Induction Chemoradiation and Surgical Resection for Superior Sulcus Non–Small-Cell Lung Carcinomas: Long-Term Results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160)

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ABSTRACT

Purpose

Traditional treatment for superior sulcus non–small-cell lung cancers (SS NSCLC), radiation plus surgery, yields a 50% rate of complete resection and a 30% 5-year survival. On the basis of improved outcomes in other subsets of stage III NSCLC, this trial tested the feasibility of induction chemoradiotherapy for SS NSCLC.

Patients and Methods

Patients with T3-4, N0-1 SS NSCLC received two cycles of cisplatin and etoposide concurrently with radiation (45 Gy). Patients with stable or responding disease underwent thoracotomy. All patients received two more cycles of chemotherapy. Survival was calculated by the Kaplan-Meier method and prognostic factors were assessed by Cox regression analysis.

Results

From April 1995 to November 1999, 110 eligible patients (76 men, 34 women) were entered onto the study (78 T3, 32 T4 tumors). Induction therapy was completed by 104 (95%) patients. Of 95 patients eligible for surgery, 88 (80%) underwent thoracotomy, two (1.8%) died postoperatively, and 83 (76%) had complete resection. Pathologic complete response (CR) or minimal microscopic disease was seen in 61 (56%) resection specimens. Five-year survival was 44% for all patients and 54% after complete resection, with no difference between T3 and T4 tumors. Pathologic CR led to better survival than when any residual disease was present ($P = .02$). Disease progression occurred mainly in distant sites.

Conclusion

This combined-modality approach is feasible and is associated with high rates of complete resection and pathologic CR in both T3 and T4 tumors. Local control and overall survival seem markedly improved relative to previous studies of radiation plus resection.

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INTRODUCTION

Non–small-cell lung carcinomas (NSCLC) of the superior sulcus (SS) are among the most challenging thoracic tumors to treat because of their involvement of adjacent vital structures including the brachial plexus, subclavian vessels, and spine. Originally described by Henry Pancoast in 1932,1 SS NSCLC were believed to be uniformly fatal until the 1950s, when preoperative radiation and en-bloc resection was found to be potentially curative.2,3 During the next 40 years, this approach remained the standard of care, with improvements limited to the development of novel surgical techniques for T4 tumors.4-6 However, complete resection was achieved in only 60% of patients and overall survival at 5 years remained 30%, indicating a clear need for novel therapy.7 During the 1990s, increasing experience with combined-modality therapy suggested that induction chemoradiotherapy followed by resection was an effective treatment strategy for stage III NSCLC.8 Small studies suggested that this approach might be appropriate for SS NSCLC.9 These experiences led us to test induction chemoradiotherapy plus resection in SS NSCLC.
Eligibility Criteria

Patients were eligible if they had solitary, previously untreated T3 or T4, N0-1 SS NSCLC. This included patients with an apical tumor and the Pancoast syndrome, or SS tumors with invasion of the chest wall, spine, or subclavian vessels by computed tomography (CT scan) or magnetic resonance imaging (MRI) with or without an associated Pancoast syndrome. Prestudy staging included a CT scan of the chest and upper abdomen through the adrenals, CT or MRI of the brain, bone scan, and mediastinoscopy. Thoracic spine and brachial plexus MRI was recommended. Positron emission tomography scans were not required because this trial predated the routine use of positron emission tomography for NSCLC staging. A Southwest Oncology Group (SWOG) performance status of 0 to 2 and adequate cardiopulmonary, renal, and neurologic function to tolerate the planned treatment were required. Tumors were stratified by T3 versus T4 status at study entry.

Induction Therapy Regimen

Induction chemotherapy and radiation began within 24 hours of each other. Chemotherapy consisted of cisplatin 50 mg/m² on days 1, 8, 29, and 36, and etoposide 50 mg/m² on days 1 through 5 and 29 to 33. The total radiation dose was 45 Gy administered in 1.8-Gy daily fractions during 5 weeks. The radiation target, defined by CT scan, included the primary tumor and ipsilateral supraclavicular region, but not the mediastinum or hilum.

