

## Phase II Trial of Postoperative Adjuvant Paclitaxel/Carboplatin and Thoracic Radiotherapy in Resected Stage II and IIIA Non–Small-Cell Lung Cancer: Promising Long-Term Results of the Radiation Therapy Oncology Group—RTOG 9705

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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### A B S T R A C T

#### Purpose

To determine the overall survival, progression-free survival, and toxicity associated with concurrent paclitaxel/carboplatin and thoracic radiotherapy for completely resected patients with stage II and IIIA non–small-cell lung cancer (NSCLC).

#### Patients and Methods

Eighty-eight eligible patients had surgical resection for pathologic stage II or IIIA disease and received postoperative paclitaxel and carboplatin. Concurrent thoracic radiotherapy at 50.4 Gy in 28 fractions for 6 weeks (1.8 Gy/d, 5 days/wk) was given during cycles 1 and 2. A boost of 10.8 Gy in six fractions was given for extracapsular nodal extension or T3 lesions.

#### Results

Treatment compliance was acceptable, with 93% compliance for radiation therapy and 86% for chemotherapy completion. The median duration of follow-up was 56.7 months (range, 17 to 61 months). The median overall survival time was 56.3 months, with 1-, 2-, and 3-year survival rates of 86%, 70%, and 61%, respectively. The 1-, 2-, and 3-year progression-free survival rates were 70%, 57%, and 50%, respectively. Brain metastasis occurred as the sole site of first failure in 11%, and 9% failed in other metastatic sites as first failure. Of the 43 patients who died, the cause of death was the treated cancer in 31 (35%). Local failure was a component of first failure in 15% of patients. Toxicities were acceptable. An overall survival comparison to Eastern Cooperative Oncology Group 3590 is favorable.

#### Conclusion

The mature results of this trial suggest an improved overall and progression-free survival in this group of resected NSCLC patients, compared with previously reported trials. A phase III trial comparing this treatment regimen with standard therapy seems warranted.

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### INTRODUCTION

Patient prognosis following surgery for stage II and III non–small-cell lung cancer (NSCLC) remains a significant concern. Survival with surgical resection for patients with pathologic stage I is reasonably high (55% to 85%).<sup>1,2</sup> However, when lymph

node involvement is identified with surgical resection, survival falls precipitously (29% to 72% for those with N1 involvement, and 26% to 67% for those with N2 involvement).<sup>2,3</sup> The patterns of failure of these patients are both local-regional and distant metastasis. Randomized trials addressing postoperative radiation therapy show improved local-regional

control and disease-free survival (primarily in stage III patients).<sup>4-6</sup> However, the trials addressing the value of postoperative radiation therapy include patients with both stage II and III disease and, thus, have limited statistical power in subgroup analyses. Retrospective series suggest that a larger trial for patients with stage III disease may potentially show a survival advantage.<sup>7</sup>

In 1997, the Radiation Therapy Oncology Group (RTOG) initiated a phase II trial to evaluate the efficacy of combining paclitaxel and carboplatin with thoracic radiation therapy postoperatively (RTOG 9705). This study was developed in the context of the large Eastern Cooperative Oncology Group (ECOG) randomized trial (E3590) of postoperative thoracic radiotherapy versus postoperative cisplatin/etoposide and thoracic radiotherapy (with which the RTOG participated) for patients with stage II and IIIA NSCLC. The trial was nearing completion with the results of the trial as yet unknown. The primary objectives of the current study were to determine the progression-free and overall survival in patients with completely resected stage II and IIIA NSCLC treated with paclitaxel and carboplatin combined with thoracic radiotherapy. In addition, we wanted to determine the qualitative and quantitative toxicity and reversibility of toxicity from this approach. It was anticipated that the results of this trial, if promising, would be compared with the best treatment regimen based on the ECOG study, which was recently published.<sup>8</sup>

