INDUCTION CHEMORADIATION AND SURGICAL RESECTION FOR NON–SMALL CELL LUNG CARCINOMAS OF THE SUPERIOR SULCUS: INITIAL RESULTS OF SOUTHWEST ONCOLOGY GROUP TRIAL 9416 (INTERGROUP TRIAL 0160)

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Objective: The rate of complete resection (50%) and the 5-year survival (30%) for non–small cell lung carcinomas of the superior sulcus have not changed for 40 years. Recently, combined modality therapy has improved outcome in other subsets of locally advanced non–small cell lung carcinoma. This trial tested the feasibility of induction chemoradiation and surgical resection in non–small cell lung carcinoma of the superior sulcus with the ultimate aim of improving resectability and survival.

Methods: Patients with mediastinoscopy-negative T3-4 N0-1 superior sulcus non–small cell lung carcinoma received 2 cycles of cisplatin and etoposide chemotherapy concurrent with 45 Gy of radiation. Patients with stable or responding disease underwent thoracotomy 3 to 5 weeks later. All patients received 2 more cycles of chemotherapy and were followed up by serial radiographs and scans. Survival was calculated by the Kaplan-Meier method and prognostic factors were assessed for significance by Cox regression analysis.

Results: From April 1995 to September 1999, 111 eligible patients (77 men, 34 women) were entered in the study, including 80 (72.1%) with T3 and 31 with T4 tumors. Induction therapy was completed as planned in 102 (92%) patients. There were 3 treatment-related deaths (2.7%). Cytopenia was the main grade 3 to 4 toxicity. Of 95 patients eligible for surgery, 83 underwent thoracotomy, 2 (2.4%) died postoperatively, and 76 (92%) had a complete resection. Fifty-four (65%) thoracotomy specimens showed either a pathologic complete response or minimal microscopic disease. The 2-year survival was 55% for all eligible patients and 70% for patients who had a complete resection. To date, survival is not significantly influenced by patient sex, T status, or pathologic response.

Conclusions: (1) This combined modality treatment is feasible in a multiinstitutional setting; (2) the pathologic complete response rates were high; and (3) resectability and overall survival were improved compared with historical experience, especially for T4 tumors, which usually have a grim prognosis. (J Thorac Cardiovasc Surg 2001;121:472-83)

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Tumors of the superior sulcus are an uncommon subset of non–small cell lung carcinomas (NSCLCs), which are particularly challenging to treat because they frequently involve the brachial plexus, subclavian vessels, or spine. Initially described by Henry Pancoast in 1932, NSCLC of the superior sulcus was considered incurable until 1956, when Chardack and MacCallum[1] reported the case of a patient who survived long term after surgical resection and postoperative radiation. Subsequently, Shaw,[2] Paulson,[3] and their associates found that preoperative radiation facilitated surgical resection and that this approach to treatment was associated with a 30% survival at 5 years. This experience has subsequently been confirmed by multiple small surgical series.[3-16] A recent review of 225 patients operated on from 1974 to 1998 for superior sulcus tumors at Memorial Sloan-Kettering Cancer Center, the largest surgical series to date, indicated that actuarial survival at 5 years was 46% for stage IIB, 0% for stage IIIA, and 13% for stage IIIB tumors. Survival was influenced by T and N status and completeness of resection. However, resection was considered pathologically complete in only 64% of T3 N0 and 39% of T4 N0 tumors.[17] Locoregional disease was the most common form of relapse.

These results emphasize the need for improved therapy for NSCLC of the superior sulcus. The success of combined modality therapy for stage IIIA (N2) NSCLC has prompted interest in using induction chemotherapy or chemoradiation for NSCLC of the superior sulcus. A small single-institution phase II trial using induction chemotherapy followed by chemoradiation and then surgical resection reported high response, resectability, and survival rates but also a 16.6% rate of treatment-related deaths.[15] In a previous large multi-institutional phase II trial, the Southwest Oncology Group showed that induction cisplatin, etoposide, and concurrent radiation followed by surgical resection was a well-tolerated and effective treatment for stage IIIA (N2) and selected IIIB NSCLC.[18,19] These results led us to test the same approach in superior sulcus tumors that did not have mediastinal nodal metastases, a situation ideally suited to the use of a concurrent induction regimen of chemotherapy and radiation. We now report the initial results of this phase II intergroup trial coordinated by the Southwest Oncology Group (SWOG).

Methods

Eligibility criteria. Patients were eligible for this study if they had pathologically proven and previously untreated NSCLC involving the superior sulcus with either a T3 or T4 primary tumor. This included patients who had (1) an apical tumor associated with the Pancoast syndrome with or without involvement of the chest wall or vertebral body or (2) superior sulcus tumors with invasion of the chest wall, spine, or subclavian vessels on computed tomographic (CT) or magnetic resonance (MR) scan with or without an associated Pancoast syndrome. Patients with 2 or more parenchymal lesions in the same lung were considered ineligible. Mediastinoscopy was required in all patients, and patients with mediastinal or supraclavicular nodal involvement (N2 or N3 disease) were not eligible for the trial. CT scans of the upper part of the abdomen through the adrenal glands, CT or MR scan of the brain, and bone scan were required to exclude the presence of distant metastatic disease. MR scan of the thoracic spine and brachial plexus was strongly recommended to assess the extent of the primary tumor. A SWOG performance status of 0 to 2 was required, and patients had to have adequate cardiopulmonary, renal, and neurologic function to tolerate the planned chemotherapy, radiation, and surgical resection. All patients were jointly evaluated before entry into the study by a medical oncologist, a radiation oncologist, and a thoracic surgeon. Patients were stratified by T3 versus T4 tumor status at study entry.

