase III trial of chemotherapy (cisplatin at 100 mg/m\(^2\) on days 1, 29 with vinblastine at 5 mg/m\(^2\) on days 1, 8, 15, 22, 29) followed by 60 Gy of radiation versus radiation therapy alone. After more than 7 years of follow-up, the combined regimen was associated with a longer median survival as compared with radiation alone (13.7 months versus 9.6 months, respectively (P=0.012), with a near tripling of 5-year survival (17% versus 6%, respectively) (Fig. 4) (Figure Not Available). Although more infections requiring hospitalization, and greater weight loss, were noted in the combined-therapy group, there were no treatment-related mortalities.

Sause et al at The Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group (RTOG-ECOG) reported a three-armed phase III trial comparing standard radiation therapy (60 Gy delivered at 2-Gy fractions), hyperfractionated radiotherapy (69.6 Gy delivered at 1.2 Gy per fraction twice daily), and induction chemotherapy (cisplatin at 100 mg/m\(^2\) on days 1, 29 and weekly vinblastine at 5 mg/m\(^2\) for 5 weeks) followed by standard radiotherapy. Survival for the combined chemoradiotherapy group was superior to that achieved with either standard or hyperfractionated radiation therapy alone. Three-year survival was 15% for the combined
group and 6% with standard radiotherapy. There were three treatment-related deaths (2%) in the combined therapy arm, and one (0.6%) in the hyperfractionated radiation group.

Shaake-Konig et al reported a three-armed phase III randomized trial conducted in Finland that evaluated split-course radiotherapy alone (30 Gy-3 week rest-25 Gy) or combined with weekly cisplatin (30 mg/m² on day 1 of radiotherapy week) or daily cisplatin (6 mg/m², daily).

Figure 4. (Figure Not Available) Long term results of CALGB trial comparing RT alone with CT-RT in patients with stage III lung cancer. No surgery was employed. (From Dillman RO, et al: Improved survival in stage III non-small cell lung cancer: Seven year follow-up of Cancer and Leukemia Group B [CALGB] 8433 trial. J Natl Cancer Inst 88:1210-1215, 1996; with permission.)

with radiotherapy). Three-year survival was significantly better in the daily cisplatin-radiation group as compared with the group receiving radiation therapy alone (16% versus 2%, respectively, \( P = 0.009 \)). The weekly cisplatin-radiotherapy group had an intermediate survival of 13% at 3 years. This group also had the only treatment-related deaths (2%).

Finally, Le Chevalier et al reported a large European randomized trial comparing standard radiotherapy (65 Gy) to the same following three cycles of VCPC chemotherapy ( vindesine at 1.5 mg/m² on days 1, 2, lomustine at 50 mg/m² on day 2 and at 25 mg/m² on day 3, cisplatin at 100 mg/m² on day 2, and cyclophosphamide at 200 mg/m² on days 2-4). Three-year survival was 4% in the radiation therapy-alone group and 12% for the combined chemoradiotherapy group (\( P < 0.02 \)). An effect on the development of distant metastasis by the chemotherapy was observed as well. The radiation therapy group had twice the risk of distant metastatic disease as did the chemoradiation group (\( P < 0.001 \)). Interestingly, despite the large dose of radiation therapy delivered (65 Gy in 26 fractions over 45 days) to the primary tumor, mediastinum, and bilateral supraclavicular areas, local tumor control at 1 year was very poor. Only 17% of the radiation therapy group and 15% of the chemoradiation group had control of the primary tumor at 1 year. There were three (1.8%) treatment-related deaths with radiation therapy and five (3%) treatment-related deaths with the combined regimen.

Unfortunately, direct comparison between most primary chemoradiation trials and most multimodality-surgical trials are impossible. Significant differences in patient population and selection criteria prevent meaningful comparison. What seems clear however is the following. A combined regimen of high-dose cisplatin-based chemotherapy and radiation therapy results in an improvement in overall survival as compared with radiotherapy alone. This modest improvement in overall survival, however, is at the cost of some treatment-related mortality (although less than 5%), and morbidity with neutropenia, infections, and significant weight loss, nausea and vomiting, and alopecia. Despite
the relative success of these combined chemoradiation trials, 5-year survival rates of only 17% are being obtained. 

