ORIGINAL REPORT

Phase III Study of Cisplatin, Etoposide, and Concurrent Chest Radiation With or Without Consolidation Docetaxel in Patients With Inoperable Stage III Non–Small-Cell Lung Cancer: The Hoosier Oncology Group and U.S. Oncology

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ABSTRACT

Purpose
Concurrent chemoradiotherapy is standard treatment for patients with inoperable stage III non–small-cell lung cancer (NSCLC). A phase II study by the Southwest Oncology Group using consolidation docetaxel after cisplatin (P), etoposide (E), and radiation (XRT) resulted in a median survival time (MST) of 26 months. This randomized phase III trial evaluated whether consolidation docetaxel was responsible for this improved survival.

Patients and Methods
Eligible patients had stage IIIA or IIIB NSCLC, baseline performance status of 0 to 1, forced expiratory volume in 1 second $\geq$ 1 L, and less than 5% weight loss. Patients received P 50 mg/m² intravenously (IV) on days 1, 8, 29, and 36 and E 50 mg/m² IV on days 1-5 and 29-33 concurrently with chest XRT to 59.40 Gy. Patients who did not experience progression were randomly assigned to docetaxel 75 mg/m² IV every 21 days for three cycles versus observation. The primary end point was to compare overall survival (Kaplan-Meier analysis).

Results
On the basis of evidence of futility, a data and safety monitoring board recommended early termination after an analysis of the initial 203 patients. Patient characteristics (n = 203) were as follows: 34% female; median age, 63 years; 39.4% stage IIIA; and 60.6% stage IIIB. One hundred forty-seven (72.4%) of 203 patients were randomly assigned to docetaxel (n = 73) or observation (n = 74). Grade 3 to 5 toxicities during docetaxel included febrile neutropenia (10.9%) and pneumonitis (9.6%); 28.8% of patients were hospitalized during docetaxel (*v* 8.1% in observation arm), and 5.5% died as a result of docetaxel. The MST for all patients (n = 203) was 21.7 months; MST was 21.2 months for docetaxel arm compared with 23.2 months for observation arm (*P* = .883).

Conclusion
Consolidation docetaxel after PE/XRT results in increased toxicities but does not further improve survival compared with PE/XRT alone in patients with stage III inoperable NSCLC.

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INTRODUCTION

Lung cancer remains a worldwide epidemic. Approximately 1.3 million people die from lung cancer each year.[1] Cure rates remain low for those diagnosed with stage III non–small-cell lung cancer (NSCLC), and only modest progress has been seen over the last 25 years. In the 1980s, studies from US cooperative groups demonstrated that two cycles of chemotherapy followed by radiation (XRT) improved median survival time by approximately 3 months and 5-year survival by 3% to 10% compared with XRT alone.[2,3] In the 1990s, studies from the United States, Japan, and elsewhere demonstrated that the concurrent administration of two cycles of chemotherapy with XRT improved median survival time by an additional 3 months and 5-year survival by an additional 5% compared with sequential chemotherapy and XRT.[4-7] Despite this progress, however, the prognosis for the vast majority of patients remains poor. The median survival time for fit patients, without significant weight loss, treated with chemoradiotherapy is approximately 15 months, and the 5-year survival rate is only 5% to 17%.

In 2001, investigators from the Southwest Oncology Group (SWOG) reported their initial results from a single-arm, phase II study (SWOG 9504).[8] Eighty-three patients with stage IIIB NSCLC were treated with two cycles of cisplatin (P) and etoposide (E) administered concurrently with 61 Gy of chest XRT. Four to 6 weeks after completing treatment, patients without progressive disease received a planned three cycles of consolidation docetaxel. The median survival time was 26 months. On the basis of the promising survival results reported on the SWOG 9504 trial, we conducted a randomized, phase III study to determine whether the consolidation docetaxel was responsible for the improved outcomes.