## PATIENTS AND METHODS

The trial was initiated by the RTOG in July 1997, and enrollment was completed in June 1998. Eligible patients were those with pathologic documentation of NSCLC completely resected with pathologic stage II or stage IIIA disease. Adjuvant therapy was to begin within 56 days of surgical resection. For pneumonectomy,  $\geq 28$  days must have elapsed between surgery and the start of radiotherapy. Following lobectomy or bilobectomy,  $\geq 14$  days must have elapsed between surgery and the start of radiotherapy. All surgical margins were to be negative for tumor. Karnofsky performance status (KPS) was to be  $\geq 70$ . A postoperative Forced Expiratory Volume (FEV1) greater than 1 L and sufficient for the patient to tolerate radiation therapy was required. Pretreatment hematologic parameters of absolute neutrophil count (ANC) greater than 2,000, platelet count greater than 100,000, serum creatinine less than 1.5 mg/dL, or creatinine clearance greater than 60 mL/min were to be obtained within 2 weeks before protocol registration. All patients were required to sign a study-specific consent. All patients required a complete history and physical examination including evaluation of performance status, recent weight loss, percent of weight loss, and concurrent nonmalignant disease and its therapy.

Patients were considered ineligible if they had received prior chemotherapy, prior thoracic radiation therapy, or prior immunotherapy within 5 years of study entry. Patients were not allowed to have a prior or concurrent other malignancy within the preced-

ing 5 years. Patients with stage I, IIIB, or IV NSCLC were not eligible. Before registration, patients were required to complete a metastatic evaluation or staging with chest x-ray; ECG; computed tomography scans of the brain, chest, and upper abdomen, including the liver and adrenals; and bone scan. All x-rays were to be obtained within 6 weeks before definitive surgery. Maximum interval between scans and the start of radiotherapy was 14 weeks (this was to allow for a scan to be up to 8 weeks before surgery and 6 weeks before beginning the protocol treatment). Pulmonary function tests (PFTs) were required postoperatively. Patients were stratified by nodal status (N1 *v* N2), histology (squamous *v* nonsquamous), and type of lymph node dissection (sampling *v* complete nodal dissection). A pathologic complete surgical resection of the tumor mass by lobectomy, bilobectomy, sleeve resection, or pneumonectomy was necessary for eligibility. A complete mediastinal lymph node dissection or nodal sampling was recommended, but not required. Complete mediastinal/nodal dissection or sampling included the following nodal levels: levels 2 and 4, level 8, levels 5 and 6 in left upper lobe primaries, level 7, level 9, and level 10. Ipsilateral lymph nodes at levels 11 to 13 were to be removed en bloc with the surgical resection. The presence or absence of evidence of invasion of the nodal capsule was required to be noted in the final pathological report for hilar and/or mediastinal lymph nodes.

Radiation therapy was initiated within 8 weeks after surgery. All patients were treated with isocentric equipment with a minimum source-to-axis distance of 80 cm. Treatment was given with photon energies of 4 to 18 MV. The use of electrons was not permitted. All patients were simulated before initiation of treatment. Patients were treated with a combination of anterior-posterior/posterior-anterior (AP/PA) portals and off-cord oblique portals and a composite isodose plan was created. The target volume for treatment was the mediastinal and ipsilateral hilar lymph nodes. The primary tumor bed was included only if invasion of the parietal pleura was documented in the operative pathology report. The target volume was thus defined in terms of anatomic landmarks rather than the preoperative appearance of the tumor. Neither the contralateral hilum, nor the supraclavicular fossae were included on a routine basis. The typical borders of the radiation therapy portals were as follows: superior, approximately the level of C5 vertebral body; inferior, 5 cm below the carina for upper lobe lesions and 8 cm below the carina for middle and lower lobe lesions or if the subcarinal lymph nodes were pathologically involved; ipsilateral, 2 cm beyond the tracheal edge and encompassing the ipsilateral hilum with a 2-cm margin; contralateral, 2 cm lateral to the edge of the trachea. In patients in whom nodal disease breached the nodal capsule, these nodal stations were included in a boost field encompassing the nodal region with a margin of 1 cm. The dose to the entire target volume was 50.4 Gy in 28 fractions for 6 weeks, daily Monday through Friday. Patients with either pathologically documented extracapsular extension of the nodal metastasis and/or pathological T3 primary were required to have a boost of 10.8 Gy to these regions. Dose was prescribed to the midplane and isocenter for the AP/PA portals and the obliques. Dose inhomogeneity corrections were not used. Recommended maximum tolerable doses, not to be exceeded, were as follows: spinal cord, 45 Gy; heart, less than 35 Gy to more than 50% of the cardiac volume; lung, 20 Gy to the entire lung; esophagus, no upper limits were advised.