Induction therapy regimen. The induction chemotherapy and radiation began within 24 hours of each other. The chemotherapy regimen consisted of cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 on days 1 to 5 and 29 to 33, both administered intravenously. Standard prehydration and antiemetic medications were used. The total dose of radiation was 45 Gy administered at 180 cGy per day, 5 days a week, over a period of 5 weeks. The radiation target was defined by CT scan and included the primary tumor and ipsilateral supraclavicular region, but not the mediastinum or hilum.

The toxicities for both the induction treatment and boost chemotherapy were recorded according to the National Cancer Institute Common Toxicity Criteria.

Evaluation after induction therapy and guidelines for surgical resection. Two to 4 weeks after completion of the induction therapy, patients were reassessed by history and physical examination, repeat pulmonary function tests, and CT scans of the chest, upper part of the abdomen, and brain. A repeat bone scan was done if the patient had new bone pain or elevation in the levels of alkaline phosphatase or lactic dehydrogenase. Patients who had no evidence of distant metastases or evidence of local progression underwent thoracotomy for resection of the primary tumor. Patients found to have progressive disease went off study but continued on follow-up. Response determinations were required at this point in the study. A *complete response* was complete radiologic disappearance of all measurable or evaluable disease. A *partial response* 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. *Stable disease* was lesions that did not meet the criteria for complete response, partial response, or progression.

Thoracotomy was performed 3 to 5 weeks after the completion of induction chemoradiation. A lobectomy or pneumonectomy was required for resection, and lesser pulmonary resections were not allowed. Areas of direct tumor extension

into the chest wall or spine were resected en bloc with the involved lung. Coverage of the bronchial stump with a muscle flap was not mandated. Thoracic surgeons were strongly encouraged to seek neurosurgical consultation preoperatively to assist in the spine resection if necessary. All visible and technically accessible bronchopulmonary, hilar, and mediastinal lymph nodes were to be removed and submitted appropriately labeled to the pathologist. For right-sided tumors, these included lymph nodes at levels 2R, 4R, 7, 8, 9, and 10R. For left-sided tumors, these included lymph nodes at levels 5, 6, 7, 8, 9, and 10L. No intraoperative radiation or brachytherapy was given.

Boost chemotherapy and follow-up. All patients, whether they had a complete or incomplete tumor resection or did not undergo a thoracotomy because they refused or were medically unfit for surgery, were to receive 2 additional cycles of chemotherapy identical to what was administered during the induction regimen but without any further radiation. On completion of all treatment, all patients were followed up. Patients were evaluated every 3 months during the first 2 years postoperatively and then every 6 months thereafter by history, physical examination, chest radiography, and blood tests. In addition, scans of the brain, chest, and upper part of the abdomen were required every 6 months for the first 3 years postoperatively. After that time, they were done only if clinically indicated.

Study coordinator and statistical analyses. All of the data forms, chemotherapy flow sheets, radiology reports including CT and MR imaging reports, operative summaries, and pathology reports were reviewed independently and jointly by the study chair (V.R.) and the medical oncology coordinator for this trial (M.K.) and either confirmed or, if incorrect, amended. In addition to the usual quality control performed by study coordinators, particular attention was given to ensuring that the initial tumor stage, response to treatment, type and extent of resection, and final pathologic stage were correctly coded. Particular attention was given to verifying the pretreatment T status, making certain that tumors were coded as T4 only if imaging studies clearly documented spine invasion or encasement of the subclavian vessels.

Survival was estimated by the product-limit method,[20] and curves were compared via log-rank tests. Potential prognostic factors were assessed for their significance in predicting survival via Cox regression analysis.[21] Groups of continuous data were compared by the Wilcoxon rank-sum test. All data were analyzed with Statistical Analysis Software, version 6.12 (SAS Institute, Inc, Cary, NC). All reported significance values were 2-tailed.

Results

Demographic information. From April 15, 1995, to August 1, 1999, 116 patients entered the study. Broad participation from all of the North American cooperative groups allowed this study to be completed in a timely manner. The cooperative groups entering patients included the Eastern Cooperative Oncology Group (ECOG, 33 patients), the Cancer and Leukemia Group B (CALGB, 29 patients), the National Cancer Institute of Canada (NCIC, 26 patients), SWOG (19 patients), and the North Central Cancer Treatment Group (NCCTG, 9 patients). Of these 116 patients, 111 were ultimately deemed eligible. The reasons for ineligibility included metastatic disease in 4 patients and postobstructive pneumonia in 1 patient, who was taken off study before receiving induction therapy. Although 93 (84%) patients were cared for in academic institutions, 16% were treated in community hospitals. Seventy-six surgeons operated on the patients entered in this trial, with the mean number of patients per surgeon being 1.42.

