Trimodality Therapy for Superior Sulcus Non-Small Cell Lung Cancer: Southwest Oncology Group-Intergroup Trial S0220

Kemp H. Kernstine, MD, PhD, James Moon, MS, Michael J. Kraut, MD, Katherine M. W. Pisters, MD, Joshua R. Sonett, MD, Valerie W. Rusch, MD, Charles R. Thomas, Jr, MD, Thomas K. Waddell, MD, PhD, James R. Jett, MD, Alan P. Lyss, MD, Steven M. Keller, MD, and David R. Gandara, MD, for the American College of Surgeons Oncology Group, Cancer and Leukemia Group B, Eastern Cooperative Oncology Group, North Central Cancer Treatment Group, National Cancer Institute of Canada Clinical Trials Group, and Southwest Oncology Group

Division of Thoracic Surgery, Department of Cardiovascular and Thoracic Surgery, Simmons Comprehensive Cancer Center, University of Texas Southwestern School of Medicine, Dallas, Texas; Southwest Oncology Group Statistical Center, Seattle, Washington; Providence Cancer Institute, Southfield, Michigan; MD Anderson Cancer Center, Houston, Texas; Columbia Presbyterian Medical Center, New York, New York; Memorial Sloan-Kettering Cancer Center, New York, New York; Department of Radiation Medicine, Knight Cancer Institute, Oregon Health Sciences University, Portland, Oregon; University Health Network/The Toronto General Hospital, Toronto, Ontario, Canada; Mayo Clinic, Rochester, Minnesota; Heartland Cancer Research Community Clinical Oncology Program/Missouri Baptist Medical Center, St. Louis, Missouri; Montefiore-Einstein Medical Center, Bronx, New York; and University of California Davis Cancer Center, Sacramento, California

Background. **Although preoperative chemotherapy (cisplatin-etoposide) and radiotherapy, followed by surgical resection, is considered a standard of care for superior sulcus cancers, treatment is rigorous and relapse limits long-term survival. The Southwest Oncology Group-Intergroup Trial S0220 was designed to incorporate an active systemic agent, docetaxel, as consolidation therapy.**

Methods. **Patients with histologically proven and radiologically defined T3 to 4, N0 to 1, M0 superior sulcus non-small cell lung cancer underwent induction therapy with cisplatin-etoposide, concurrently with thoracic radiotherapy at 45 Gy. Nonprogressing patients underwent surgical resection within 7 weeks. Consolidation consisted of docetaxel every 3 weeks for 3 doses. The accrual goal was 45 eligible patients. The primary objective was feasibility.**

Results. **Of 46 patients registered, 44 were eligible and assessable; 38 (86%) completed induction, 29 (66%) underwent surgical resection, and 20 (45% of eligible, 69% surgical, and 91% of those initiating consolidation therapy) completed consolidation docetaxel; 28 of 29 (97%) underwent a complete (R0) resection; 2 (7%) died of adult respiratory distress syndrome. In resected patients, 21 of 29 (72%) had a pathologic complete or nearly complete response. The known site of first recurrence was local in 2, local-systemic in 1, and systemic in 10, with 7 in the brain only. The 3-year progression-free survival was 56%, and 3-year overall survival was 61%.**

Conclusions. **Although trimodality therapy provides excellent R0 and local control, only 66% of patients underwent surgical resection and only 45% completed the treatment regimen. Even in this subset, distant recurrence continues to be a major problem, particularly brain-only relapse. Future strategies to improve treatment outcomes in this patient population must increase the effectiveness of systemic therapy and reduce the incidence of brain-only metastases.**

(Ann Thorac Surg 2014;98:402–10)

Accepted for publication April 10, 2014.

Presented at the Late-Breaking Abstract Session at the Forty-ninth Annual Meeting of The Society of Thoracic Surgeons, Los Angeles, CA, Jan 26–30, 2013.

Address correspondence to Dr Kernstine, Division of Thoracic Surgery, Department of Cardiovascular and Thoracic Surgery, The Harold C. Simmons Comprehensive Cancer Center, University of Texas, Southwestern Medical Center and School of Medicine, 5323 Harry Hines Blvd, 9th Flr, Ste HA09.134, Dallas, TX 75390–8879; e-mail: kemp.kernstine@utsouthwestern.edu.

Superior sulcus (SS) non-small cell lung cancer (NSCLC) is a form of locally advanced lung cancer that originates in the apex of the lung. Invasion of the chest wall and, potentially, the mediastinal structures makes resection challenging. Surgical resection by itself is infrequently curative. A combined modality approach of radiotherapy and resection, first adopted by Shaw et al [1] in the 1950s, resulted in 5-year survival rates of 25% to 30%.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2014.04.129

Abbreviations and Acronyms

ARDS = adult respiratory distress syndrome
BID = twice per day
CDDP = cisplatin
Chem Rx = chemotherapy
CI = confidence interval
csf = cerebrospinal fluid
CT = computed tomography
CTCAE = Common Terminology Criteria for Adverse Events
DFS = disease-free survival
Dox = docetaxel
JCOG = Japan Clinical Oncology Group
Min Res = minimum residual tumor
MMC = mitomycin C
MRI = magnetic resonance imaging
MST = median survival time
NA = not available
NSCLC = non-small cell lung cancer
OS = overall survival
PCI = prophylactic cranial irradiation
pCR = pathologically complete response
PET = positron emission tomography
PFS = progression-free survival
PS = performance status
PTX = paclitaxel
Rad Rx = radiotherapy
RT = radiotherapy
SS = superior sulcus
SWOG = Southwest Oncology Group
VND = vindesine
VP-16 = etoposide