**Table 1.** Patient Pretreatment Characteristics

	Patients (N = 88)	
	No.	%
Age, years		
< 60	49	56
≥ 60	39	44
Sex		
Male	57	65
Female	31	35
Race/ethnicity		
White	79	90
Black	5	6
Hispanic	2	2
Asian	1	1
Other/unknown	1	1
Karnofsky performance status		
70-80	16	18
90-100	72	82
Weight loss		
≤ 5%	66	75
> 5%	21	24
Unknown	1	1
Histology		
Squamous cell carcinoma	22	25
Adenocarcinoma	50	57
Carcinoma NOS	2	2
Large cell	7	8
Combined squamous and adenocarcinoma	2	2
Other	5	6
Pathologic stage		
T stage		
T1	29	33
T2	49	56
T3	10	11
N stage		
N0	3	3
N1	42	48
N2	42	48
Stage group		
Stage II	39	44
Stage IIIA	49	56

Abbreviation: NOS, not otherwise specified.

The chemotherapy regimen was composed of paclitaxel and carboplatin for a total of four cycles. The paclitaxel was given 135 mg/m<sup>2</sup> intravenously over 3 hours on days 1 and 22 (cycles 1 and 2). The dose was increased to 225 mg/m<sup>2</sup> on days 43 and 64 (cycles 3 and 4). The carboplatin was delivered with an area under the concentration-time curve (AUC) of 5 mg/m<sup>2</sup>/min over 30 to 60 minutes intravenously days 1 and 22, and an AUC of 6 mg/m<sup>2</sup>/min for days 43 and 64. Chemotherapy was initiated on day 1 concurrently with radiation therapy. Higher dose chemotherapy was delayed by 2 weeks if the patient received a radiation therapy boost. Choice of antiemetics and intravenous fluids were given at the discretion of the treating physicians. Granulocyte colony-stimulating factor to prevent febrile neutropenia was allowed during cycles 3 or 4, but not during cycles 1 or 2 when radiation therapy was also being

**Table 2.** Surgical Procedure

	Patients (N = 88)	
	No.	%
Type of procedure		
Wedge resection	1	1
Lobectomy	55	63
Sleeve lobectomy	1	1
Lobectomy and chest wall resection	2	2
Bilobectomy	5	6
Bilobectomy and chest wall resection	1	1
Intrapericardial lobectomy	2	2
Simple pneumonectomy	12	14
Sleeve pneumonectomy	1	1
Intrapericardial pneumonectomy	6	7
Other	2	2
Complete resection	88	100
Margins clear		
Yes	87	99
No	1	1
Lymph node resection		
Dissection	38	44
Sampling	49	56
None	1	1

administered. Amifostine was not allowed. All courses of chemotherapy were held pending hematologic recovery to ANC greater than 1,500 and platelets greater than 100,000 on day 1 of a cycle.

Follow-up evaluations included medical history and physical examination, routine laboratory tests including liver function tests, and a chest computed tomography scan every 6 months for 2 years, then yearly thereafter. Chest x-rays, brain imaging, and bone scans were left to the discretion of the treating physician.