Additionally, as important as overall survival is the quality of life. Although not strictly synonymous with local control, there is little doubt that poor local tumor control limits the enjoyment the patient derives from his or her remaining time. As noted, Le Chevalier et al had a high local failure rate of 83% 1 year following combined primary chemoradiotherapy. The significant morbidity of disabling cough, hemoptysis, dyspnea, postobstructive pneumonitis, and eventual asphyxiation often go unmeasured in "favorable" nonoperative trials. Local control of the primary is essential and lends justification to exploring multimodality treatment regimens that include eventual surgical resection.

*Induction Chemo(radio)therapy Followed by Surgery*

Although postresection adjuvant trials have been disappointing, the administration of chemotherapy alone or with radiation therapy, sequentially or concurrently, in the preoperative setting has shown definite promise in recent phase II and III trials. Prior to formal resection, two to three treatment courses are routinely able to be carried to completion. Reduction in the size of the primary tumor with improved resectability and maintenance of local control is the primary aim of this approach. Additionally, by the earlier treatment of micrometastasis, improvement in overall survival may be possible by decreasing distant sites of failure.

*Preoperative Radiotherapy.*

The multimodality treatment of non-small cell lung cancer dates back to 1955, when Bromley treated patients preoperatively with 45 Gy of radiotherapy with a 3% 5-year survival. Since then, numerous trials of preoperative radiotherapy have been attempted. Shields reported for the Veterans Administration a prospectively randomized trial of 331 men with biopsy proven bronchial cancer who received either preoperative radiation or immediate surgery. The preoperative radiation group had a worse (12.5%) overall survival than did the surgery-alone group (21%). Warram reported in another randomized multiinstitutional study very similar results, with the radiotherapy-surgery group (n=290) having a 5-year survival of 14% and the surgery-alone group (n=278) having a 5-year survival of 16%. With the exception of large tumors located in the superior pulmonary sulcus, we do not utilize preoperative radiotherapy, preferring to reserve its use for the postoperative setting.

*Preoperative Chemotherapy (Tables 1 and 2).*
One of the best-known regimens for the treatment of clinical N2 disease was that developed at MSKCC. Over 7 years, 136 patients with histologically confirmed N2-IIIa non-small cell lung cancer were treated with two to three cycles of mitomycin, vindesine or vinblastine, and high-dose cisplatin (MVP). Major response was 77%, with a complete resection possible in 65%. Overall survival was 17% at 5 years, with a median of 19 months (Fig. 5) (Figure Not Available). For those with completely resections, 5-year survival was 26%, with a median of 27 months. There were seven (5.1%) treatment-related deaths in this series. Of those explored (n=98), complete sterilization of the tumor was noted in 19 patients (19.4%).

<table>
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<th>TABLE 1 -- SELECTED PHASE II TRIALS IN STAGE IIIa AND IIIb DISEASE</th>
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MVP = mitomycin, vindesine or vinblastine, cisplatin; FVP = 5-FU, vinblastine, cisplatin; CE = cisplatin, etoposide

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<tr>
<th>TABLE 2 -- PHASE III TRIALS IN STAGE IIIa DISEASE: INDUCTION CHEMOTHERAPY FOLLOWED BY SURGERY VERSUS IMMEDIATE SURGERY</th>
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*Rosell, 1994*<sup>[44]</sup>  
*Roth, 1994*<sup>[45]</sup>
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MIP = mitomycin, ifosfamide, cisplatin; CEP = cyclophosphamide, etoposide, cisplatin

In a confirmatory trial, Burkes et al at the University of Toronto treated 39 patients with N2-IIIa disease with two cycles of MVP. Major response was seen in 64%, and complete resection was possible in 46%. Of those explored (n=22), three pathologic complete responses were documented (13.6%). Overall, 3-year survival was 26%, with a median of 18.6 months. Of those with completely resections, 3-year survival was 40%, with a median of 29.7 months. In this series, there were seven treatment-related deaths (17.9%) (two from bronchopleural fistula, one from mitomycin pulmonary toxicity, and four septic deaths in patients with postobstructive pneumonitis).