Induction treatment and boost chemotherapy toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Evaluation After Induction Therapy and Guidelines for Surgical Resection

Two to 4 weeks after induction therapy, patients were reassessed by history, physical examination, and CT scans of the chest, upper abdomen, and brain. Bone scan was done if new bone pain or elevated alkaline phosphatase or lactate dehydrogenase were present. Patients without distant metastases or local progression underwent thoracotomy. Patients with disease progression were removed from the study but were observed in follow-up visits. Response determinations were required at this point in the study. A complete response (CR) was complete radiologic disappearance of all measurable or assessable disease. A partial response (PR) was a 50% or greater decrease under baseline in the sum of products of perpendicular diameter of all measurable lesions. Progression was a 25% or greater increase in the sum of products of all measurable lesions. Patients with stable disease had lesions that did not meet the criteria for CR, PR, or progression.

Thoracotomy was performed 3 to 5 weeks after induction chemoradiotherapy. A lobectomy or pneumonectomy was required for resection. Areas of direct tumor extension into the chest wall or spine were resected en-bloc with the involved lung. For right-sided tumors, lymph nodes at levels 2R, 4R, 7, 8, 9, and 10R were removed; for left-sided tumors, nodes at levels 5, 6, 7, 8, 9, and 10L were removed.

Boost Chemotherapy and Follow-Up

All patients, whether or not they had a resection, were to receive two additional cycles of cisplatin and etoposide chemotherapy, without additional radiation. Patients were then observed every 3 months during the first 2 years, then every 6 months with history, physical examination, chest x-ray, and blood tests. CT scans of the brain, chest, and upper abdomen were required every 6 months for the first 3 years postoperatively.

Data Quality Control and Statistical Analyses

All data forms, chemotherapy flow sheets, radiology reports, and operative and pathology reports were reviewed by the study chair (V.R.) and the medical oncology coordinator (M.K.). T4 stage was verified by imaging studies documenting spine invasion or encasement of subclavian vessels.

Survival, calculated from the date of study entry, was estimated by the product-limit method, and survival curves were compared via log-rank tests. Prognostic factors were assessed for their significance in predicting survival via Cox regression analysis. Groups of continuous data were compared using the Wilcoxon rank sum test. Data were analyzed using Statistical Analysis Software, version 6.12 (SAS Institute, Cary, NC). All reported significance values were two tailed.

RESULTS

Demographic and Clinical Characteristics

From April 15, 1995 to August 1, 1999, 116 patients entered onto the study. All of the North American cooperative groups participated in this trial, including the Eastern Cooperative Oncology Group (33 patients), the Cancer and Leukemia Group B (29 patients), the National Cancer Institute of Canada (26 patients), SWOG (19 patients), and the North Central Cancer Treatment Group (nine patients). Of 116 total patients, 110 were ultimately deemed eligible. Five patients had metastatic disease and one patient with pneumonia were removed from the study before treatment. Seventy-six surgeons operated on patients entered onto this trial; the mean number of patients per surgeon was 1.42. Prestudy characteristics are outlined in Table 1. Most patients were male (69%), white (88%), had T3 tumors (71%), and a performance status of 0 to 1 (98%). The median patient age was 56 years (range, 36 to 77 years). Primary tumors were usually large, with a median tumor size of 6 cm (range, 2 to 14.5 cm).

Induction Therapy

The protocol schema and the numbers of patients treated at key points in the study are shown in Figure 1. Induction therapy was completed by 104 patients (95%). There were three (2.7%) treatment-related deaths (one neutropenic sepsis, two myocardial infarctions). One patient developed progressive disease and one patient received only one cycle of chemotherapy because of a lung abscess.

Nine patients were removed from the study because of disease progression at postinduction restaging. Of 95 patients eligible for thoracotomy, 88 were registered to the surgery step of the protocol, and 83 (76% of all patients) underwent complete (R0) resection.

