Induction Therapy for Non-small Cell Lung Cancer With Involved Mediastinal Nodes in Multiple Stations*

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Background: Metastasis to multiple stations of mediastinal nodes is associated with a poor prognosis.

Objective: We prospectively examined the efficacy of induction therapy plus surgery in patients with non-small cell lung cancer and metastases at multiple stations of mediastinal (N2) lymph nodes.

Methods: Among the 1,085 patients who underwent surgery for primary non-small cell lung carcinoma from 1985 to 1997, those with clinical N2 disease of involved multiple stations, defined as bulky, mediastinal, lymph node metastases on CT scans, received induction therapy, consisting of cisplatin-based chemotherapy and radiation of 40 Gy.

Results: Of the 88 eligible patients entered into the study, 51 (58%) had multiple stations of N2 nodes affected preoperatively, as demonstrated by pathologic examination. Neither operative mortality nor fatal, treatment-related complications occurred during hospitalization. Patients who underwent complete resection had significantly longer survivals than did those who underwent incomplete resection (p = 0.001). Among patients who underwent complete resection, the survival rate for patients with pathologically downstaged disease was significantly higher than that for patients whose disease was not downstaged (p = 0.009). Among patients with multiple stations of pN2 nodes involved who had undergone complete resection, those who received induction therapy for bulky N2 disease had a significantly better prognosis than did those undergoing surgery alone for nonbulky N2 disease (p = 0.03).

Conclusions: Induction therapy prolonged the survival of patients with non-small cell lung cancer and mediastinal nodes involved at multiple stations. Survival was better when complete resection and downstaging of the disease were achieved after induction therapy.

Key words: bulky N2 disease; induction therapy; lung cancer; neoadjuvant therapy; surgery

Abbreviations: N2 = mediastinal lymph node; pN2 = pathological proven N2

Although most patients with clinical N2 non-small cell lung cancer are not candidates for surgical treatment, the opportunity for cure should not be denied, because some of these patients have a relatively good prognosis after complete resection.1–3 Therefore, we thought that patients with known N2 disease might be candidates for surgical treatment.4

There have been reports showing that patients with involvement of multiple N2 nodal stations have worse prognoses than those with involvement of only single N2 nodal stations.3,5–8 Mountain3 recommended no surgery for patients who had evidence of N2 disease at more than one mediastinal level. Accordingly, we thought a new therapeutic approach was necessary. In an effort to improve curability and survival in this group of patients, we began using induction therapy in patients with non-small cell lung cancer and bulky N2 disease with multiple mediastinal stations involved clinically. We entered patients prospectively into a preoperative trial of chemoradiotherapy. The purpose of this study was to assess the efficacy of induction therapy in patients with pathologically confirmed non-small cell lung cancer and involvement of mediastinal lymph nodes at multiple levels.

Materials and Methods

From January 1985 to December 1997, 1,085 patients were operated on, by the same surgical team, for primary non-small...
cell lung cancer. Of these, only patients having pathologically proven non-small cell lung cancer, with clinical bulky N2 disease, defined as documented metastases at multiple stations of the ipsilateral mediastinal lymph nodes, were eligible for the study. Lymphadenopathy was evaluated by CT. Bulky metastatic lymph nodes were defined as mediastinal nodes larger than 15 mm along their long axis and 10 mm along their short axis at more than one level. It has been our policy to undertake thoracotomy for patients in whom N2 disease is identified by pretreatment investigations. Hematologic, hepatic, and renal functions, as determined by a screening CBC count, chemical profile, and the calculated creatinine clearance, had to be adequate to permit cisplatin chemotherapy. Patients were required to have granulocyte counts >2,000 cells/µL, platelet counts >100,000 cells/µL, hemoglobin levels >10 g/dL, and creatinine levels <1.5 mg/dL or creatinine clearance >60 mL/min. Before initiation of the treatment protocol, evaluation of the patients was performed by thoracic surgeons, medical oncologists, and radiation oncologists. All patients were monitored for toxic effects of induction therapy, tolerance to treatments, complications, ability to complete all treatments, surgical results, and survival. Informed consent was obtained from all patients.