PATIENTS AND METHODS

Patients with histologic or cytologic confirmation of NSCLC with unresectable stage IIIA or IIIB disease were assessed for eligibility. Unresectable stage IIIA disease was defined by multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) scan such that, in the opinion of the treating investigator, the patient was not a candidate for surgical resection. N2 disease must have been documented by biopsy, fluorodeoxyglucose positron emission tomography (PET), or CT if nodes were more than 2 cm. Stage IIIB patients must have had N3 or T4 status. N3 status must have been documented by the presence of a contralateral (to the primary tumor) mediastinal lymph node or supraclavicular or scalene lymph node proven by biopsy, fluorodeoxyglucose PET, or more than 2 cm on CT scan. Patients with disease extending into the cervical region were not eligible. Eligible patients for initial PE/XRT also met the following criteria: measurable or assessable disease; no prior chemotherapy or XRT; preregistration forced expiratory volume in 1 second (FEV_1) $\geq$ 1 L by spirometry within 42 days of study treatment; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 at baseline; unintended weight loss of less than 5% in the 3 months preceding study treatment; and adequate bone marrow (absolute neutrophil count $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, and hemoglobin $\geq$ 8 g/dL), renal (serum creatinine $\leq$ 2 mg/dL or calculated creatinine clearance $\geq$ 50 mL/min), and hepatic function (bilirubin $\leq$ institutional upper limit of normal [ULN], AST $\leq$ 2.5$\times$ ULN if alkaline phosphatase is $\leq$ ULN, or alkaline phosphatase $\leq$ 4$\times$ ULN if AST is $\leq$ ULN). Patients were excluded if they had symptomatic peripheral neuropathy (must be $\leq$ grade 1) at baseline, malignant effusions (pleural or pericardial), superior sulcus (Pancoast) tumors, or significant cardiac disease (uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction in prior year, or ventricular arrhythmias requiring medication). Eligibility for consolidation therapy required completion of initial chemoradiotherapy within 4 to 8 weeks of random assignment without local progression or distant metastases, ECOG PS of 0 to 2 at random assignment, adequate bone marrow and hepatic function (same as baseline requirements), and absence of symptomatic peripheral neuropathy before random assignment. The study was conducted by the Hoosier Oncology Group, a community-based cooperative group and subsequently joined by U.S. Oncology. The protocol was approved by institutional ethics review boards, and all patients provided written informed consent before treatment.

Treatment Plan

Eligible patients received P 50 mg/m^2 intravenously (IV) on days 1, 8, 29, and 36 with E 50 mg/m^2 IV on days 1 through 5 and 29 to 33. XRT was administered as 1.8-Gy daily treatments 5 days a week for a total of 25 fractions (45 Gy) to the primary and mediastinum followed by a boost to the primary and involved nodes to 1.8 Gy daily in eight fractions (14.40 Gy). The total dose of XRT was 59.40 Gy in 33 fractions. XRT planning underwent central review. Gross target volumes included the primary tumor and abnormally enlarged regional lymph nodes more than 1 cm in short axis. The primary and secondary target volumes included a minimum of a 2-cm margin. Elective treatment of supraclavicular lymph nodes was not allowed. Two-centimeter margins were required for XRT to the ipsilateral hilar lymph nodes and superior mediastinal lymph nodes, and at least 3-cm margins were required below the carina for subcarinal lymph nodes. Treatment interruptions of XRT were discouraged unless grade 3 or greater nonhematologic toxicity or grade 4 hematologic toxicity necessitated disruptions. Patients underwent repeat tumor measurements within 4 to 8 weeks of completing PE/XRT. Patient random assignment was stratified by PS (0 to 1 v 2), stage (IIIA v IIIB), and initial response (complete response v no complete response). Patients were randomly assigned to either observation or docetaxel 75 mg/m^2 IV every 3 weeks for three cycles. Patients were allowed to receive prophylactic granulocyte colony-stimulating factor support during consolidation docetaxel treatment.

Baseline history and physical examination, assessment of ECOG PS, FEV_1, CBC with platelet count, serum chemistries (repeated on days 8, 29, and 36), and disease evaluation (CT of chest through the upper abdomen) were obtained on all patients. Bone scan was performed only if clinically indicated. PET scans were not mandated. Brain imaging (either CT or magnetic resonance imaging) was mandatory at baseline. Toxicity assessments and CBC with platelets were obtained weekly throughout PE/XRT. For patients randomly assigned to receive consolidation docetaxel, baseline CBC with platelets and serum chemistries were obtained and repeated before each cycle. On completion of all assigned therapy, responses were to be confirmed within 4 weeks, and follow-up continued every 3 months for the first 2 years, every 6 months for years 2 to 5, and yearly thereafter, with repeat CT of chest through the adrenals on each visit.