### Statistical Analysis

The primary end point of this study was progression-free and overall survival. The secondary end point was to evaluate the frequency of acute and late toxicity. A sample size of 79 patients was planned on the basis of 80% power to detect a 10% increase in 1-year progression-free survival in relation to standard therapy with a one-sided test of .10. We expected a 1-year progression-free survival of 70% (from historical controls). Time to events (eg, survivals) was calculated by the Kaplan-Meier life-table method, and survival results from this study and RTOG patients enrolled on ECOG 3590 were compared using a log-rank test.

## RESULTS

Ninety-three patients from 35 participating institutions were enrolled on this study from July 1997 through June 1998. (Appendix). Five patients were ultimately ineligible for the following reasons: surgery performed more than 8 weeks before start of radiotherapy, incorrect nodal staging, positive surgical margins, metastasis (to pancreas), and stage IIIB (N3) disease. There were 88 eligible and

**Table 3.** Acute Toxicities

	Grade (N = 88)				
	1	2	3	4	5
Diarrhea	13	6	1	0	0
Skin	39	24	1	0	0
Lung	30	9	4	1	0
Leukopenia	5	17	49	13	0
Granulocytopenia	12	6	26	36	1
Thrombocytopenia	47	1	2	3	0
Nausea + vomiting	24	25	8	2	0
Stomatitis	11	5	2	0	0
Neurologic	17	13	4	0	0
Other	14	52	1	0	1
Hepatic	15	1	0	0	0
Bleeding	1	0	0	0	0
Anemia	48	26	2	1	0
Fever	8	8	0	0	0
Esophagus	33	31	13	1	0
Infection	7	3	1	0	1
Genitourinary	8	1	0	0	0
Cardiac	4	5	1	0	0
Allergy	3	0	0	0	0
Renal	2	0	0	0	0
Pain	23	7	1	0	0
Maximum overall toxicity per patient	0	16	27	43	1
Maximum nonhematologic toxicity per patient	8	51	24	3	1

analyzable cases. Table 1 lists the patient pretreatment characteristics. In general, the study population represented a favorable group of patients with young age (56% younger than 60 years), good performance status (82% with KPS  $\geq$  90), and absence of weight loss (75% had  $\leq$  5% weight loss). The majority of patients had adenocarcinomas (57%), with squamous cell histology being the next most common (25%). Almost half of the patients were stage II (N1), and half, stage IIIA (N2). Type of surgery performed is presented in Table 2. The majority of patients had a

**Table 4.** Acute Grade  $\geq$  3 Toxicities by Chemotherapy Cycle

Grade	Toxicity	Cycle	No. of Patients
3	Esophagus	1	1
3	Esophagus	2	7
3	Esophagus	3	4
3	Esophagus	4	1
4	Esophagus	2	1
4	Nausea	2	2
3	Neurologic	3	3
3	Respiratory	2	1
3	Respiratory	3	1
3	Respiratory	4	2
3	Cardiac	2	1
4	Respiratory	4	1
5	Sepsis	4	1

lobectomy (63%), with a simple pneumonectomy being the next most common procedure (14%).

The therapy records and radiation portal films were centrally reviewed. Surgical therapy was per protocol in 53 patients (60%). A lymph node dissection was carried out in 38 cases (44%). Lymph node sampling was carried out in 49 cases (56%). Surgery was not per protocol in 20 patients (40%), due to having fewer than three lymph node stations sampled. Radiation therapy was delivered per protocol, or with minor variations in 77 (88%) and four (5%) patients, respectively. Unacceptable deviations occurred in three patients (3%). There were two patients who failed to complete radiation therapy due to progression or death. The radiation portals were not assessable for two patients. Chemotherapy was delivered per protocol or with acceptable deviations in 39 (44%) and 37 (42%) patients, respectively. Reasons for chemotherapy termination were death in three patients (3%), progression in two patients (2%), toxicity in one patient (1%), patient refusal in four patients (5%), patient condition in two patients (2%), and unknown in one patient (1%).