This became a standard of therapy until 2001, when the Southwest Oncology Group (SWOG)/North American Intergroup published the results of a prospective phase II clinical trial (SWOG 9416/Intergroup 0160), establishing induction chemoradiotherapy, followed by surgical resection, as the new standard of care, with an 80% surgical resection rate and a 44% 5-year overall survival [2, 3]. This result was mimicked by a phase II trial performed by the Japan Clinical Oncology Group, protocol 9806, using a similar therapeutic approach that resulted in a 5-year overall survival of 56% [4]. Systemic failure was the major contributor to long-term death for both trials, present in approximately 80% of patients who recurred.

One strategy to control systemic recurrence is the administration of postoperative consolidation chemotherapy. SWOG 9416 planned for 2 cycles of additional etoposide and cisplatin after surgical resection. However, only 83% of the surgically treated patients received the prescribed therapy. Others have attempted to deliver postoperative chemotherapy after induction chemoradiotherapy and surgical resection to NSCLC patients, including SS tumor patients, with limited success and questionable benefit [5].

In 2001 when this study was conceived, docetaxel had been proved to be active in patients with NSCLC recurrent after platinum-based therapy, showing improved response and survival compared with best supportive care [6]. SWOG experience with docetaxel consolidation in stage IIIB NSCLC after definitive cisplatin, etoposide, and concurrent thoracic radiotherapy suggested that this might be a more effective and better tolerated approach to further cisplatin-etoposide in the postoperative treatment of SS cancers [7]. We designed a phase II trial to determine the feasibility of treating SS NSCLC with induction chemoradiotherapy and definitive resection, followed by consolidation docetaxel.

Patients and Methods

The protocol for this study (ClinicalTrials.gov Identifier: NCT00062439; http://clinicaltrials.gov/) was approved by the Institutional Review Boards at the participating institutions. Patients were informed of the investigational nature of the study and provided written informed consent in accordance with institutional and federal guidelines.

Eligibility Criteria

Patients with a single, primary, previously untreated histologically or cytologically confirmed SS NSCLC, with selected stage IIB (T3 N0), IIIA (T3 N1), or IIIB (T4 N0 to 1), according to the American Joint Committee on Cancer, Cancer Staging Manual, 6th edition, NSCLC were eligible. SS cancer was defined as apical lung tumor, with or without associated Pancoast syndrome (neurologic symptoms secondary to invasion of the inferior brachial plexus); apical lung tumors with computed tomography (CT) scan or magnetic resonance imaging (MRI) evidence of invasion of upper chest wall, usually with involvement of ribs 1 or 2; upper thoracic vertebral bodies; or subclavian vessels. Lack of N2 nodal involvement was confirmed by negative results on mediastinoscopy or CT scan and negative positron emission tomography (PET) of the mediastinum. CT scan of the abdomen and bone scan or PET, and CT scan or MRI of the brain were used to assess for metastatic disease. Pulmonary function testing with diffusion capacity and routine laboratory testing were used to assess for fitness for planned treatment. Patients were required to have a Zubrod performance status of 0 to 2.

Treatment Regimen

After informed consent, eligible patients received induction chemoradiotherapy with cisplatin (50 mg/m^2 intravenously) on days 1, 8, 29, and 36, and etoposide (50 mg/m^2 intravenously) days 1 through 5 and 29 through 33, initiated simultaneously with thoracic radiotherapy given daily Monday through Friday in 1.8-Gy fractions to a total dose of 45 Gy. Radiotherapy included computerized treatment planning and delivery to the primary tumor and ipsilateral supraclavicular

region. Coverage of the mediastinum or hilum was not mandated.

Nonprogressing patients underwent thoracotomy 3 to 7 weeks after completion of induction therapy. Resection was through an upper lobectomy, bilobectomy, or pneumonectomy, with involved areas of the chest wall or spine, or both, resected en bloc with the involved lung. Appropriate hilar and mediastinal lymph nodes were removed (levels 2R, 4R, 7, 8, 9, and 10R for right-sided tumors, and levels 5, 6, 7, 8, 9, and 10L for left-sided lesions). Patients who did not progress, but were deemed unfit for surgical intervention or who refused the operation, were continued on radiotherapy to a total dose of 61 to 61.2 Gy.

Patients with resection and full-dose radiotherapy who did not undergo an operation were to receive consolidation docetaxel (75 mg/m^2 intravenously) every 21 days for 3 doses beginning 3 to 8 weeks after completion of the operation or definitive radiotherapy.

Response Evaluations

Response was evaluated using Response Evaluation Criteria In Solid Tumors [8], with assessments after 2 to 4 weeks after completion of induction chemoradiotherapy. Patients were restaged with CT scan of the chest and upper abdomen, CT scan or MRI of the brain, and pulmonary function tests. Bone scans were repeated only if new symptoms or elevated alkaline phosphatase occurred.