The prestudy characteristics of the 111 eligible patients are outlined in Table I. The majority of patients were male (69.4%) and white (88%) and had T3 primary tumors (72.1%). Most patients had a performance status of 1 (72.1%), consistent with the fact that most patients have significant symptoms at presentation, and most had 5% or less weight loss. The median patient age was 56 years (range 36-77 years). The primary tumors were generally large at diagnosis, and the median tumor size was 6 cm (range 2-14.5 cm).

Induction therapy. The protocol schema and the numbers of patients treated at key points in the study are shown in Fig 1. Complete documentation of induction therapy is available for 109 of the 111 patients, 2 patients having been lost to follow-up. Seven of these did not complete induction as planned. There were 3 (2.7%) treatment-related deaths during induction therapy, which were related to neutropenic sepsis in 1 patient and to myocardial infarction in 2 patients. Progressive disease developed in 1 patient, and another patient received only 1 cycle of chemotherapy preoperatively because of the development of a lung abscess. The remaining 2 patients underwent surgery but the details of their induction therapy have not yet been received.

Ten patients were taken off study because of progressive disease found at postinduction restaging. Eighty-seven of the 95 patients potentially eligible for thoracotomy (ie, alive and progression-free, known to have completed induction without being taken off study) were registered to the surgery step of the protocol. Four patients were deemed not to have technically resectable tumors by the surgeon. Four patients were taken off study at the discretion of the investigators because of excessive delay in going to surgery, poor performance status, or poor cardiopulmonary function. Four patients were registered to surgery but have no documentation that surgery was actually performed. Therefore, 83 (75%) of the 111 eligible patients underwent surgery.

The most common toxicities of the induction treatment according to grade are shown in Table II.

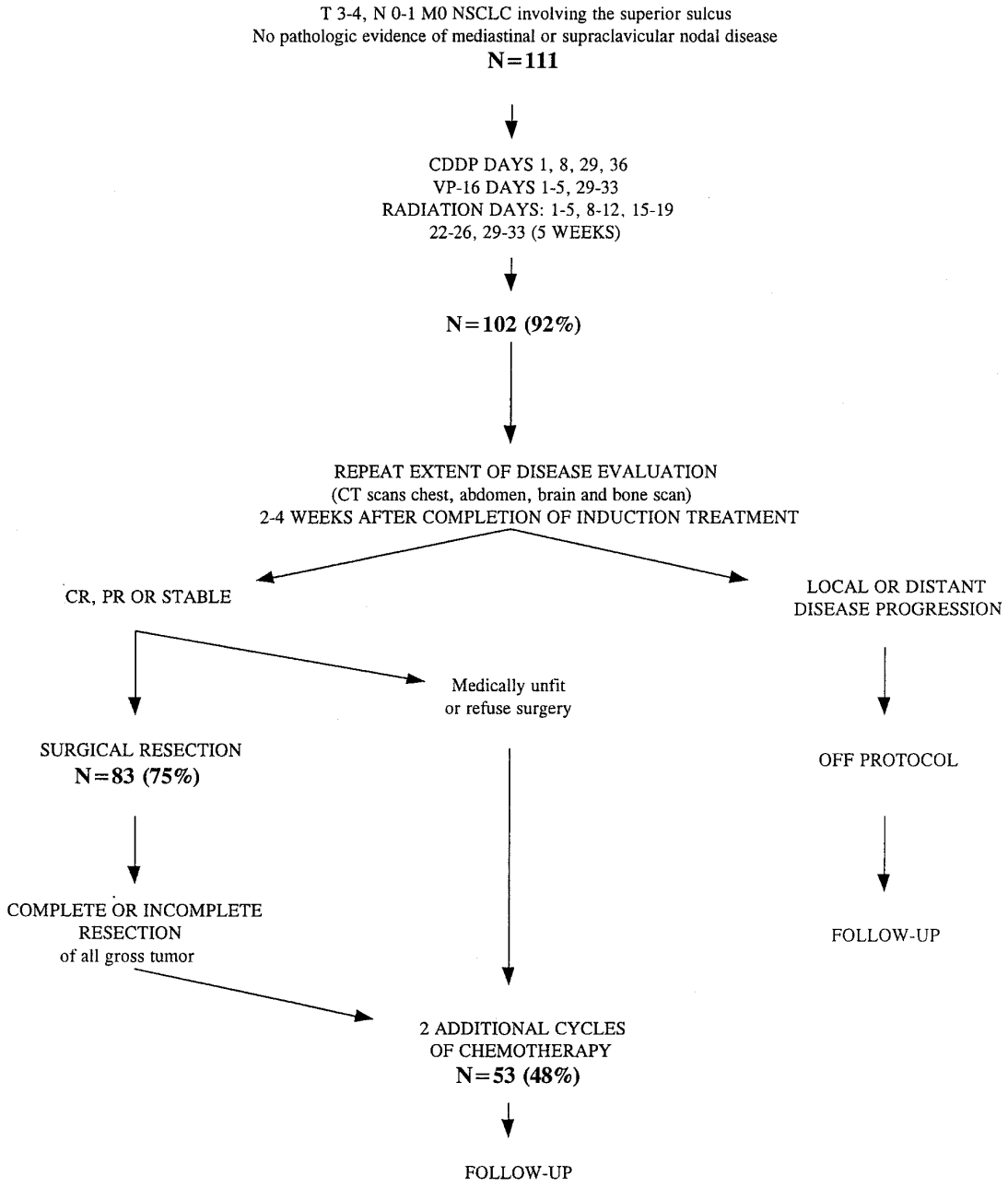

Fig 1. Schema of SWOG 9416, also showing the number of patients treated at each of the major steps of the study.