Acute toxicities of treatment are listed in Table 3. The majority of acute toxicity was hematologic. There was one septic death during cycle 4 of chemotherapy. The other acute toxicities  $\geq$  grade 3 were esophagitis (16%), neurologic toxicity (5%), and respiratory toxicity (6%). The toxicities  $\geq$  grade 3 are listed in Table 4 with their timing by cycle of chemotherapy.

Table 5 lists late toxicities by grade. There was a 6% crude incidence of late  $\geq$  grade 3 pulmonary toxicity. There was also a 5% crude rate of late cardiac toxicity

**Table 5.** Late Toxicities

	Grade (n = 83)			
	1	2	3	4
Skin	7	5	0	0
Lung	16	13	3	1
Heart	1	1	3	1
Anemia	10	2	0	0
Leukopenia	6	5	3	1
Granulocytopenia	3	1	0	1
Thrombocytopenia	4	3	0	0
Esophagus	12	8	3	0
Stomatitis	2	2	0	0
Nausea/vomiting	2	4	1	0
Allergy	2	0	0	0
Neurologic	12	9	0	0
Renal	3	0	0	0
Subcutaneous	1	1	0	0
Spinal	1	0	0	0
Other	9	10	2	0
Maximum overall toxicity per patient	18	25	12	4
Maximum nonhematologic toxicity per patient	17	26	10	2

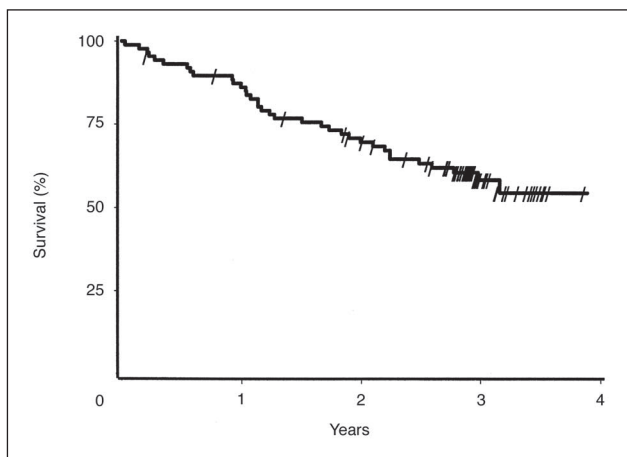
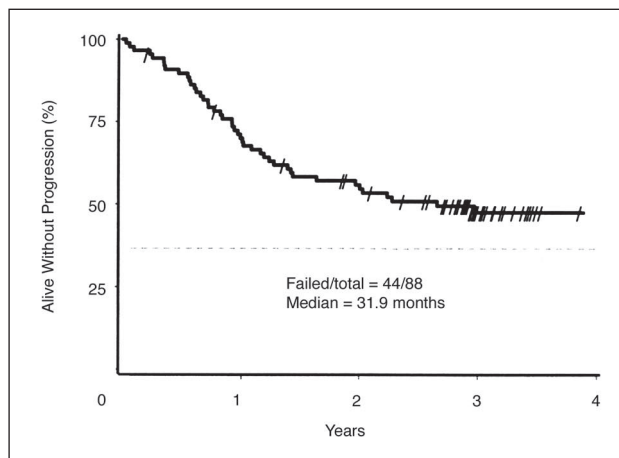
**Table 6.** Late Toxicities by Days From Start of Radiotherapy

No. of Cases	Grade	Toxicity	Days From Radiotherapy
3	3	Esophageal (dysphagia)	93, 239, 240
3	3	Pulmonary	109, 117, 477
1	4	Pulmonary	152
3	3	Cardiac	120, 267, 338
1	4	Cardiac (pericardial effusion)	253
1	3	Lymphocytopenia	165

( $\geq$  grade 3). This included two pericardial effusions, one myocardial infarction, and one nonspecified cardiac toxicity. Table 6 lists the late nonhematologic toxicity and the time to occurrence.