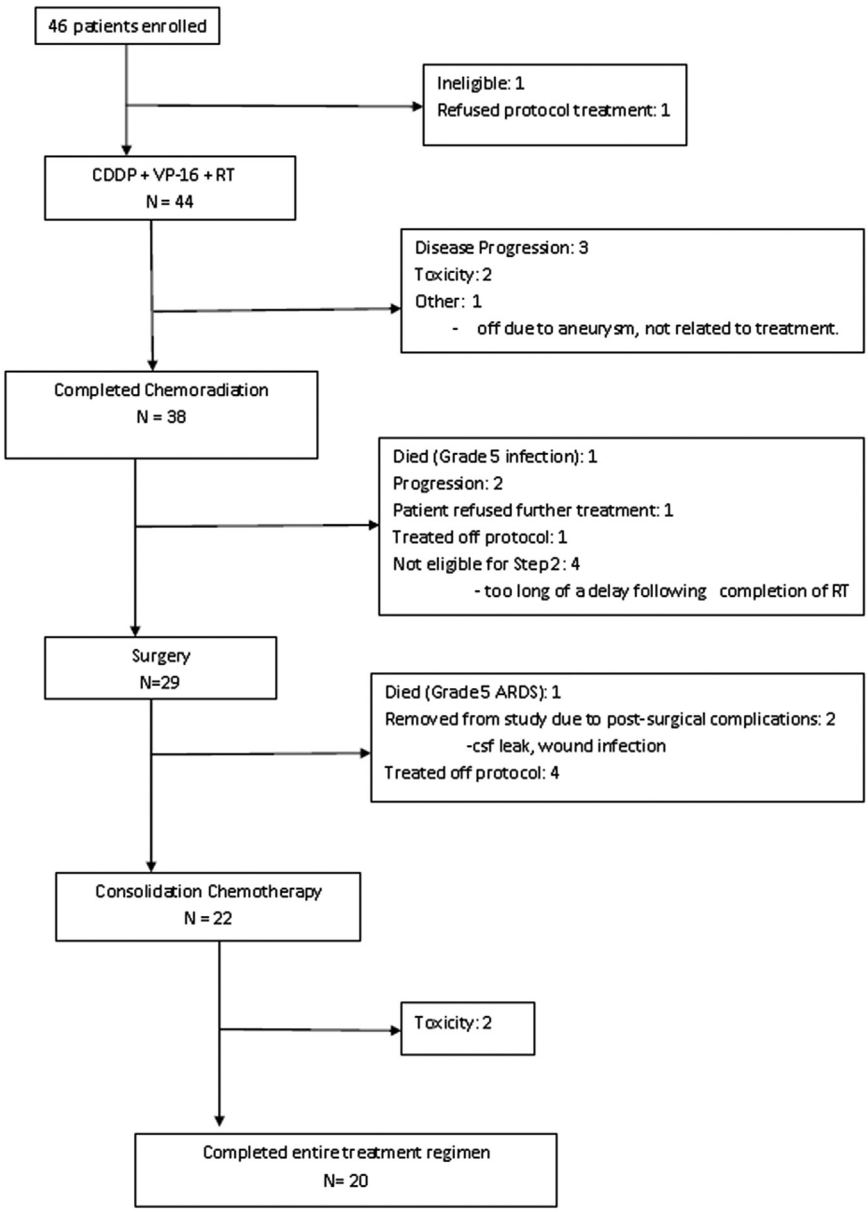

Fig 1. Protocol schema is shown for the Southwest Oncology Group S0220 trial. (ARDS = adult respiratory distress syndrome; CDDP = cisplatin; csf = cerebrospinal fluid; VP-16 = etoposide; RT = radiotherapy.)

Table 1. Baseline Patient Characteristics

Variables	Median (range) or No. (%)
Age, y	59 (44–75)
Sex	
Males	32 (73)
Females	12 (27)
Race	
White	40 (91)
Asian	3 (7)
Native American	1 (2)
Performance status	
0	15 (34)
1	29 (66)
Histology	
Adenocarcinoma	17 (39)
Large cell	4 (9)
Squamous	10 (23)
Other non-small cell	13 (30)
N stage	
N0	39 (89)
N1	5 (11)
T stage	
T3	32 (73)
T4	12 (27)

Patients were restaged at the completion of all therapy (4 to 6 weeks after completion of consolidation chemotherapy) and at 3-month intervals for 2 years and then 6-month intervals for 3 more years, for a total of 5 years or until death. At each follow-up visit, a routine history, physical examination, routine laboratory tests, a chest roentgenogram, and chest and upper abdomen CTs were performed. Other tests were obtained as necessary. Posttreatment brain scanning (contrast-enhanced CT or MRI) was recommended at 6 and 12 months.

Toxicity Evaluation

All patients were monitored for toxicity from treatment, recorded using Common Terminology Criteria for Adverse Events version 3.0 [9].