Leukopenia, neutropenia, and anemia were the most common grade 3 or higher toxicities. Five patients had grade 3 or higher toxicity from esophagitis. Overall, the induction therapy was well tolerated. Eighteen patients had a deterioration in their performance status with induction therapy. There were no complete radiologic responses among the 109 patients known to have received induction therapy. Thirty-nine (36%) of these patients had a partial response and 45 (41%) were judged to have stable disease.

Data on preoperative and postoperative pulmonary function were available in 108 patients. Changes in pulmonary function were assessed by examining the difference between the percent of predicted values for FEV_1 (forced expiratory volume in 1 second) and for the DLCO (diffusion capacity). The median changes in

Table I. *Prestudy characteristics of all eligible patients (N = 111)*

Prestudy characteristic	*No. of patients*	*Percent of all patients*
Sex		
Male	77	69.4
Female	34	30.6
Ethnicity		
White (non-Hispanic)	98	88
Black (non-Hispanic)	9	8
Asian or Pacific Islander	1	1
Native American	1	1
Other	2	2
T status		
T3	80	72.1
T4	31	27.9
Performance status		
No data	1	0.9
0	28	25.2
1	80	72.1
2	2	19.8
Weight loss		
No data	7	6.3
≤5%	82	73.9
>5%	22	19.8

Table II. *The most common toxicities of induction therapy (N = 106)*

	Grade			
Toxicity type	*≤ 2*	*3*	*4*	*5*
Leukopenia	66	29	11	0
Neutropenia	65	25	16	0
Anemia	89	14	3	0
Esophagitis	103	3	0	0
Mucositis	104	2	0	0
Nausea	99	7	0	0
Vomiting	98	7	1	0
Fatigue/malaise	98	8	0	0

The numbers of patients are listed by grade of each form of toxicity.

percent predicted FEV_1 and DLCO were +2.0% and –7.0%, respectively.

Surgery. Data on the operations performed are summarized in Table III. As might be expected for NSCLC in this location, the most frequent operation was a lobectomy and chest wall resection. The 12 patients who had only a pulmonary resection all had such marked tumor regression after the induction therapy that chest wall resection was no longer considered necessary. The data forms for this study did not allow for more detailed coding of complex procedures such as vertebral body resection and reconstruction, and the small number of patients undergoing such additional procedures are listed in Table III under "other." The resections were surgically complete (R0 or R1 resection) in 55 (92%) of the 60 patients with T3 tumors and 21 (91%) of the 23 patients with T4 tumors. Similarly, 92% of the patients T3 disease and 87% of those with T4 disease had resections that proved to be pathologically complete (R0 resection).

Table III. *Data on surgical resections performed on patients entered in SWOG 9416 (N = 83)*

Study characteristic	*No. of patients*	*Percent of all patients*
Operation type		
Exploratory thoracotomy	2	2.4
Lobectomy	11	13.3
Lobectomy + chest wall	56	67.5
Pneumonectomy	1	1.2
Pneumonectomy + chest wall	2	2.4
Other	11	13.2
Completeness of resection		
Surgically complete (R0, R1)	76	91.6
T3	55/60	92.0
T4	21/23	91.0
Pathologically complete (R0)	75	90.4
T3	55/60	91.3
T4	20/23	87.0

The median duration of the operation was 4.48 hours (range 0.85-9.32 hours) and the median estimated blood loss was 450 mL (range 10-2100 mL). Postoperative complications are listed in Table IV. Two patients (2.4%) died postoperatively. These 2 patients had postoperative respiratory failure and eventual multisystem failure. The most common complications were pulmonary, specifically atelectasis and pneumonia, occurring in 14.5% and 12.0% of patients, respectively. There were several other major but infrequent complications including atrial or ventricular arrhythmias, myocardial infarction, bronchopleural fistula, hemorrhage necessitating reoperation, and empyema. The median length of hospital stay was 7 days (range 3-64 days). With the use of the Wilcoxon rank-sum test, the occurrence of postoperative complications was examined in relation to the changes in pulmonary function as noted previously, specifically, the difference in percent of predicted values for FEV_1 and DLCO before and after induction therapy. There were no significant differences in FEV_1 changes (P = .77) or in DLCO changes (P = .83) between patients with no complications versus those who had at least 1 postoperative complication.

Review of the postinduction therapy CT scan reports and of the pathology reports from the pulmonary resections suggested 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 3 categories: pathologic complete response (no residual microscopic tumor), minimal microscopic residual (few scattered tumor foci within mostly necrotic or fibrotic mass), and gross residual disease (mostly or entirely viable tumor). Each of these categories was found to include roughly one third of the resected specimens, which meant that 65% of patients had either a complete pathologic response or minimal microscopic residual tumor. Table V illustrates the correlation between radiologic and pathologic responses and shows a substantial discrepancy between them. Of the 38 patients considered to have a radiologic partial response, 28 (73%) proved to have a pathologic complete response or minimal microscopic residual disease. Even more important, of the 40 patients deemed to have stable disease, 22 (55%) were found to have either a pathologic complete response or minimal microscopic residual disease.