Induction therapy was well tolerated (Appendix Table A1, online only). Leukopenia, neutropenia, and anemia were the most common...
Pancoast Tumors, Chemoradiotherapy, and Surgery

Surgical data are summarized in Appendix Table A2 (online only). The most frequent operation was a lobectomy and chest wall resection. The 13 patients who had only a pulmonary resection per-

Surgical resection

Complete or incomplete resection of all gross tumor

2 Additional cycles of chemotherapy

Follow-up

Follow-up

Radiation:

Cisplatin: 50 mg/m², days 1, 8, 29, 36
Etoposide: 50 mg/m², days 1-5, 29-33

Etoposide:

Cisplatin:

180 cGy daily X 5 weeks (45 Gy total)

Fig 1. Study schema of Southwest Oncology Group (SWOG) 9416. *Percentages calculated based on the total number of eligible patients. Reprinted with permission.12 CR, complete response; PR, partial response; NSCLC, non–small-cell lung cancer; CT, computed tomography.

No pathologic evidence of mediastinal or supraclavicular nodal disease

N = 110

Cisplatin: 50 mg/m², days 1, 8, 29, 36
Etoposide: 50 mg/m², days 1-5, 29-33

Radiation: 180 cGy daily X 5 weeks (45 Gy total)

n = 104 (92%)*

2 did not complete therapy

Medically unfit or refuse surgery

n = 6

Off Protocol

Follow-up

CR, PR or stable

n = 95 (86%)*

Disease progression

Repeat extent of disease evaluation

(CT scans chest, abdomen, brain and bone scan)

2-4 Weeks after completion of induction treatment

Fig 2. Overall survival of all eligible patients and by T status.

T 3-4, N 0-1 M0 NSCLC involving the superior sulcus

No pathologic evidence of mediastinal or supraclavicular nodal disease

N = 110

CR, complete response; CT, computed tomography.

grade 3 or higher toxicities. Five patients had grade 3 or higher esoph- agitis. After induction therapy, no patients had a CR, 46 (42%) had a PR, and 40 (36%) had stable disease.

Surgery

Surgical data are summarized in Appendix Table A2 (online only). The most frequent operation was a lobectomy and chest wall resection. The 13 patients who had only a pulmonary resection performed had such marked tumor regression after induction therapy that chest wall resection was no longer considered necessary. A small number of patients undergoing more complex procedures, such as vertebral body resection, are listed under “other.” Resections were pathologically complete (R0) in 61 of 65 patients (94%) with T3 tumors and 22 of 23 (96%) with T4 tumors.

Postoperative complications are listed in Appendix Table A3 (online only). Two patients (2.3%) died postoperatively of multisystem failure. Pulmonary complications were the most common, with pneumonia occurring in 13.6% of patients. Arrhythmias, myocardial infarction, bronchopleural fistula, hemorrhage requiring reoperation, and empyema were other major but infrequent complications. The median length of hospital stay was 7 days (range, 3 to 64 days).

Review of postinduction therapy CT scan reports and pathology reports showed that many patients had a large residual mass on CT but only a few scattered foci of tumor within mostly residual fibrosis at operation. Therefore, the final pathologic response was divided into three categories: pathologic CR (no residual microscopic tumor), minimal microscopic residual (few scattered tumor foci within a mostly necrotic or fibrotic mass), and gross residual disease (mostly or entirely viable tumor). Each of these categories included roughly one third of the resected specimens, with 61% of patients having either a pathologic CR or minimal microscopic residual tumor. Appendix Table A4 (online only) shows the substantial discrepancy between radiologic and pathologic response. Of 46 patients considered to have a radiologic PR, 33 (72%) had pathologic CR or minimal microscopic residual disease. Of the 40 patients deemed to have stable disease, 26 (65%) had either pathologic CR or minimal microscopic residual disease.