Table 2. Toxicity During Concurrent Chemoradiotherapy in 44 Evaluable Patients

	Toxicity Grade		
Adverse Event	3 (No.)	4 (No.)	5 (No.)
Allergic reaction	0	1	0
Dehydration	1	1	0
Diarrhea	1	0	0
Nausea	1	0	0
Vomiting	2	0	0
Thrombosis/embolism	0	1	0
Esophagitis	1	0	0
Mucositis	1	0	0
Fatigue	2	0	0
Hyponatremia	1	0	0
Hemoglobin	3	0	0
Infection w/neutropenia ≥grade 3	1	0	1
Neutrophils	10	5	0
Febrile neutropenia	1	1	0
Total	11	7	1

Statistical Methods

The primary objective of this phase II study was to assess the feasibility of treating patients with stage IIB/IIIB SS NSCLC with a regimen of induction chemoradiotherapy, followed by surgical resection and consolidation docetaxel. Feasibility was defined by the percentage of patients completing all protocol treatment. The design specified that if the true rate was 55% or less, the regimen would not warrant further consideration, whereas if the rate were at least 75%, it would be promising. The accrual goal was 45 eligible patients and 30 to complete all protocol treatment. This design had an exact one-sided α level of 4% and exact power of 87%. With 45 patients accrued over 48 months and an additional 24 months of follow-up, this design also had 84% power to reject the null hypothesis of median survival time of 27 months in favor of median survival time of 45 months using a one-sided -0.05 level test.

Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method.

Table 3. Surgical Stage in the 29 Operable Patients

	Pathologic Stage at Operation						
Clinical Stage at Baseline	T0 N0 (No.)	T1 N0 (No.)	T2 N0 (No.)	T3 N0 (No.)	T4 N0 (No.)	T4 N3 (No.)	Total (No.)
T3 N0	6	7	1	4	1	0	19
T3 N1	1	2	0	0	0	0	3
T4 N0	1	1	0	3	0	1	6
T4 N1	0	1	0	0	0	0	1
Total	8	11	1	7	1	1	29

Table 4. Toxicity During Consolidation Chemotherapy in 22 Patients

	Toxicity Grade		
	3	4	5
Adverse Event	(No.)	(No.)	(No.)
Dehydration	2	0	0
Diarrhea	1	0	0
Dyspnea	2	0	0
Fatigue	1	0	0
Nausea	1	0	0
Vomiting	1	0	0
Weight Loss	1	0	0
Hypoxia	1	0	0
Infection w/neutropenia ≥grade 3	1	0	0
Neutropenia	3	5	0
Total	7	6	0

Exact binomial 95% confidence intervals (CIs) were calculated for the response rate (confirmed and unconfirmed, complete and partial responses) to induction chemoradiotherapy and the rate of complete resection (R0) after induction therapy. Estimation of locoregional failure rates and their 95% CIs were calculated [10].

For patients who underwent surgical resection, Kaplan-Meier estimates of recurrence-free survival and OS from the date of the operation were calculated. A log-rank test was used to compare survival between patients who had achieved a pathologically complete response (pCR), defined as less than 5% viable tumor in margins, and those who had less than a pCR.

Results

Accrual to the three phases of the trial is shown in Figure 1. Between July 1, 2003, and October 1, 2007, 46 patients were registered. Of these, 44 patients were eligible, with 1 patient ineligible due to N3 disease and 1 patient refused protocol treatment. Table 1 reports the baseline characteristics of the 44 eligible patients.

Of the 44 patients, 29 (66%) underwent surgical resection. Twenty-two patients (50% of 44 eligible and 76% of the 29 resected) received some consolidation chemotherapy, and of those, 20 (91%) completed all 3 cycles. Therefore, 45% (95% CI, 30% to 61%) of patients completed all protocol treatment.

Induction Chemoradiotherapy

Of the 44 patients who received induction chemotherapy, 1 patient (2%) died of infection with grade 3 to 4 neutropenia. Seven additional patients experienced grade 4 toxicity (16%), which included neutropenia in 5 patients, and 1 patient each with allergic reaction, dehydration, febrile neutropenia, lymphopenia, and thrombosis/embolism. Thirty-eight patients (86%) completed the induction regimen. Table 2 reports the number of patients with a given type and grade of toxicity during induction chemoradiotherapy.

Surgical Resection

Twenty-nine patients underwent surgical resection. Lobectomy was performed in 24 (83%), segmentectomy in 2 (7%), bilobectomy in 2 (7%), and wedge resection in 1 patient (3%). The 3 patients who underwent sublobar resection were protocol violations and were removed from study. Chest wall or adjacent organ resection was performed in 25 patients (86%). Each had one or more of the following structures resected:chest wall in 22, major vascular in 1, pericardium in 1, and other in 10, and more than 1 adjacent structure was resected in 7 patients. A median number of 5 lymph node stations (range, 0 to 9) were examined, with no nodes examined in 10% of the patients. Table 3 summarizes the operative stage for the patients who underwent resection. Comparing the preclinical stage with the surgical stage, 4 of 29 (14%) were unchanged, 2 (7%) were upstaged, and 23 of 29 (79%) were downstaged.

The median operating room time, defined as the time from entrance to exit from the operating room, was 4.3 hours (range, 1.4 to 9.5 hours), and the median estimated blood loss was 0.5 L (range, 0 to 7.5 L). Eleven patients (38%) received intraoperative or postoperative (≤7 days of the operation) transfusions, or both, and were given a median number of 2 units (range, 1 to 22 units).