Boost chemotherapy. Fifty-nine patients were registered to boost chemotherapy, including 58 who had surgery and 1 who did not. Among the 29 patients who were registered to surgery but not to boost chemotherapy, the reasons for not registering to boost chemotherapy, in addition to the 2 postoperative deaths, were as follows: disease progression detected after surgery (3 patients), inadequate postoperative recovery or patient fragility precluding further chemotherapy (11 patients), change in histologic diagnosis after tumor resection (2 patients), patient refusal (4 patients), and other reasons or no reason given (7 patients). For the patients registered to boost chemotherapy, 47 patients (81% of patients registered to this step, 42% of all eligible patients entered on study) actually received the 2 cycles of chemotherapy planned, and an additional 6 patients received 1 cycle of chemotherapy.

Survival and relapse information. As of March 28, 2000, 72 of the 111 eligible patients are still alive. One patient has no follow-up beyond the date of registration and is excluded from the survival analysis. The median follow-up among the 72 patients still living is 21 months. The overall survival for all eligible patients and the postoperative survival for the patients who had a complete resection are shown in Figs 2 and 3. The median survival for both groups of patients has not yet been reached. The overall survival for all eligible patients appears to reach a plateau of approximately 55% at 2 years after initial chemotherapy; for the patients who had a complete resection, the plateau was approximately 70% at 2 years postoperatively.

The overall survival by initial T status is shown in Fig 4. Although the total number of patients with T4 tumors was relatively small, there was no significant difference in survival between patients with T3 and those with T4 tumors, calculated either for all eligible patients (P = .65) or for patients undergoing resection (P = .33). The overall postoperative survival of patients by pathologic response is shown in Fig 5. The median survival for each of these 3 groups has not yet been reached. The survival parallels the pathologic response, with the patients who had a pathologic complete response having the best survival and those who had gross residual disease faring the worst. However, these apparent differences are not statistically significant (P = .49).

To guard against the detection of what are more likely to be spurious associations, we first assessed the potential prognostic factors for their significance in predicting survival by using a univariate Cox regression analysis. Those factors found to be significant in the univariate setting would have been further evaluated in a model with multiple covariates. In this study, potential prognostic factors included initial T status (T3 vs T4), sex (male vs female), and pathologic response (pathologic complete response vs microscopic residual disease vs gross residual disease). None of these factors was found to be significant at the .05 level in univariate analyses of survival; therefore, multivariate Cox regression analysis was not indicated. The association between these factors and overall survival is further defined in Table VI, which shows the relative risks of death after surgery according to T status, pathologic response, and patient sex.

Information about the first postoperative site of relapse has been received on 39 patients at the time of this analysis, including 29 patients who originally had T3 and 10 patients who were considered to have T4 tumors at study entry. The most common single site of relapse was the brain, with recurrence confined to this site in 16 (41%) of the 39 patients. Local recurrence

Table IV. *Postoperative complications in SWOG 9416*

Complication type	*No. of patients*	*Percent of patients*
Atelectasis	12	14.5
Pneumonia	10	12.0
Atrial arrhythmia	9	10.8
Empyema	4	4.8
Hemorrhage, reoperation	2	2.4
Myocardial infarction	2	2.4
Bronchopleural fistula	2	2.4
Ventricular arrhythmia	2	2.4
Wound infection	1	1.2

Of the 83 patients who underwent thoracotomy, 14 (17.5%) had no complications reported. In 3 patients no information was submitted about complications. Some patients had more than 1 complication.

Table V. *Comparison of pathologic and radiologic responses in the 83 patients entered in SWOG 9416 who underwent thoracotomy*

	Radiologic response				
	Total	*PR*	*PRNM*	*STA*	*NASS*
Pathologic stage					
Pathologic CR	28	14	0	12	2
Minimal microscopic residual disease	26	13	1	10	2
Gross residual disease	29	10	0	18	1
Total	83	37	1	40	5

PR, Partial response; *PRNM,* partial response, evaluable not measurable; *STA,* stable; *NASS,* not assessable.

Table VI. *SWOG 9416 relative risk of death after surgery*

Prognostic factors	*RR*	*95% CI*	P *value*
T3 vs T4	1.61	0.69-3.71	.27
Microscopic residual disease vs CR*	1.60	0.56-4.63	.38
Gross residual disease vs CR	1.86	0.66-5.24	.24
Men vs women	1.93	0.71-5.20	.20

RR, Risk ratio; *CI,* confidence interval; *CR,* complete response.

only was uncommon, occurring in 9 (23%) patients. Including brain relapses, the most frequent form of recurrence was distant only (26/39 or 66%). The numbers of recurrences are too small to allow comparisons between T3 and T4 tumors or according to the degree of pathologic response.