These two single-institution phase II trials demonstrate the feasibility

**Figure 5.** (Figure Not Available) Overall survival (n=136). (From Martini, et al: Preoperative chemotherapy for stage IIIa (N2) lung cancer: The Sloan-Kettering experience with 136 patients. Ann Thorac Surg 55:1365-74, 1993; with permission.)

and effectiveness of MVP, with high major response and resectability rates. Following complete resection, survival rates are quite acceptable, with 40% of patients alive at 3 years in Toronto and 29% alive at 5 years at MSKCC. Although treatment-related mortality was 5.1% at MSKCC, the Toronto experience was notable for a mortality of 17.9%. Four of these deaths were septic in nature in patients with obstructing tumors who were then immunosuppressed with chemotherapy. We believe that prior to the administration of MVP chemotherapy, complete resolution of tumor obstruction, by either rigid bronchoscopy and debridement or laser ablation, is prudent. Problems still exist, however, from mitomycin-associated pulmonary toxicity (incidence of 11% in the MSKCC experience in patients who received a cumulative dose of 24 mg/m²) and the complications associated with high-dose cisplatin. For these reasons other regimens without mitomycin or with lower doses of cisplatin have been tried. In general, these regimens have lower major response and resectability rates than those experienced with MVP.

In a landmark phase III trial, a group from Barcelona randomly assigned 60 patients with stage IIIa non-small cell lung cancer (27% T3N0 or T3N1, 83% N2) to one of two treatment arms: immediate surgery followed by postoperative radiotherapy (50 Gy), or
three courses of preoperative chemotherapy (mitomycin at 6 mg/m$^2$, ifosfamide at 3 mg/m$^2$, and cisplatin at 50 mg/m$^2$) followed by surgical resection and the same postoperative radiotherapy (Table 2). Of those receiving preoperative chemotherapy (n=30), major response was 60%. Twenty-seven patients ultimately went on to surgery, with a complete resection in 23 (85%). The preoperative regimen was well tolerated with no chemotherapy-related mortality, although two patients in each treatment group died postoperatively. Both disease-free and overall median survival were significantly improved for the group receiving preoperative chemotherapy (20 months and 26 months, respectively) as compared with the immediate surgery group (5 months and 8 months, respectively). Interestingly, tumor specimens were analyzed for the presence of mutated K-ras oncogenes (a known negative prognostic parameter), as well as by flow cytometry. The immediate surgery group had tumors with a much higher incidence of K-ras (42% versus 15%) and aneuploid cellular content (70% versus 29%) than did the preoperative chemotherapy group. Although this may be a treatment effect of the chemotherapy by destruction of those tumor cells with aneuploid content (as the authors suggest), an alternative explanation may be some inhomogeneity between the two patient groups, favoring the chemotherapy group. In Rosell et al’s experience, non-small cell lung tumors have approximately a 20% incidence of K-ras mutation. Yet the immediate surgery group, in this series, had a 42% incidence of this mutation. This may help explain the poorer than usual survival of the immediate surgery group as compared with the preoperative chemotherapy group, as well as compared with similarly treated historical controls.

Roth et al, in another small phase III trial at M.D. Anderson, compared chemotherapy plus surgery with surgical resection alone for stage IIIa non-small cell lung cancer. Over 6 years, 60 patients were randomly assigned to receive either perioperative chemotherapy (cyclophosphamide at 500 mg/m$^2$, etoposide at 100 mg/m$^2$ on days 1-3, and cisplatin at 100 mg/m$^2$) with surgical resection (n=28) or surgical resection alone (n=32). Major response rate was 35%. With a median follow-up of 37 months, the chemotherapy-surgery group had a median survival of 64 months as compared with only 11 months with surgical resection alone (P=0.008), with an estimated 3-year survival of 56% versus 15%, respectively (Fig. 6) (Figure Not Available). Treatment-related mortality was 3% for chemotherapy-surgery and 6% with surgical resection alone.