There were 2 surgical deaths (2 of 29 [7%]), both due to adult respiratory distress syndrome. Two additional

Table 5. Outcomes by Clinical Stage at Baseline

		Clinical Stage at Baseline			
Variable	Total (N = 44) No. (%)	T3 N0 (n = 28) No. (%)	T3 N1 (n = 4) No. (%)	T4 N0 (n = 11) No. (%)	T4 N1 (n = 1) No. (%)
Completed induction	38 (86)	23 (82)	4 (100)	10 (91)	1 (100)
Surgical resection per protocol	29 (66)	19 (68)	3 (75)	6 (55)	1 (100)
R0 resection	28 (64)	18 (64)	3 (75)	6 (55)	1 (100)
Pathologic complete response	21 (48)	14 (50)	3 (75)	3 (27)	1 (100)
With minimal residual disease	13 (30)	8 (29)	2 (50)	2 (18)	1 (100)
No minimal residual disease	8 (18)	6 (21)	1 (25)	1 (9)	0 (0)
Completed consolidation	20 (45)	15 (54)	3 (75)	2 (18)	0 (0)

patients experienced grade 4 toxicity related to the operation, and 1 patient each experienced adult respiratory distress syndrome, cerebrospinal fluid leak, chylothorax, hemorrhage, hypoxia, lung infection, respiratory insufficiency, renal failure, and ventricular fibrillation. An intraoperative or postoperative complication occurred in 16 patients (55%), the most common of which was atrial arrhythmia in 9 patients (31%).

An R0 resection was achieved in 28 of the 29 patients (97%) who underwent operations; the remaining patient had an R1 resection and was treated with adjuvant radiotherapy. The postresection pathologic analysis revealed no evidence of residual tumor (pCR) in 8 (28%), minimal residual tumor (<5%) in 13 (45%), and the remaining 8 (28%) had gross residual tumor (>5% viable tumor).

Consolidation Docetaxel

Consolidation docetaxel was initiated in 22 patients, and 20 completed the planned treatment. No deaths occurred related to consolidation therapy, but 6 patients experienced grade 4 adverse events, which included 5 with neutropenia. Table 4 shows toxicity during consolidation chemotherapy.

Response, PFS, and OS

Table 5 summarizes the number of patients by lung cancer clinical stage over the course of the protocol into each of the major protocol categories. Thirty-two eligible patients had measurable disease according to the Response Evaluation Criteria In Solid Tumors at baseline and were included in the response analysis. Two patients stopped treatment due to toxicity before their first follow-up disease assessment and were counted as nonresponders. Partial responses were documented in 9 of 32 patients, for an estimated response rate of 28% (95% CI, 14% to 47%).

The median follow-up among the 25 patients still alive is 45 months (range, 2 to 75 months). The median PFS is 43 months (95% CI, 20 to 43 months), and the OS is 50 months (95% CI, 20 to 50 months). The 3-year PFS is 56% (95% CI, 40% to 70%), and the 3-year OS is 61% (95% CI, 44% to 74%; Fig 2). Figure 3 demonstrates the trend toward improved survival in those surgically resected patients who were found to have a pathologically complete response. Figure 4 illustrates the cumulative incidence of PFS failure types. The first recurrence was

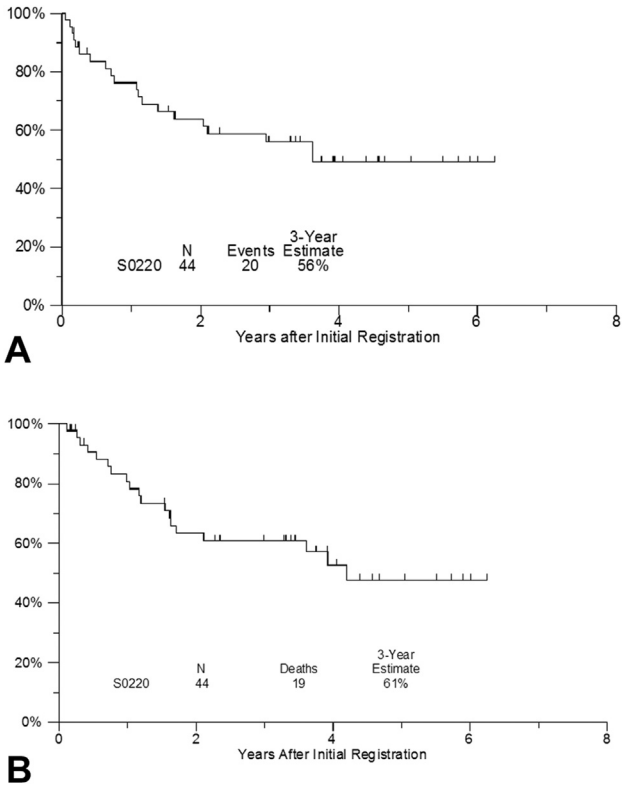

Fig 2. (A) Progression-free survival and (B) overall survival are shown from date of enrollment.

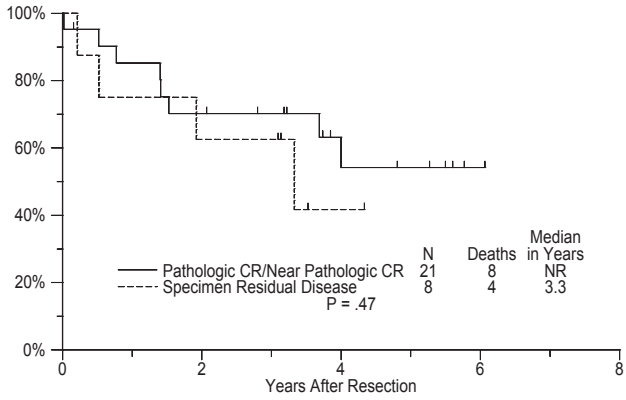

Fig 3. Overall survival from date of surgical resection for patients with specimens showing pathologically complete response (CR) or near-pathologically CR (solid line) compared with specimens showing residual disease (dashed line).