Discussion

Preoperative radiation and surgical resection became the standard management of NSCLC of the superior sulcus after Shaw and associates[1] described this in 1961. The feasibility of this approach has been confirmed by multiple surgical series that have reported a relatively consistent overall survival of approximately 30% at 5 years.[5,7,9-12,14,16,22-25] Radiation alone has been associated with a 5-year actuarial survival of 23%,[8,26] but these results probably cannot be compared with those of surgical series because of variability in patient selection. Recent surgical series have focused on exploring the use of extended operations to achieve complete resection of T4 tumors that invade the subclavian vessels or spine and on defining prognostic factors. The development of the anterior transcervical approach by Dartevelle,[12] Macchiarini,[27] and their colleagues now allows complete resection of anteriorly located tumors involving the subclavian vessels, which were previously considered unresectable. Likewise, the thoracic and neurosurgical groups at the Memorial Sloan-Kettering and MD Anderson Cancer Centers have highlighted the benefit of a multidisciplinary approach to posteriorly located tumors that can only be removed by formal spine resection and stabilization.[28,29] Although both of these experiences represent important contributions to the surgical management of NSCLC of the superior sulcus, the overall survival and rates of complete resection of these patients remain relatively low.

A recent review of 225 patients operated on between 1974 and 1998 at Memorial Sloan-Kettering Cancer Center summarizes important aspects of the traditional surgical management of superior sulcus tumors and clearly defines prognostic factors that have been suggested by previous series.[17,30] This experience confirms that surgical resection can be accomplished with a low mortality (4%) but emphasizes that complete resection (R0 resection) was achieved in only 64% of T3 N0 and 39% of T4 N0 tumors. The actuarial 5-year survival was 46% for stage IIB (T3 N0) and 13% for stage IIIB disease, most of which were T4 N0 tumors. By univariate and multivariable analyses, T and N status and complete resection had a significant impact on survival. Locoregional recurrence was the most common form of relapse, occurring in 40% of patients. Within this large series, the more recent experience encompassing the years of 1992 to 1998 did not differ substantially from the earlier reported experience covering the years 1974 through 1991. However, the negative prognostic impact of N2 disease, the inadequacy of limited pulmonary resection in these patients, and the lack of benefit of brachytherapy in incomplete resections have now been recognized.[13,17]

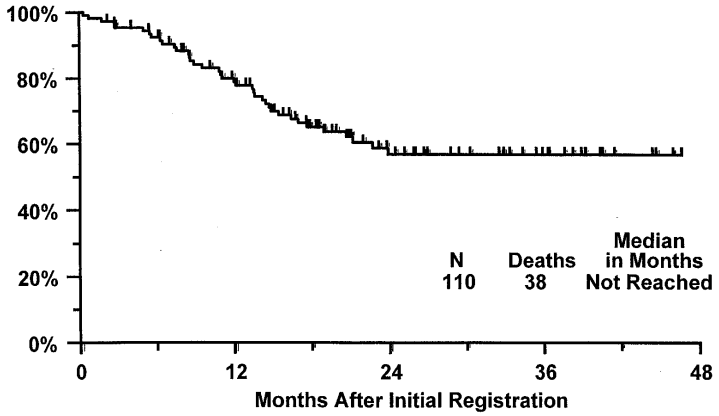

Fig 2. Overall survival of all eligible patients with follow-up.

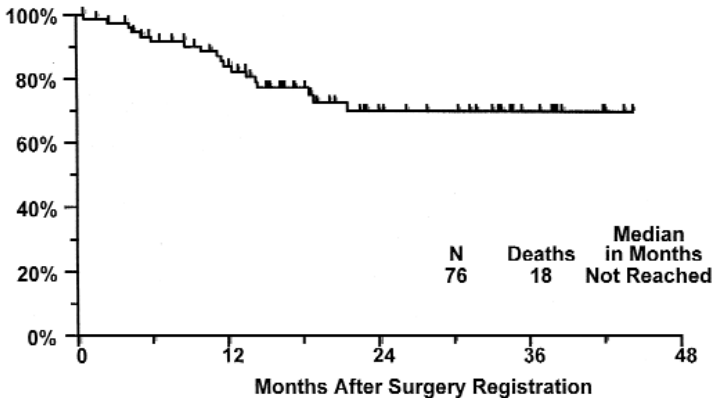

Fig 3. Overall survival after surgery for eligible patients with complete resections.

The Memorial Sloan-Kettering series and others emphasize the need for improved treatment of superior sulcus tumors, especially with respect to achieving complete resection and, by extension, long-term local control. The success of induction chemotherapy and chemoradiation in the treatment of stage IIIa (N2) NSCLC has prompted interest in applying this approach to superior sulcus tumors.[31] A small phase II trial reported by Martínez-Monge and coworkers[15] suggested that induction chemotherapy and radiation might lead to improved results. From 1988 to 1992, 18 patients with either T3 or T4 NSCLC of the superior sulcus were treated with induction chemotherapy (mitomycin, vindesine, and cisplatin or carboplatin) for 1 to 3 cycles followed by combined chemotherapy and radiation (total doses of 46 to 50 Gy) and then surgical resection. Although the induction therapy was not uniform across the entire group of patients, the resectability rate was 76.4%, the complete pathologic response rate was 70.5%, and the actuarial 4-year survival was 56.2%. These encouraging results indicate that further study of a combined modality approach is warranted. However, the high rate of treatment-related death (16.6%) mandates use of a different induction regimen.[15]