The median duration of follow-up was 56.7 months (range, 17 to 61 months). The median overall survival was 56.3 months, but the median progression-free survival was 35.6 months. The 1-, 2-, and 3-year survival rates were 86%, 70%, and 61%, respectively. The 1-, 2-, and 3-year progression-free rates were 70%, 57%, and 50%, respectively. The actuarial overall survival and progression-free survival curves are shown in Figures 1 and 2.

Patterns of failure analysis revealed brain and other metastases as the sole site of first failure in 11% and 9%, respectively (Table 7). The overall brain failure rate was 20%. An intrathoracic recurrence was a component of first failure in 13 patients (15%). There were no differences in survival or failure patterns between stage II and stage III patients, though there was a slight trend for increased local-regional progression as first failure in the stage III patients as compared with stage II patients ( $P = .087$ ). Systemic metastasis was a component of first failure in 33 patients (38%). Of the 43 patients who have died, the cause of death was the treated cancer in 31 (35%). Death without evidence of cancer occurred

**Fig 1.** Overall survival.**Fig 2.** Progression-free survival.

in 10 patients (11%). The recorded causes of death in these patients were four cardiac failures, one pneumonia, one adult respiratory distress syndrome (ARDS), and one accident. Only one patient died of complications of protocol treatment (sepsis). Two patients died of unknown causes.

Overall survival data from RTOG 9705 are presented in Table 8 with the results of the recent ECOG trial.<sup>8</sup> There was a statistically significant difference in survival between the results of this trial and that of the randomized ECOG trial, with the results of this trial having a longer median overall survival and improved late survival percentages ( $P = .0315$ , log-rank test). The current study showed a lower intrathoracic recurrence rate than in the ECOG trial (15% v 28% to 29%, respectively) and a higher brain metastasis rate (20% v 14%, respectively). The RTOG 9705 trial was designed with an expected 1-year progression-free survival of 70% (from historical controls). The trial was to be compared in a randomized trial with the best arm of the ECOG trial if the

**Table 7.** Pattern of First Failure

Site of First Failure	Patients (n = 46)	
	No.	%
Primary only	3	7
Brain mets only	10	22
Other mets only	8	17
Primary + brain mets	1	2
Primary + other mets	3	7
Nodes + other mets	2	4
Primary + nodes + other mets	2	4
Brain mets + other mets	5	11
Primary + brain mets + other mets	1	2
Nodes + brain mets + other mets	1	2
Death, no progression	10	22

Abbreviation: mets, metastases.

**Table 8.** Overall Survival Comparison Between RTOG 9705 and ECOG 9105

Time (months)	RTOG		ECOG	
	% Alive	No. at Risk	% Alive	No. at Risk
0	100	88	100	181
12	86	76	77	139
24	70	61	58	105
36	61	52	49	87
48	52	36	40	72
60	46	26	34	60
Dead/total	43/88		139/181	
Median time	56.3		33.7	
P	.0315			

Abbreviations: RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group.

1-year progression-free survival was greater than 80%. Not only was the 1-year survival greater at 86%, the 2- and 3-year survivals were 6% to 11% improved ( $P = .039$ ; Fig 3). The median follow-up period for the ECOG study was 87 months (range, 28 to 135 months).

## DISCUSSION

The cumulative experience of adjuvant postoperative therapy for stage II and III NSCLC has shown that adjuvant therapy is of, at best, marginal benefit. The majority of patients still die of lung cancer, with the second most common cause being comorbid disease.