Statistical Analysis

The primary end point of this study was to compare overall survival (OS) between the two randomly assigned groups (observation v docetaxel). It was projected that the control group (observation) would achieve a median OS time of 15 months, whereas the treatment group (docetaxel) would have an increase in median OS time to 25 months (based on the median OS noted in SWOG 9504). Initially, 230 patients were to be registered to randomly assign 210 patients (over 18 months). It was expected that 10% of patients accrued would not be randomly assigned as a result of progressive disease or toxicity. The sample size was calculated assuming a 5% two-sided type I error and 85% power. Approximately 137 deaths were expected at the time of final data analysis. However, because of a slower than expected accrual rate (projected rate, 11.7 patients per month; actual rate, 3.3 patients per month) and a higher than expected dropout rate (projected rate, 10%; actual rage, 27%), the study was amended in March 2005 to increase the sample size to 259 patients, reduce the number of patients to be randomly assigned to 180 (90 per arm over 55 months with 10-month follow-up after the last patient was enrolled), maintain a 5% two-sided type I error, and reduce the power to 80%. In this revised design, the final survival analysis (using the Kaplan-Meier method) was to take place after the expected 124 deaths of randomly assigned patients had occurred. An interim analysis was scheduled after 50% of the expected deaths (62 deaths) in the randomly assigned patients. These analyses were to be reviewed by a data and safety monitoring board (DSMB). Early stopping rules were predefined (using O'Brien-Fleming boundaries) for superiority ($P < .0031$) or futility ($P > .7271$). These were calculated using the East Software version 4.0 (Cytel Corporation, Cambridge, MA). The DSMB analyzed the first 203 patients entered and 147 patients randomly assigned, and on the basis of their recommendation (finding of futility), the study was closed early. The secondary end points of this study included a comparison of progression-free survival between the two randomly assigned groups and further characterization of the toxicities of consolidation docetaxel. Baseline characteristics were compared between treatment groups using Kruskal-Wallis tests for continuous variables and Fisher's exact test for discrete variables. Rates of occurrence of specific toxicities were compared between the groups using Fisher's exact test. Toxicities were analyzed using the Common Terminology Criteria for Adverse Events (version 3).

RESULTS

From March 2002 until August 2006, 243 patients were entered onto the trial, and 167 patients were randomly assigned. The DSMB evaluated the first 203 patients entered and the first 147 patients randomly assigned. This is the analysis cohort in this report. Patient demographics and disease characteristics for enrolled patients (n = 203) are listed

in Table 1. Approximately one third of patients entered were female, and approximately 40% had stage IIIA disease. All patients had an FEV_1 of more than 1 L at baseline, and almost half of the patients had an FEV_1 of more than 2 L. Two thirds of patients were staged by PET. Randomly assigned patients (n = 147) shared similar patient and disease characteristics with all patients entered. There were no statistically significant differences in patient characteristics between the two arms, although a higher percentage of patients on the observation arm than the docetaxel arm (59.5% v 41.1%, respectively; $P = .066$) had an FEV_1 of more than 2 L.

Treatment Administered

Of 203 patients entered, 147 (72.4%) were randomly assigned (74 patients to the observation arm and 73 patients to the docetaxel arm). Fifty-six patients were not randomly assigned as a result of the following reasons: toxicities during PE/XRT (30.4%), progressive disease before random assignment (21.4%), ineligible for random assignment (7.1%), patient decision (7.1%), death before random assignment (5.4%), physician decision (3.6%), and miscellaneous reasons such as not completing PE/XRT for other reasons, requiring a procedure, insurance issues, and so on (25%).

Of the 73 patients randomly assigned to the docetaxel arm, 80.8% completed all three planned cycles, 8.2% completed two cycles, 6.9% completed one cycle, and 4.1% did not receive consolidation treatment. The reasons for not completing three cycles of docetaxel included early death (n = 6), progressive disease (n = 3), and toxicities or patient decision (n = 11); 32.4% of patients received granulocyte colony-stimulating factor support.