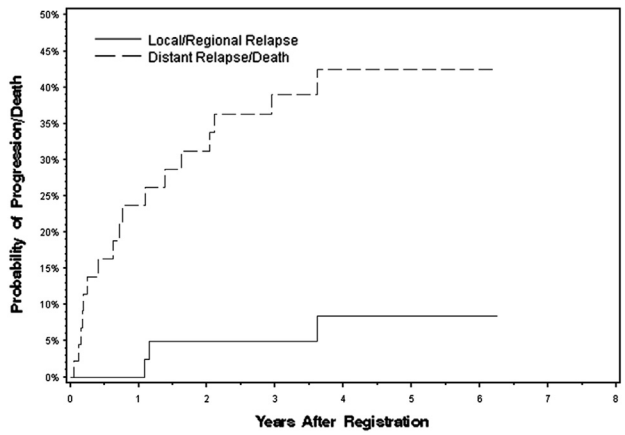

Fig 4. Cumulative incidence of progression-free survival failure types, with rate of local recurrence (solid line) compared with distant relapse or death (dashed line).

Table 6. Phase II Trials for the Treatment of Superior Sulcus Non-Small Cell Lung Cancer, 2001 to Present

First Author (Institution or Group + Trial #), Publ Year	No. of Patients (After Exclusions)	Inclusion Criteria	Chem Rx Regimen	Rad Rx Dose	Grade 3 + 4 Toxicity	Induction Deaths	Induction Disease Progression
Rusch (SWOG 9416), 2001, 2007 [2, 3]	110	Histologically or cytologically proven, cT3-4, cN0-1 NSCLC, mediastinoscopy AI, no wedge allowed, PS ≤2, cT3 71%, cN0 not reported	CDDP/VP-16 ×2	Concurrent 45 Gy to include ipsilateral supraclavicular nodes, not mediastinum or hilum	Combination not reported	3 (2.7%)	9/110 (8.2%)
Marra (University of Essen), 2007 [21]	31	Histologically or cytologically proven cT3-4, cN0-3 NSCLC, mediastinoscopy all, PS ≤2, wedge allowed cT3 81%, cN0 67.7%	CDDP/VP-16 ×3 in first 22, remaining 9 PTX instead of VP-16 during Rad Rx	At 10th wk, concurrent 45 Gy (1.5 BID) including ipsilateral supraclavicular nodes, if cN2-3 target mediastinum, IIIB treated w PCI	32%, not graded according to CTCAE	0	NA
Kunitoh (JCOG 9806), 2008 [4]	75	Histologically or cytologically proven cT3-4, cN0-1 NSCLC, CT criteria node <1 cm, mediastinoscopy to R/O disease, no wedge allowed, ipsilateral N3 included, PS ≤1, cT3 74%, cN0 78%	MMC/VND/CDDP ×2	Concurrent 45 Gy (split-course 1-wk) includes ipsilateral supraclavicular nodes, not mediastinum or hilum	Combination not reported	1 (1.3%)	5/75 (6.7%)
Gomez (MD Anderson) 2012 [20]	32	Histologic cT3-4, cN0-2 NSCLC, no wedge allowed, PS ≤70%, cT3 81%, cN0 84.5%	Post-op CDDP/VP-16 ×5, first 2 cycles concurrent w Rad Rx, included hilum & mediastinum	Concurrent post-op 60 Gy (1.2 Gy fractions BID); if margin neg, 64.8 Gy if margin pos, 11 Rx prophylactic PCI	Not applicable	Not applicable	Not applicable
Kernstine (SWOG S0220), 2014	44	Histologically or cytologically proven NSCLC cT3-4, N0-1 negative mediastinum confirmed by mediastinoscopy or negative PET + CT, PS ≤2, no wedge allowed, cT3 73%, cN0 89%	CDDP/VP-16 ×2	Concurrent 45 Gy to include the ipsilateral supraclavicular area, hilum & mediastinum not mandated	18 (41%)	1 (2%) from neutropenic infection	5/44 (11%)

local in 3 patients and at a distant site in 10 patients, and 7 patients died before documentation of disease recurrence. Recurrence was documented in the brain in 7 patients, and each had no other site of recurrence.

Comment

The current study failed to achieve its primary end point, feasibility: 20 (45%) completed the planned therapy, a rate was not dissimilar from SWOG 9416. Through the SWOG S0220 design, we have defined the reasons for non-completion of the trimodality induction protocol. Future trials must address the findings to increase the likelihood for protocol completion.

Although survival was not the primary end point, the current regimen appeared to have a survival benefit. With modest power of 84% to reject the null hypothesis, the observed median OS was 50 months from enrollment, greater than the 41 months that would be sufficient to conclude that the true median OS is greater than 27 months (see Statistical Methods). Despite not reaching the accrual goal, this trial confirms the efficacy of the core therapy.