Boost Chemotherapy

Sixty patients were registered to receive boost chemotherapy, including 59 who had surgery and one who did not. Among 28 patients registered to surgery but not to boost chemotherapy, the reasons for no boost chemotherapy were postoperative death (two patients), disease progression after surgery (three patients), patient too frail to continue chemotherapy (11 patients), change in histologic diagnosis after tumor resection (two patients), patient refusal (four patients), and other reasons (eight patients). Of patients registered to boost chemotherapy, only 49 (81% of patients registered to this step, 45% of all eligible patients) received the two planned cycles of chemotherapy, and six patients received one cycle of chemotherapy.

Survival and Relapse Information

As of June 22, 2006, 44 patients, observed for a median of 82 months, are still alive. Overall survival for all eligible patients (by T status) and for patients who had an R0 resection is shown in Figure 2. The median survival for all eligible patients is 33 months and 94 months for the patients who had an R0 resection (Fig 3).

There was no significant difference between T3 and T4 tumors (P = .30). The overall survival by pathologic response is shown in Appendix Figure A1 (online only). Median survival was not
reached for patients with pathologic CR, and was 30 months with minimal microscopic disease and 29 months with gross residual disease. The difference in overall survival between patients who had a pathologic CR and those who had any residual disease (Fig 4) was significant ($P = .02$).

Potential prognostic factors included initial T status (T3 vs T4), sex (male vs female), and pathologic response (pathologic CR vs microscopic residual vs gross residual disease). Only pathologic CR ($P = .02$) was found to be significant at the .05 level (Table 2).

The first sites of relapse, listed in Appendix Table A5 (online only), were predominantly distant metastases. The most common single site was the brain, with recurrence in this site only in 19 of 57 patients (41%). Local recurrence occurred in only 10 patients. The numbers of recurrences are too small to allow comparisons between T3 and T4 tumors, or according to the degree of pathologic response.

**DISCUSSION**

Evolutions in the management of SS NSCLC during the last 70 years can be classified into four eras. These tumors were first described in 1932 by a radiologist, Henry Pancoast, as “a peculiar neoplastic entity found in the upper portion of the pulmonary sulcus of the thorax. . . . its exact origin is uncertain. . . . It produces constant and characteristic clinical phenomena of pain in the eighth cervical and first and second thoracic trunk distribution, wasting of the muscles of the hand and Horner’s syndrome.”

During the ensuing 20 years, these tumors became recognized as primary lung carcinomas but were believed to be incurable. In 1956, Chardack and MacCallum reported prolonged survival after en-bloc resection of a superior sulcus NSCLC along with the involved chest wall and nerve roots, and adjuvant radiation. In 1956, Shaw referred for radiotherapy a patient presenting with the Pancoast syndrome. When 30 Gy of radiation led to resolution of the pain and a decrease in tumor size, Shaw undertook resection. The complete resection and long-term survival achieved in this patient prompted additional evaluation of this treatment strategy.

In 1961, Shaw et al reported 18 patients who received 30 to 35 Gy of radiation during 2 weeks, followed by en-bloc resection of the involved lobe, chest wall, and nerve roots, with excellent local control and prolonged survival.

For the next 30 years, induction radiation and en-bloc resection via an extended posterolateral thoracotomy became standard care for SS NSCLC. Multiple series confirmed the original results of Shaw et al.

The largest series, from Memorial Sloan-Kettering Cancer Center, included 225 patients and reported an operative mortality of 4%; a complete resection rate of 64% in T3, N0; and 39% in T4, N0 tumors. Locoregional recurrence was the most common form of relapse. Lobectomy was associated with a better overall survival than limited pulmonary resection and the addition of intraoperative brachytherapy to resection did not improve survival. Overall survival at 5 years was 46% for T3, N0; 13% for T4, N0; and 0% for tumors with N2 disease. These results emphasized the need for new treatment strategies.

During the late 1980s and the 1990s, novel approaches were developed for the resection of tumors involving the spine and subclavian vessels. Darteville et al described an anterior transcervical-thoracic approach for tumors involving the subclavian vessels. Several improvements were later made to this approach. For tumors involving the spine, techniques for multilevel vertebrectomy and spine reconstruction were developed. New techniques for complete resection of T4 tumors were important advances in surgical management, but survival at 5 years remained approximately 30%.