These two phase III randomized studies are small, each involving only 60 patients, and other limitations are apparent. Nevertheless, taken in the context of the numerous phase II trials in the literature that seem to indicate a benefit of a multimodality treatment approach to the locally advanced lesion, and the distinct aforementioned limitations of nonoperative regimens, we believe that cautious optimism for a multimodality treatment approach that includes surgical resection is warranted.
Preoperative Chemoradiotherapy Plus Surgery (Table 1).

Many trials have attempted preoperative chemotherapy and radiation therapy, with eventual surgical resection to improve local and distant control. The Cancer and Leukemia Group B reported one such trial in 1992. In Figure 6, A random assignment trial from MD Anderson demonstrates improved survival using chemotherapy plus surgery versus surgery alone. (From Roth JA, et al: A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIa non-small cell lung cancer. J Natl Cancer Inst 86:673-680, 1994; with permission)

In this study, 41 stage IIIa patients (80% N2, 20% T3N0 or T3N1) underwent concurrent chemotherapy and split-course radiation therapy, followed by surgical resection. The preoperative regimen consisted of two cycles of cisplatin, vinblastine, and 5-FU with concurrent radiation therapy to 30 Gy. After surgical resection, 30 Gy more was given with an additional course of chemotherapy. A major response was seen in 46%, and 25 patients (61%) were able to have completely resections. One-year survival was 58% overall, with a median of 15.5 months. Treatment-related mortality was 15%.

Albain and colleagues of the Southwest Oncology Group (SWOG) reported the mature results of a phase II trial of concurrent chemotherapy (two cycles of cisplatin and etoposide) and radiation therapy (45 Gy), followed by surgical resection in 126 patients with biopsy-proven stage IIIa (N2)(n=75) and IIIb (n=51) disease. With a median follow-up of 2.4 years, the major response rate was 59%, with 80% of patients having complete resections. Of 89 surgical specimens, 19 (21%) had complete histologic sterilization of tumor and nodes. Three-year survival for stage IIIa and stage IIIb disease was 27% and 24%, respectively, with no statistical difference observed between these two groups. The strongest predictor of long-term survival was absence of tumor in the mediastinal nodes at surgery, with a 3-year survival of 44% versus 18% with persistent nodal disease (P = 0.0005). Treatment-related mortality was 10%.

In conclusion, it has been demonstrated fairly convincingly that primary surgery or radiotherapy fails to control most patients with stage IIIa (N2) disease. Combined modality therapy that includes induction chemotherapy improves long-term survival. Whether surgery or radiotherapy should be used as the primary modality to achieve local control is now the subject of a North American phase III trial comparing chemoradiotherapy to chemoradiotherapy plus surgery in patients with this stage of disease.

**TREATMENT OF STAGE IIIB NON-SMALL CELL LUNG CARCINOMA**
Stage IIIb disease includes patients with more extensive locally advanced lesions (T4 and N3 disease). T4 tumors may invade mediastinal structures (carina, trachea, heart, great vessels, esophagus, vertebral bodies) and/or may cause a malignant pleural effusion. N3 disease includes patients with metastatic involvement of the contralateral mediastinal or hilar nodes or ipsilateral or contralateral supraclavicular/scalene nodes.

Such disease is usually considered unresectable, and standard radiation treatment has been associated with 5-year survival rates of less than 5%. Combining the modalities of chemotherapy and radiation therapy has thus become the accepted "standard" for this stage of disease.