Treatment of nonmetastatic SS cancers with a trimodality approach is the de facto standard of care [11–16]. In a phase II clinical trial studying trimodality therapy (SWOG 8805) in 126 IIIA (N2) and IIIB NSCLC patients, of which Pancoast NSCLC is a subset, chemoradiotherapy cytoreduced the primary cancer, potentially downstaging patients [17]. On the basis of these results and the poor outcomes of SS therapy, SWOG 9416 used the identical regimen as in SWOG 8805 [2, 3]. With 110 eligible patients, this was the largest trial performed in SS cancers and used meticulous surgical staging. It demonstrated the effectiveness of the trimodality approach, with 95% completing induction; median survival was 33 months and the 5-year OS was 44%. The R0 resection was 94%, and in that group, median survival was 94 months and 5-year survival was 54%. Although not a phase III trial, SWOG 9416 established induction chemoradiotherapy with cisplatin-etoposide and concurrent radiotherapy as a standard of care for SS NSCLC. Two major evidenced-based guidelines have now accepted this trimodality approach as a standard of care for SS cancers [15, 16, 18].

Perhaps the greatest hurdle to improving survival using this treatment regimen is the relatively high rate of brain-only metastasis seen after therapy. In a retrospective review of SWOG combined-modality lung cancer trials, Gaspar and colleagues [19] demonstrated that 20% of patients relapse in the brain only and an additional 6% in the brain plus other sites. Of the 13 patients in the current study for whom the first site of relapse was

First Author (Institution or Group + Trial #), Publ Year	No. of Surgically Resected	No. of R0	pCR + Min Residual = Total	Surgical Mortality	No. of Surgically Resected With Consolidation Therapy	Planned Consolidation Regimen	Consolidation Deaths, Grade 3 + 4 Toxicity	No. of Surgically Resected Who Started and Completed Consolidation	Survival
Rusch (SWOG 9416), 2001, 2007 [2, 3]	88 (80%)	83 (94%)	32/88 (36%) + 29/88 (33%) = 61/88 (69%)	2/88 (2.3%)	59/88 (67%)	CDDP/VP-16 ×2	Complications during this phase not reported	49/59 (83%)	MST 33 mos all 110 patients, 94 mos if R0; 2-yr OS 55%, 5-yr OS 44%; 54% for R0, if pCR + Min Res 45%; pCR better survival
Marra (University of Essen), 2007 [21]	29 (94%)	27/29 (93.5%) on final analysis	13/29 (45%) + 7/29 (24%) = 20/29 (69%)	2/29 (7%)	NA	NA	NA	NA	MST 54 mos, 2-yr OS 74%, 5-yr DFS 52%, 5-yr OS 46%
Kunitoh (JCOG 9806), 2008 [4]	57/75 (76%)	51/57 (89%)	12/57 (21%), min residual disease not reported	2/57 (3.5%)	Boost Rad Rx to 66.6 Gy if not R0, no consolidation Chem Rx	NA	NA	NA	DFS 28 mos, OS not reached, DFS 3-yr 49%, 5-yr 45%; OS 3-yr 61%; 5-yr 56%; R0 patients OS 5-yr 70%
Gomez (MD Anderson) 2012 [20]	32 (100%)	23 (72%)	Not applicable	0%	Not applicable	Adjuvant provided, not consolidation	No deaths; dysphagia, 10; pneumonitis, 1; lung fibrosis, 1; leukopenia, 1; granulocytopenia; 1	78% completed protocol	DFS 2-yr 49%, 5-yr 45%, 10-yr 45%; OS 2-yr 72%, 5-yr 50%, 10-yr 45%
Kernstine (SWOG S0220), 2014	29 (66%)	28 (97%)	8/29 (28%) + 13/29 (45%) = 21/29 (72%)	2/29 (7%), both from ARDS	22/29 (76%)	Dox ×3	0%, 13/22 (59%)	20/22 (91%)	PFS 1-yr 76%, 3-yr 56%; OS 61%; median OS 4 yrs

ARDS = adult respiratory distress syndrome; BID = twice daily; CDDP = cisplatin; Chem Rx = chemotherapy; CTCAE = Common Terminology Criteria for Adverse Events; CT = computed tomography; DFS = disease-free survival; Dox = docetaxel; JCOG = Japan Clinical Oncology Group; Min Res = minimum residual tumor; MMC = mitomycin C; MST = median survival time; NA = not available; OS = overall survival; PCI = prophylactic cranial irradiation; pCR = pathologically complete response, no viable tumor in the resected specimen; PET = positron emission tomography; PFS = progression-free survival; PS = performance status (Zubrod); PTX = paclitaxel; R0 = complete resection, all margins microscopically clear of disease; Rad Rx = radiotherapy; SWOG = Southwest Oncology Group; VND = vindesine; VP-16 = etoposide.

known, the recurrence was only in the brain in 7 patients. Efforts to evaluate the use of prophylactic cranial irradiation in locally advanced NSCLC in the clinical trial setting have been hampered by poor accrual, and it is unlikely that a data-driven answer to this problem will be obtained. Fortunately, the availability of high-quality imaging, minimally invasive neurosurgical techniques, and stereotactic radiotherapy have improved the salvage rate for these patients, but strategies to mitigate this problem are still sorely needed.