The use of combined chemotherapy and radiation is particularly attractive for the treatment of T3 and T4 superior sulcus tumors, especially if patients with N2 disease are excluded. This strategy exploits the synergy of concurrent therapy to treat tumors that present first and foremost a major problem in local control. The regimen used in this trial was extensively tested in previous trials conducted by SWOG, particularly in stages IIIa (N2) and selected stage IIIb NSCLC, and found to

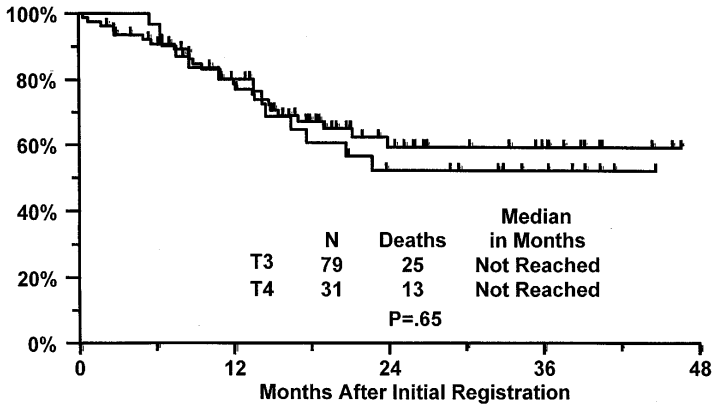

Fig 4. Overall survival by stage for all eligible patients with follow-up.

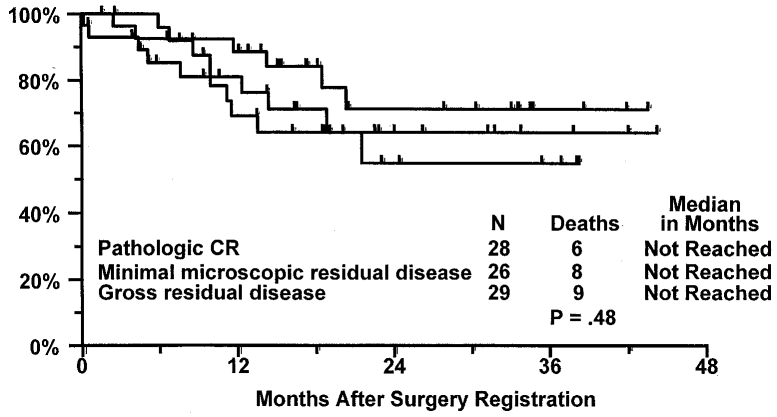

Fig 5. Overall survival after surgery by pathologic response.

be feasible and effective in the multi-institutional setting.[18,19] Thus, there was a strong rationale for testing the same induction regimen in superior sulcus tumors.

The results of this trial, with an overall treatment-related mortality of only 4.5%, show that induction cisplatin and etoposide with concurrent radiation followed by surgical resection is a feasible and well-tolerated regimen even when used across a broad range of institutions and surgeons, including community hospitals. The rates of pathologic response, complete resection, and overall survival appear to be significantly better than in past surgical experience. This is particularly true of patients with T4 tumors and suggests that a combined modality approach provides a far more favorable outcome for these tumors, which have usually been considered unresectable and incurable. The effectiveness of this regimen is also notable given the large size of most of the tumors at diagnosis, a situation in which radiation alone has limited impact.

This study highlights several other important findings. The discrepancy between radiologic and pathologic response after combined chemotherapy and radiation was noted in the previous SWOG trial with this regimen[18] but is particularly striking here. Only 40% of the patients with radiologically stable disease and 27% of the patients with a radiologic partial response actually had significant gross residual tumor at thoracotomy. This finding underscores the importance of not using radiologic response as a criterion for resection in this setting. Another important finding is that a relatively small proportion of patients were able to receive postoperative boost chemotherapy as planned. This reconfirms the experience of virtually all previous adjuvant chemotherapy trials.[32] Most patients with lung cancer recovering from a major operation tolerate postoperative chemotherapy poorly.

This treatment regimen also appears to have changed the patterns of relapse from predominantly local to

mostly distant.[14,17,23,30] The high frequency of relapse in the brain has been observed in other reports of superior sulcus tumors[26,30] and raises the complex question of whether patients who have a better prognosis (ie, major or complete pathologic response and complete resection) should be offered prophylactic cranial radiation. An identical problem has been observed in the patients who receive combined modality therapy for stage IIIa (N2) NSCLC.[18]

To our knowledge, this is the first prospective multi-institutional trial in NSCLC of the superior sulcus. Although a phase II trial, this study effectively sets a new standard of care by virtue of the substantially better outcome achieved compared with recent surgical series reporting the results of radiation and resection without chemotherapy. Unfortunately, the large number of institutions and of surgeons across North America required to complete this trial over a 5-year period attests to the rarity of this subset of NSCLC and indicates that it is unlikely that a phase III trial confirming the superiority of this approach could be performed in a timely manner. Therefore, future trials, also of phase II design, will have to address the areas where this regimen appears to have failed.