During this same time, other studies reported the results of treatment with radiation only. These are difficult to interpret because they are retrospective, include small numbers of patients who were only clinically staged and were treated in a highly variable manner. In general, local control and survival seem inferior to...
those reported in surgical series, but this may reflect patient selection and variable treatment.

The success of combined-modality therapy for stage IIIa (N2) NSCLC during the 1980s and 1990s led directly to the development of this study, the only prospective multicenter trial to date for SS NSCLC. Induction chemoradiotherapy followed by resection is a logical strategy for a group of tumors that present a formidable challenge in local control. The induction regimen in this trial was feasible and effective in previous multicenter studies. The trial design is particularly important, with inclusion of a homogeneous group of patients through systematic staging including mediastinoscopy and stratification of T3 versus T4 tumors. The excellent results obtained with respect to response to induction treatment, low operative mortality, R0 resection, local control rates, and long-term survival effectively establish the treatment regimen used as a new standard of care, for both T3 and T4 tumors. Recent single-institution studies corroborate our results.9,37

The long-term results of this study confirm and also clarify our previously reported initial results.12 Early analysis showed that induction chemoradiotherapy and resection were feasible, and were associated with higher rates of R0 resection than previously reported. The mature results now show that overall survival at 5 years is far better than in previous series using preoperative radiation and resection without chemotherapy. Initial analyses suggested that minimal microscopic residual disease at surgery was associated with an overall survival intermediate between that seen with either a pathologic CR or gross residual disease. Current results show that any amount of residual disease, even when completely resected, is associated with a significantly worse survival than when a pathologic CR occurs. However, the 5-year survival for patients who had residual disease substantially exceeds the approximate 30% survival historically reported for patients treated with induction radiation and resection. Moreover, in patients with SS NSCLC, local recurrence has a marked impact on patient quality of life because it causes excruciating pain and loss of arm function. The patterns of disease recurrence in this study, namely a very low rate of local relapse, are different from those reported with radiation alone plus resection, and have important implications for patient quality of life.

Accrual to this trial was completed successfully within the planned time frame, but required the efforts of 76 surgeons from all of the North American cooperative groups to enroll 110 eligible patients. This experience makes it unlikely that future randomized trials including resection could be completed within an acceptable length of time for this uncommon NSCLC subset. However, several questions could be studied in future single-arm or randomized phase II trials. First, other induction chemotherapy regimens (ie, cytotoxic or targeted therapies) leading to a higher rate of pathologic CR may improve results. Whatever newer drugs are used, however, will have to be not only more effective but also no more toxic when combined with radiation and surgery. The induction regimen could be intensified by adding a third cycle of chemotherapy or by increasing the dose of radiation. Recently, Suntharalingam et al38 and Kwong et al39 reported using a median preoperative radiation dose of 59.4 Gy in combination with platinum-based chemotherapy, with a resulting pathologic CR of 46% and a 5-year survival of 49% in 23 patients. It is not clear that the higher radiation dose improves survival or is safe in the multi-institutional setting.

Our trial emphasizes the difficulty of delivering cisplatin-based therapy postoperatively to this group of NSCLC patients. On the basis of the results of other SWOG trials in patients with locally advanced NSCLC, docetaxel currently is being tested as single-agent adjuvant therapy in an ongoing phase II intergroup trial. In the future, other agents or targeted therapies may prove to be less toxic and more effective adjuvant therapy. Given the patterns of relapse seen in this study, improved systemic therapy, either induction or adjuvant, is needed to achieve improved outcomes. Finally, the high risk of brain relapse seen in this trial is similar to what has been reported in other combined-modality trials for patients with locally advanced NSCLC, and raises the issue of whether patients should be considered for prophylactic cranial radiation. It is hoped that the results of an ongoing randomized trial testing the use of prophylactic cranial radiation in patients with locally advanced NSCLC will answer this question. Certainly, at present, the combined-modality regimen used in this trial offers patients with SS NSCLC substantially better treatment results than seen previously.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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**AUTHOR CONTRIBUTIONS**
REFERENCES


Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).