Toxicity

Table 2 lists grade 3 and 4 hematologic toxicities, and Table 3 lists grade 3 to 5 nonhematologic toxicities. Toxicities related to PE/XRT were as expected. In patients receiving docetaxel, 10.9% experienced febrile neutropenia, 9.6% had grade 3 to 5 pneumonitis, and 5.5% prematurely died as a result of docetaxel. In comparison, only 1.4% of patients assigned to the observation arm experienced grade 3 to 4 pneumonitis during a comparable period of time, and no patients died during the first 9 weeks after random assignment. Furthermore, 36.5% of patients required hospitalization during PE/XRT. During

the 9 weeks after random assignment, 28.8% of patients required hospitalization during docetaxel treatment compared with 8.1% of patients on the observation arm. More patients on the docetaxel arm (5.5%) required a blood transfusion compared with patients on the observation arm (1.4%). This difference, however, did not reach statistical significance ($P = .210$).

Efficacy

In July 2006, the DSMB reviewed the interim analysis of study data and recommended earlier closure of the trial based on a log-rank $P = .9087$ comparing survival between the two arms (meeting the predefined rule for futility; prespecified O'Brien-Fleming boundary of $P = .7271$). At the time of the analysis, there were 62 observed deaths in randomly assigned patients (30 in the docetaxel arm and 32 in the observation arm). Current data (as of December 2007) of the 203 patients considered by the DSMB adhere to this established trend. With a median follow-up time of 41.6 months, 100 of the 147 randomly assigned patients have died (50 in each arm). The median OS time (on an intent-to-treat basis) of all patients enrolled (n = 203) was 21.7 months (Fig 2), and the 3-year OS rate was 30.2%. There was no difference in survival between the two arms, with a median OS time of 23.2 months in the observation arm and 21.2 months in the docetaxel arm (log-rank $P = .883$) and 3-year OS rates of 26.1% and 27.1%, respectively (Fig 3). There was also no difference in progression-free survival between the two arms ($P = .960$; Fig 4).

DISCUSSION

This randomized phase III trial failed to achieve the primary objective of improved survival with the addition of consolidation docetaxel after PE/XRT for this population of patients with stage III NSCLC. Despite the use of older chemotherapeutic agents (PE) and only 59.4 Gy of

Table 2. Grade 3 or 4 Hematologic Toxicities

	% of Patients	
Toxicity	PE/XRT	Docetaxel
Neutropenia	32.0	24.7
Febrile neutropenia	9.9	10.9
Anemia	5.9	1.3
Thrombocytopenia	10.8	0.0

Abbreviation: PE/XRT, cisplatin, etoposide, and radiation therapy.

Table 1. Patient Demographics and Disease Characteristics

	% of Patients				
Demographic/ Characteristic	All Patients (N = 203)	Randomly Assigned Patients (n = 147)	Docetaxel Arm (n = 73)	Observation Arm (n = 74)	P^*
Female	34	29.9	34.2	25.7	.284
Median age, years	63	62	62	62	.801
Stage IIIA	39.4	40.8	42.5	39.2	.739
PS 0	58.6	58.5	57.5	59.5	.868
Current smoker	45.7	47.1	50.0	43.9	.497
Staged by PET	67	64.6	58.9	70.3	.170
$FEV_1 > 2$ L	46.7	50.3	41.1	59.5	.066

Abbreviations: PS, performance status; PET, positron emission tomography; FEV_1, forced expiratory volume in 1 second.
*Docetaxel v observation group comparisons; categorical data: Fisher's exact test; continuous data: Kruskal-Wallis test.