There have been nine randomized trials evaluating the role of postoperative radiation therapy.<sup>4-6,9-13</sup> Unfortunately, many of these trials were flawed. Major deficiencies include the inclusion of early-stage patients, lack of stratifi-

cation for known risk factors, cobalt irradiation, lack of computer planning, use of spinal cord blocks, and inferior dose-fractionation schedules.

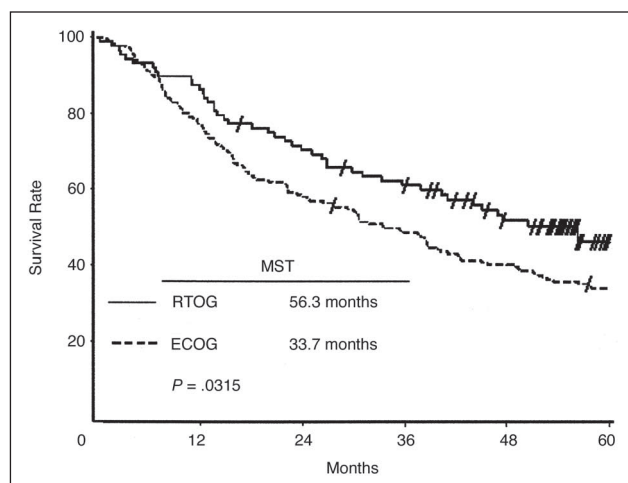
A report from the Meta-analysis Trialists Group performed a meta-analysis reviewing these nine randomized trials to assess the value of postoperative radiation therapy.<sup>14</sup> They reported no apparent benefit to radiation therapy, and in the early stages, a survival decrement. This study may have been influenced by Dautzenberg et al, which used larger fraction sizes and reported an increased death rate due to intercurrent cardiovascular disease.<sup>11</sup>

There have now been three large randomized trials that have evaluated adjuvant chemotherapy and thoracic radiotherapy.<sup>8,15,16</sup> While some modest increase in disease-free survival has been noted in some, no overall survival advantage has been seen in any. These trials included patients with both stages II and III disease, further limiting the ability to detect a benefit for smaller patient subsets.

Two meta-analyses have been reported, assessing the value of adjuvant chemotherapy or thoracic radiotherapy given adjvantly after surgical resection.<sup>14,17</sup> Most of the trials in the analysis evaluating chemotherapy used cisplatin-based regimens. Neither of these analyses could find a statistically significant benefit to either modality being given postoperatively.

The current study attempted to utilize current cytotoxic chemotherapy in combination with thoracic radiotherapy, to evaluate whether this would result in a  $\geq 10\%$  disease-free survival benefit. Bonomi et al reported, subsequent to the design of the trial, that cisplatin/paclitaxel regimens resulted in an improved survival over cisplatin/etoposide in patients with advanced disease.<sup>18</sup> However, Schiller et al<sup>19</sup> reported no survival advantage of any of four different doublets also in patients with advanced NSCLC, and without radiation therapy. However, in that large randomized trial, there was no cisplatin/etoposide arm.

A recent report from the International Adjuvant Lung Cancer trial reported a 5% improvement in 5-year survival with the adjuvant use of three to four cycles of cisplatin-based chemotherapy after resection of NSCLC.<sup>20</sup> Approximately one-quarter of the patients in each arm received postoperative radiation therapy to a median dose of 50 Gy.<sup>21</sup> In this large trial, 36% of the eligible patients had stage I disease, while the remaining had stage II-III disease. Although this trial reported a 5-year survival of 67% in the adjuvant chemotherapy arm, this is clearly skewed by the large number of stage I patients in the trial. Nonetheless, it does seem to support the use of adjuvant systemic therapy in resected NSCLC patients, with improved overall survival, local control, and distant recurrence rates.



**Fig 3.** Radiation Therapy Oncology Group (RTOG) 9705 versus Eastern Cooperative Oncology Group (ECOG) 3590. MST, median survival time.