After registration in the study, each patient was started on induction treatment of chemoradiation therapy. The chemotherapeutic regimen consisted of 1 to 3 cycles of vindesine sulfate (3 mg/m² body-surface area) and cisplatin (80 mg/m² body-surface area) given IV over a period of 1 h, at 4-week intervals. After 1990, mitomycin (8 mg/m² body-surface area) was added to the regimen. Radiotherapy to the primary tumor and mediastinum was delivered, 5 d/wk, at a daily dose of 2.0 Gy in the central axis at the midplane, until the patient had received a cumulative dose of 40 Gy. Surgical exploration was scheduled about 4 weeks after the last dose of cisplatin. After surgery, none of the patients were subjected to additional chemotherapy or radiotherapy.

Initially, to improve curability, induction therapy was given to patients with tumors that were judged to be resectable. Therefore, all patients in this series were considered to have resectable tumors before induction therapy. The surgical procedure was based on the extent of the lesion at the time of initial presentation rather than at the time of thoracotomy. The choice of operative procedure was based on curative intent, while preserving as much functional lung volume as possible.10 Routine systematic dissection of all the hilar and mediastinal nodes was performed in every case.11 At the time of surgery, all resected nodes were individually labeled by the surgeon, for pathologic examination during and after the operation. Diseased margins, diseased highest nodes, gross disease left, and malignant effusion were considered to indicate incomplete resection.12 Because of the potential for complications of the bronchial stump, special precautions were taken to cover the bronchial stump with pedicled tissue flaps. Postoperative pathologic findings indicating complete fibrosis, scar, or granulation of nodes, with neither normal nodal formation nor cancer cell, meant downstaging.

Resected specimens were examined histopathologically, with histologic typing done according to the World Health Organization classification.13 Surgical-pathologic staging was assigned according to the New International Staging System for Lung Cancer.14 The lymph node classification schema, recommended by the American Joint Committee on Cancer and adapted from Naruke et al,15 was used to designate N disease. Operative mortality was defined as death within 30 days after surgery.

All patients were followed until the time of death. Survival was estimated by the Kaplan Meier method,16 and statistical significance of differences in survival was determined by log-rank analysis. A multivariate analysis of independent factors was performed using Cox’s proportional hazards regression model when the number of patients in the subgroups was small. Zero time was the date induction therapy was began, and the terminal event was death attributable to cancer, noncancer, or unknown cause. Operative mortality was included. Significance was defined as p < 0.05.

Results

Classification and progression of patients through this study are shown in Figure 1. Of the total, 790 patients had confirmed non-small cell carcinoma, received no induction therapy, and underwent complete resection. The status of pathologic lymph node involvement was N0 in 514 (65%) of the 790 patients evaluated, N1 in 134 (17%), and N2 in 142 (18%). The 5-year survival rate of these patients with N0, N1, and N2 disease was 69%, 48%, and 24%, respectively. Patients with N2 disease had a significantly worse survival than did those with N0 or N1 disease (N0 vs N1, p = 0.0002; and N1 vs N2, p = 0.0001). Of the N2 patients who had not received induction therapy and whose clinical evaluation was nonbulky N2 disease, 78 showed nodal involvement at one station, while the others showed multiple involvement. The 5-year survival of these patients was 39% and 11%, respectively. There was a statistically significant difference favoring long-term survival in patients in whom only one nodal station was involved (p = 0.0001).

A total of 98 patients were ultimately considered eligible for entry into the protocol of induction therapy. Of these, 51 patients (58%) were considered to have multiple stations of N2 nodes involved at the time induction therapy was begun, which was demonstrated postoperatively by pathologic examination. There were 42 men and 9 women, with a mean (SD) age of 60 years (range, 33 to 71 years). Overall follow-up ranged from 13 to 144 months, with a median of 62 months. The histopathologic diagnosis was adenocarcinoma in 28 patients (55%), squamous cell carcinomas in 21 (41%), adenosquamous carcinoma in 1 (2%), and large cell carcinoma in 1 (2%). Concerning nodal status, 38 patients (75%) were found to have two positive stations of N2 nodes. Three stations were affected in 7 patients (14%) and three stations in 6 (12%). Thirteen patients (25%) received one cycle of preoperative chemotherapy, 30 (59%) received two cycles, and 8 (16%) received three cycles. The latest 28 patients (55%) received concurrent chemoradiotherapy. Toxic effects of treatment were manageable in all patients. Moderate leukopenia was noted in 50% of patients. Thrombocytopenia requiring platelet transfusion was not observed. Acute emesis after cisplatin administration was controlled. No patients experienced major nephrotoxicity caused by cisplatin or pulmonary toxicity attributed to mitomycin. Life-threatening episodes
were not evident, and there were no drug- or irradiation-related deaths. Lobectomy was the most common procedure in 33 patients (65%). Pneumonectomy was carried out in nine patients (18%), and segmentectomy or lesser resection was carried out in nine (18%). Complete resection was performed in 33 patients (65%). Ten patients had a diseased margin or a diseased highest node resected, eight had an intrapulmonary metastasis, and six had a malignant effusion or a positive pleural lavage cytology.9,12 Thirteen of 51 patients (25%) had all their hilar and mediastinal nodes sterilized; complete resection was performed in these patients. Downstaging by sterilization of the mediastinal nodes was allowed in 14 of the 51 patients (27%). Of the 28 patients who underwent concurrent chemoradiotherapy, 23 (82%) could undergo complete resection, while in 12 (43%) downstaging of the disease was allowed. However, of 23 patients with no concurrent chemoradiotherapy, 10 (43%) could undergo complete resection, and downstaging was allowed in only one (4%). There was no operative mortality. Postoperative complications during hospitalization were infrequent and nonfatal. One patient with severe pneumonia was successfully treated with corticosteroids. Late complications after discharge from hospital occurred in three patients with empyema due to bronchopleural fistula or lung fistula, the onset of which was 2 months after their discharge. Two of them died secondary to this complication; these were considered treatment-related deaths. Only nonfatal postoperative complications (pneumonia in one patient and bronchopleural fistula in one patient) were observed in the remaining 37 patients who were eligible for entry into the protocol of induction therapy but were not confirmed to have nodal involvement at multiple stations of N2 nodes.