Table 6 summarizes the SS cancer prospective clinical trial literature and provides insight into the nature of the disease and treatment. All are phase II trials, with 2 single-institution and 3 multiinstitution cooperative group trials. Approximately 75% of patients were T3 and the remainder T4, and approximately 70% to 90% were clinically N0. Use of brain imaging, PET scanning, or surgical mediastinal staging was not consistent. Four of the trials used induction chemoradiotherapy, whereas the Gomez and colleagues [20] trial used adjuvant chemoradiotherapy. The induction programs were all platinum-based. Etoposide was most commonly used as the additional chemotherapeutic agent. The dose of radiotherapy was 45 Gy concurrently with the chemotherapy, although there were some variations in using hyperfractionated radiotherapy and whether the mediastinum was included. At the end of the induction program, 70% to 80% of the patients were surgically resectable, with the exception of 95% in the Marra and colleagues [21] trial, a single-institutional trial. All patients in the Gomez trial were resected.

The pCR rates for the SWOG 9416 and S0220 trials, were between 28% and 36%, and were 45% for the Marra and colleagues [21] trial and 21% for the Kunitoh and

colleagues [4] trial. The SWOG 9416 and SWOG 0220 trials offered consolidation therapy. The number of surgical patients that were able to receive consolidation therapy was similar, 67% and 76%.

No deaths occurred from the postoperative treatment phase in the 3 postoperative treatment trials, the 2 SWOG trials, and the Gomez and colleagues trial. Postoperative chemotherapy was completed in 80% to 90%. The median OS for the SWOG trials was between 3 and 4 years. A survival advantage was conferred if there was a complete or nearly complete response and if the surgical margin was negative for malignancy.

Finally, taken together, these trials demonstrate excellent local control in resected patients but relatively high failure rates in distant sites. Time to recurrence was within the 2 to 3 years after the operation, and the most frequent location of recurrence was the brain.

We conclude that induction chemoradiotherapy with etoposide and cisplatin provides an excellent rate of response and an excellent margin-free (R0) rate of resection. Whether postoperative consolidation therapy of any type adds to efficacy remains unclear. Further studies designed to improve the pCR as a surrogate for increasing survival, are warranted, as are investigations designed to prevent or reduce the incidence of brain relapse, the most common cause of distant failure.

This investigation was supported in part by the following Public Health Service Cooperative Agreement grant numbers awarded by the National Cancer Institute, U.S. Department of Health and Human Services: CA32102, CA38926, CA63848, CA76429, CA67575, CA20319, CA95860, CA46368, CA45377, CA35178, CA35176, CA46282, CA45808, CA42777, CA35431, CA86780, CA31946, CA14958, CA21115, and CA25224, and in part Sanofi-Aventis. The funding agencies had no involvement in the study design, data collection, analysis and interpretation, in the writing of the report, or in its submission.

References

1. Shaw RR, Paulson DL, Kee JL. Treatment of superior sulcus tumor by irradiation followed by resection. Ann Surg 1961;154:29–40.
2. Rusch VW, Giroux DJ, Kraut MJ, et al. 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). J Thorac Cardiovasc Surg 2001;121:472–83.
3. Rusch VW, Giroux DJ, Kraut MJ, et al. 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). J Clin Oncol 2007;25:313–8.
4. Kunitoh H, Kato H, Tsuboi M, et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. J Clin Oncol 2008;26:644–9.
5. Felip E, Rosell R. New strategies in the treatment of resectable non-small cell lung cancer. Expert Rev Anticancer Ther 2001;1:224–8.
6. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.
7. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 2003;21:2004–10.
8. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
9. Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed February 17, 2013.
10. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695–706.
11. Narayan S, Thomas CR Jr. Multimodality therapy for Pancoast tumor. Nat Clin Pract Oncol 2006;3:484–91.
12. Kraut MJ, Vallieres E, Thomas CR Jr. Pancoast (superior sulcus) neoplasms. Curr Probl Cancer 2003;27:81–104.
13. Garcia JA, Bhakta S, Fuller CD, Thomas CR Jr. Multidisciplinary approach to superior sulcus tumors. Cancer J 2005;11:189–97.
14. Sanborn RE, Thomas CR. Current status and future directions of multimodality therapy for non-small cell lung cancer of the superior sulcus. Curr Cancer Ther Rev 2011;7:2–9.
15. Detterbeck FC, Jones DR, Kernstine KH, Naunheim KS. Lung cancer. Special treatment issues. Chest 2003;123:244S–58S.
16. National Comprehensive Cancer Network. Non-small cell lung cancer. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed February 17, 2013.
17. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995;13:1880–92.
18. Shen KR, Meyers BF, Larner JM, Jones DR. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:290S–305S.
19. Gaspar LE, Chansky K, Albain KS, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non–small-cell lung cancer: a retrospective review by the Southwest Oncology Group. J Clin Oncol 2005;23:2955–61.
20. Gomez DR, Cox JD, Roth JA, et al. A prospective phase 2 study of surgery followed by chemotherapy and radiation for superior sulcus tumors. Cancer 2012;118:444–51.
21. Marra A, Eberhardt W, Pottgen C, et al. Induction chemotherapy, concurrent chemoradiation and surgery for Pancoast tumour. Eur Respir J 2007;29:117–26.