The combination of cisplatin and etoposide is widely considered an "old fashioned" chemotherapy regimen and has been discarded by many oncologists in favor of more recently developed agents including carboplatin, paclitaxel, vinorelbine, and gemcitabine. However, the superiority of these agents in combination with radiation as an induction regimen remains unproven. The low toxicity and high response rates seen with etoposide, cisplatin, and radiation in this study emphasize that this approach remains a highly effective, well-tolerated, and therefore standard regimen in the multi-institutional setting. Future trials should probably not seek to alter this particular chemotherapy and radiation combination, but instead add to it to diminish the risk of systemic relapse. Possible approaches include the addition of a chemotherapy agent such as docetaxel, which appears to be effective even in tumors previously treated with or resistant to cisplatin,[33] or biologic agents such as antiangiogenesis agents or tyrosine kinase inhibitors, which may enhance the response to chemotherapy or decrease the risk of systemic relapse. The design of a new trial that will build on the results presented here is currently under discussion. In the interim, the initial results of intergroup 0160 offer improved treatment for patients with T3 and T4 N0-1 NSCLC of the superior sulcus.

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Discussion

Dr Douglas J. Mathisen *(Boston, Mass).* I congratulate Dr Rusch and her colleagues on this very important work. It represents the first major step forward in the treatment of this difficult tumor. It is important to emphasize the historical perspective that Dr Rusch alluded to.

Just over 40 years ago this tumor was thought to be incurable. Then Dr Paulson (the 61st president of our Association) and his colleagues presented their work using preoperative radiotherapy and en bloc resection, achieving a 30% to 35% cure rate. As Dr Rusch mentioned, this has been the standard of care for all of these years.

We at the Massachusetts General Hospital had followed Dr Paulson's lead and achieved similar results, with a cure rate of about 30% and a local recurrence rate of about 30%. About 4 years ago we also instituted within our own institution a trial similar to the one presented today, using a slightly higher dose of radiotherapy but achieving very similar results: a 94% complete resection rate, an 87% 4-year actuarial survival, and no local recurrences to date. We would applaud the results that you have achieved, Dr Rusch. They are very similar to our results, and we are excited about this development.

I have 3 questions. You mentioned the issue of brain metastases. Was this figure higher than you anticipated compared with historical controls? You alluded to the complete response rate, but were you able to draw any conclusions relative to brain metastases between histology and complete response rate, which might be important in determining who would benefit from prophylactic cranial irradiation?

Second, I was very impressed with the results in the T4 group. Could you elaborate about the extent of initial involvement to provide some guidelines in that area? Were there any operative details that would be important to share with the audience?

Third, are there currently any contraindications to this approach using preoperative chemoradiotherapy for Pancoast tumors, and does it now have some role to play in patients with N2 disease in superior sulcus tumors who were previously thought to be incurable?

I am certain that in years to come this paper will be considered a milestone in the treatment of this tumor, much as Dr Paulson's paper is.

Dr Rusch. Thank you, Dr Mathisen. With respect to brain metastases, the pattern of relapse that I have shown here is analogous to the pattern of relapse that has been seen in virtually every neoadjuvant and adjuvant trial in resectable NSCLC and, indeed, is very much the pattern of relapse that is seen in patients who are treated solely with surgical resection without chemotherapy.

Many years ago, the Lung Cancer Study Group tried to assess whether it would be feasible to do a randomized trial testing the use of prophylactic cranial irradiation in patients who had undergone resection for NSCLC. That paper was published in *The New England Journal of Medicine,* with Dr Robert Figlin as the first author. Basically, we found that such a trial would be statistically impossible, because the sample size required would be too large. At some point in the next 5 or 10 years we may need to grapple with this issue at an international level, because clearly brain metastases are a major problem. We need to examine whether an approach similar to what has been done in limited staged small cell lung cancer would

be appropriate, that is, the use of prophylactic cranial irradiation in patients who have successfully completed management of the local problem and appear to be disease-free in the chest.

With respect to the correlation of histology versus brain metastases, we have not yet done that analysis, but that will be appropriate as we obtain further follow-up. In fact, we are planning to re-analyze this study for long-term results in approximately 2 years, so we will bear that issue in mind.

I do not have any guidelines for the management of T4 tumors. We included those tumors but stratified them specifically in this study, because we wanted to learn whether there was any potential role for combined modality treatment of those tumors. These patients have done surprisingly well. I have reviewed all of the CT reports and operative reports, so I do believe that the patients who are listed here as having T4 tumors truly have T4 tumors. They are predominantly patients who had tumors invading the spine. I see this as a major step forward for that tumor subset.

I can identify no particular contraindications with respect to the use of this induction regimen, aside from the usual considerations of using platinum-based treatment in patients for induction therapy, that is, adequate renal, neurologic, and cardiopulmonary function.

Finally, you asked about the use of this approach in patients with N2 disease. It is certainly to be considered. As you know, we have used a similar regimen and have reported that, again, in the SWOG trial several years ago, for patients who have stage IIIa N2 disease, with excellent results.

We are hoping to extend these results by increasing the amount of chemotherapy, adding docetaxel to the induction regimen. This approach may be particularly appropriate for patients who have Pancoast tumors with N2 disease.