The overall survival rates of the 51 patients studied were 68% at 1 year, 30% at 3 years, and 25% at 5 years. The survival rates of patients who underwent complete resection (n = 33) and of those who underwent incomplete resection (n = 18) were 33% and 8% at 5 years, respectively (p = 0.001) (Fig. 2). The multivariate analysis revealed that the differences in survival between the two groups were statistically significant irrespective of the patient’s age, sex, and histology (hazard ratio, 2.859; 95% confidence interval, 1.319 to 6.195). However, among patients with nodal involvement at multiple stations of N2 nodes who underwent complete resection, those who received induction therapy for bulky cN2 disease (n = 33) had a significantly better prognosis (p = 0.03) than those undergoing surgery alone for nonbulky cN2 disease (n = 64) (Fig 3). The 5-year survival rates of these patients were 33% and 11%, respectively. The multivariate analysis showed significant differences in survival between the two groups regardless of their age, sex, and histology (hazard ratio, 2.078; 95% confidence interval, 1.125 to 3.836). Of the 33 patients who underwent complete resection, 13 were considered to have downstaged disease; their survival rates were 79% at 3
years and 48% at 5 years (Fig 4). The survival of patients with downstaged disease \( n = 13 \) was higher than that of patients in whom downstaging of the disease was not achieved \( n = 20 \), and this represented a significant statistical difference \( p = 0.009 \). As a result of a multivariate analysis, downstaging of disease was identified to be an independent prognostic factor, independent of age, sex, and histology (hazard ratio, 4.341; 95% confidence interval, 1.113 to 16.936).

**Discussion**

There is a spectrum of disease that is classified as N2. Routine radical mediastinal lymphadenectomy is essential because it significantly increases the percentage of patients in whom N2 involvement at multiple levels can be detected.\(^8\) Although clinical bulky N2 disease with nodal involvement at multiple stations does not suggest surgery, \(^3\) the opportunity for cure should not be denied because of rigid policies. In fact, no documentation exists to support a surgical approach for patients who might meet the criteria for potentially complete resection.

We have acknowledged no pathologic confirmation for staging prior induction therapy as a serious problem with this article. At some hospitals mediastinoscopy is routinely used as part of the preoperative assessment, and thoracotomy is not performed in the great majority of patients in whom N2 disease is detected before the operation. In contrast, Martini and Flehinger\(^{18}\) reported that, without the benefit of mediastinoscopy, a 5-year survival of 30% could be attained in N2 patients subjected to complete resection. Similarly, Naruke et al\(^{19}\) and Watanabe et al\(^{5}\) have published data on many patients with N2 disease who underwent thoracotomy without prior mediastinoscopy. Mediastinoscopy permits direct access to the middle and posterior portions of the superior mediastinum for exploration and biopsy. However, the lymph nodes of the anterior and inferior mediastinum are not routinely accessible. The subcarinal lymph node, which was involved in most of N2 patients with a lower-lobe tumor, and which was considered as a key node,\(^{11}\) is poorly accessible through mediastinoscopy. Goldstraw et al\(^6\) also noted that this was a serious drawback of mediastinoscopy. Furthermore, when mediastinoscopy is performed before induction therapy, the
effect of induction therapy on lymph nodes cannot be evaluated, since the involved nodes will not be there. For these reasons, it has been our policy not to do additional invasive procedures before thoracotomy.