<table>
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<tr>
<th>Author name, year (ref no.)</th>
<th>No. Patients</th>
<th>Chemo</th>
<th>Radiation</th>
<th>Groups</th>
<th>Survival</th>
<th>P value</th>
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<tbody>
<tr>
<td>Trovo, 1990 (55)</td>
<td>111</td>
<td>CAMP</td>
<td>45 Gy</td>
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<td>3.6 3.8 18% 13% 9% 3% 5% 2% NS</td>
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<td>Dillman et al, 1990, 1996 (12, 13)</td>
<td>180</td>
<td>CDDP+ Vinblastine</td>
<td>60 Gy</td>
<td>CT+XRT XRT</td>
<td>13.7 9.6 26% 13% 24% 10% 17% 6% &lt;0.05</td>
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<td>Le Chevalier et al, 1991 (24)</td>
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<td>CDDP+ Vinblastine</td>
<td>60 Gy</td>
<td>CT+XRT XRT</td>
<td>13.8 11.4 32% 19% 15% 6% &lt;0.05</td>
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<tr>
<td>Author name, year (ref no.)</td>
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<td>Chemo</td>
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<td>Survival</td>
<td>P value</td>
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<td>(47) HFX XRT</td>
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<td>Median (mos.)</td>
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<tr>
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<td>9.97</td>
<td>10.3</td>
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</table>

CAMP = cyclophosphamide, Adriamycin, methotrexate, procarbazine; MACC = methotrexate, Adriamycin, cyclophosphamide, CCNU; CDDP = cisplatin; VCPC = vindesine, cisplatin, lomustine, cyclophosphamide; CT = chemotherapy; XRT = radiation therapy; NS = not significant

Of the four previously reviewed trials that showed a survival benefit of chemoradiotherapy compared to radiation therapy alone in locally advanced disease (Table 3), Sause et al estimated 50% of their patients to have clinical stage IIIb disease. Le Chevalier et al estimated 14% of their series had clinical stage IIIb disease, whereas both Schaake-Koning et al and Dillman et al excluded these patients (see Table 3). Because clinical stage IIIb disease was not separately analyzed, it is difficult to assess the optimal treatment regimen for stage IIIb disease. Compared with standard radiation therapy alone, however, a small survival advantage seems to be derived from the combination of chemotherapy and radiation therapy, with up to 24% of patients alive at 3 years and 17% alive at 5 years.

The role of surgical resection in stage IIIb disease remains controversial. Certain T4 sites allow for complete resection, and some surgeons will attempt surgical resection of selected T4N0 tumors. The addition of surgical resection to induction chemoradiation would theoretically lead to improved local control while maintaining the effect of chemotherapy on distant disease. In a SWOG trial of preoperative concurrent chemotherapy (two cycles of cisplatin and etoposide) and radiation therapy (45 Gy), followed by surgical resection in 126 patients with biopsy-proven stage IIIa (N2)(n=75) and IIIb (n=51) disease, Albain et al reported a 3-year survival of 27% and 24%,
respectively, for stage IIIa and IIIb disease. Subset analysis of the 51 stage IIIb patients in this series identified certain favorable and unfavorable subgroups, however. Those staged IIIb owing to T4 disease alone (T4N0, N1 or NX, n=17) had a better overall median survival than did all other patients in the study (28 months versus 13 months). Conversely, of the nine patients with N3-contralateral nodal disease, all were dead within 2 years.

Our current approach to stage IIIb disease is thus based largely on our findings at cervical mediastinoscopy. If the lesion is IIIb by virtue of N3 nodal involvement, the patient is referred for primary chemoradiation therapy without consideration of a surgical approach. Only for the rare patient with isolated completely resectable T4 disease with no nodal involvement is surgical resection considered. These "resectable" T4 tumors include those with minimal organ involvement that can be resected "en-bloc", for example, aortic adventitia, esophageal muscle, superior vena caval adventitia, minimal atrial involvement, minimal tracheal involvement. In this latter situation, sleeve pneumoectomy is the treatment of choice (see Fig. 3).

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