This study was developed by the RTOG during completion of the ECOG randomized trial of postoperative radiation therapy versus postoperative cisplatin/etoposide and thoracic radiation therapy. Though it was later determined that the experimental chemotherapy arm of the ECOG trial was of no benefit, the data serve as a suitable comparison to RTOG 9705 for the purposes of formulating future phase III trials. The patient characteristics in both trials are similar. The median age of the ECOG trial was 60 years, ECOG performance status was 0 or 1, more than three fourths of the patients had less than 5% weight loss, adenocarcinoma histology predominated, and 58% of patients enrolled had stage IIIA disease. Both trials excluded patients with stage IIIB cancers. Likewise, the radiation therapy techniques and doses employed in both trials are similar. Local failures were similar in both arms of ECOG 3590 (12% and 13%, respectively), similar to the 15% intrathoracic recurrence rate in RTOG 9705.

The following may be possible explanations for why the results of RTOG 9705 appear improved compared with the ECOG study: (1) There is a synergistic effect between paclitaxel/carboplatin and radiation therapy, resulting in improved local-regional control, which resulted in subsequently fewer distant metastatic failures. (2) There were decreased distant metastases in this trial, resulting in improved survival, similar to the Bonomi trial. (3) Because this was not a randomized trial, and despite a careful attempt to control for known prognostic variables, there was stage migration and inadvertent selection bias in the patient selection, resulting in an apparent improved survival.

Patterns of failure analysis revealed that patients primarily fail with distant metastasis, including brain metastasis. This probably largely reflects the last two-decade shift from squamous cell carcinomas to adenocarcinomas as the primary histologic subtype. In addition, if local-regional control and other systemic metastases are better controlled, an apparent increase in brain metastasis may be seen, as with the treatment of small-cell lung cancer. With brain metastasis occurring in nearly one quarter of patients, also a similar statistic with small cell lung cancer, the value of prophylactic brain irradiation may be important to evaluate, especially in patients receiving aggressive multimodal therapy.

The use of adjuvant paclitaxel, carboplatin, and chest radiation therapy for resected stage II or IIIA NSCLC is supported based on the results of this trial. However, because of the small sample size, a further randomized trial comparing this regimen to standard therapy appears warranted.

#### Appendix. Participating Institutions

Ann Arbor, Michigan
U. of Pennsylvania
Washington University
M.D. Anderson
Southeast CCOP
Jefferson University
LDS Hospital
U. of Alabama
U. of California, San Francisco
Carle CCOP
Fox Chase Cancer Center
Mayo Clinic
Wayne State
Christiana Care
Columbus CCOP
Einstein
Johns Hopkins University
Kansas City CCOP
U. of Miami
Mt Sinai CCOP
U. of Rochester
Toledo
W. Michigan Cancer Center
Wconsin Medical Center
Central Illinois CCOP
Greenville CCOP
U. of Kentucky
Main Line CCOP
N. Y. University
S. Nevada
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Upstate Carolina
Washington CA Institute

#### Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have 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. Consultant/Advisory Role: David S. Ettinger, AstraZeneca, Aventis, Bristol-Myers Squibb, Cell Therapeutics, Eli Lilly, GlaxoSmithKline, Merck, MGI Pharma, Pfizer; Mitchell Machtay, Bristol-Myers Squibb; Ritsuko Komaki, Amgen; Walter J. Curran, Bristol-Myers Squibb. Honoraria: David S. Ettinger, AstraZeneca, Aventis, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, MGI Pharma, Pfizer; Mitchell Machtay, Bristol-Myers Squibb; Ritsuko Komaki, MedImmune Speakers Bureau; Walter J. Curran, Bristol-Myers Squibb. Research Funding: Rebecca Paulus, Bristol-Myers Squibb; David S. Ettinger, Aventis, Eli Lilly. Expert Testimony: David S. Ettinger, list available upon request from the Editorial Office.

For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declara-

tion and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

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