Multiple affected nodal sites have been found to carry a worse prognosis than a single affected nodal site, reducing survival by about 50%. Because surgical treatment alone for nodal involvement at multiple N2 stations is associated with a worse prognosis, as demonstrated in our series and as shown by other studies,1,3,5,20 these patients need to be offered a new therapeutic regimen. Over the past decade, many preoperative trials with induction therapy, that is, the so-called neoadjuvant therapy, for locally advanced non-small cell lung cancer have been reported.21–24 Induction chemotherapy trials have been based on the hypothesis that they should increase long-term survival by preventing metastatic progression, which is universally recognized as a primary cause of long-term deaths after resection. Recently, two randomized studies have revealed a dramatic benefit of chemotherapy followed by operation in patients with stage IIIA disease compared with operation alone.21,22 There is no reason why drugs that are ineffective postoperatively should have such dramatic results preoperatively.

Although high-dose cisplatin and vinca alkaloid combination chemotherapy has led to improved survival in patients with non-small cell lung cancer,25 these two-drug regimens are not curative and do not benefit all patients treated. Since mitomycin is one of the most effective agents among those used to treat non-small cell lung cancer, we have added it to our regimen from the 1990 study. Mitomycin has been reported to cause acute pulmonary toxicity, and to be related to postoperative death.26 In our series, there were no mitomycin-related deaths.

The ultimate assessment of any induction therapy rests on the survival rate. The survival of patients with N2 disease whose mediastinal metastasis was identified by standard radiographic studies was significantly worse than that of patients whose N2 lesion was found only at surgery.27,28 This study demonstrated that induction therapy plus surgery for bulky N2 disease produced a significantly better survival than surgery alone for nonbulky N2 disease, suggesting a greater efficacy of induction therapy on survival. The overall 5-year survival was 25% in our series for patients with nodal involvement at multiple stations. However, Martini et al29 and Mathisen et al24 reported 5-year survival rates of 17% and 43%, respectively, for patients with all N2 disease. The possibility of downstaging the disease with preoperative regimens has been reported by various authors.21–24, 29 Downstaging by sterilization of mediastinal nodes was achieved in 27% of the patients in this study, and with complete sterilization of all lymph nodes in 25%. Martini et al29 and Sugarbaker et al23 reported downstaging figures of 21% and 22%, respectively, whereas the downstaging percentage reported by Mathisen et al24 was 46%. A preponderance of patients with favorable single nodal involvement would obviously skew the results of any study of induction therapy. Because other reports regarding induction therapy included many patients with involvement of only a single N2 station, their results simply could not be compared with ours. In the series of Mathisen et al,24 those with single nodal involvement accounted for 27 of 40 patients (67%). The possibility of sterilizing the mediastimun using induction therapy is an important aspect of this form of therapy and may translate into improved survival.

We believe that downstaging by induction therapy, followed by complete resection, prolonged survival. In this group of our series, the 3-year and 5-year survival rates were 79% and 48%, respectively. It is noteworthy that survival after complete resectability and downstaging with concurrent chemoradiotherapy was much longer than with other therapies. The degree of radiographic response was not a perfect predictor of surgical and histologic findings,24 because complete sterilization of any tumor was noted in partial responders; conversely, persistent disease was also found in complete responders, supporting the need for histologic confirmation following surgery.

The operative mortality rate was as good as or better than that of most other series, which was approximately 5%.21,23,24 Because we always kept lung-saving procedures in mind,9 and because pneumonectomy was performed infrequently,4,30 curative resection could be done with low postoperative morbidity and mortality. There were two treatment-related deaths among the 88 patients entered into the protocol. Both patients had empyema secondary to bronchopleural fistulas a few months after surgery. It is important to cover the bronchial stump with a pedicle, using viable tissue to reduce the risk of postoperative bronchopleural fistula, and to closely follow up even after the patient has left the hospital.

Our study revealed several important findings. First, available combination induction therapy can result in a significantly improved survival for patients with pathologically proven involvement at multiple N2 node stations. Second, treatment-related mortality is low. Third, the greatest contribution of this treatment is the increased possibility of downstaging, with concomitant increased possibility of completely resecting the tumor.
REFERENCES