Table 3. Select Grade 3 to 5 Nonhematologic Toxicities

	% of Patients			
Toxicity	PE/XRT	Docetaxel	Observation	P^*
Esophagitis	17.2	—	—	—
Infections	8.9	11.0	0.0	.003
Pneumonitis	—	9.6†	1.4	< .001
Treatment-related death	1.5	5.5	0.0	.058

Abbreviation: PE/XRT, cisplatin, etoposide, and radiation therapy.
*P value corresponds to comparison of docetaxel v observation groups.
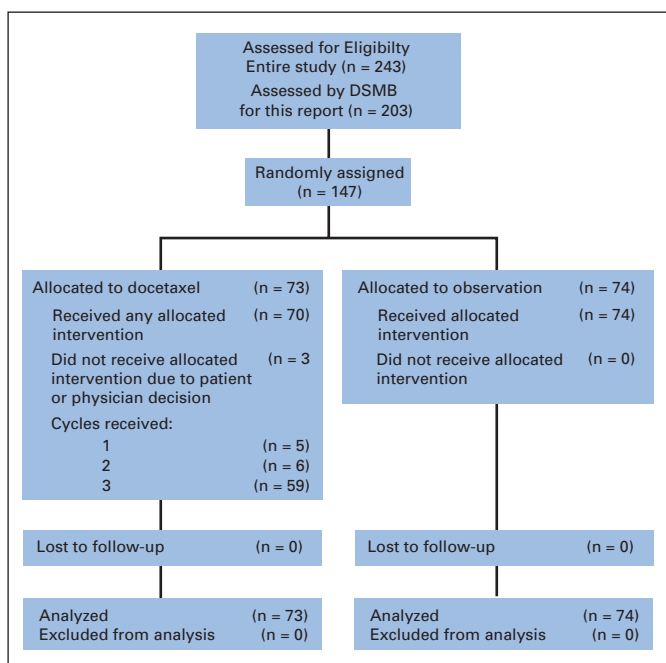†Includes one patient death.

Fig 1. CONSORT diagram. A total of 203 patients were analyzed by the data and safety monitoring board. Of these, 147 completed the initial chemoradiation and were randomly assigned. All patients in both randomized arms were included in the primary analysis.

Fig 3. Overall survival comparison of the two randomly assigned arms.

XRT, the PE/XRT regimen in this study resulted in a median survival time superior to historic controls and a 3-year survival rate comparable with other regimens using newer chemotherapeutic agents and higher doses of XRT. Our study also demonstrated that consolidation docetaxel substantially increases the risk for febrile neutropenia, grade 3 to 4 pneumonitis (defined as requiring supplemental oxygen or mechanical ventilation), hospitalization, and premature death in some patients. An increased risk for pneumonitis and worse outcomes in patients with a volume of lung receiving at least 20 Gy exceeding 35% have previously been reported.[9] Therefore, caution should be used when considering this regimen in patients with a high volume of lung receiving at least 20 Gy, particularly those with significantly compromised lung function ($FEV_1 < 2$ L). There
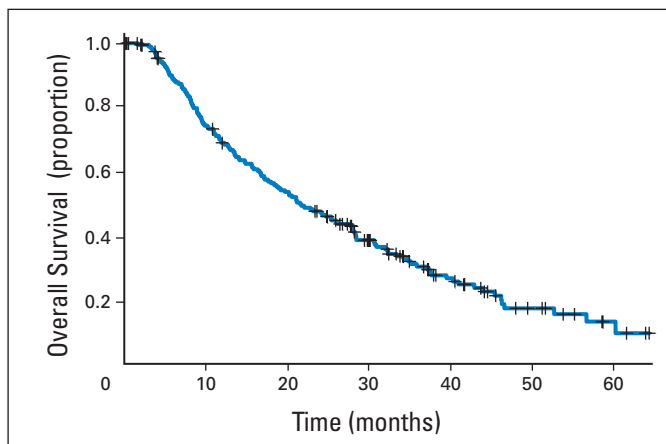
was a slight imbalance (P = not significant) of patients who had an $FEV_1 \geq 2$ L, favoring the control arm. This may have partially contributed to the higher rates of pneumonitis in the docetaxel arm. The rates of toxicities observed with consolidation docetaxel on this study are consistent with those seen in other studies, including SWOG 9504 and, more recently, SWOG 0023, a trial of 571 patients who were to receive PE/XRT and consolidation docetaxel.[10] Given the results of our trial, we do not recommend the use of consolidation docetaxel.

Why did our study fail to confirm the favorable results of the SWOG 9504 study? The patient and disease characteristics between these studies were similar, with the exception of the inclusion of stage IIIA patients on our trial and the more strict entry criteria for pulmonary function on the SWOG trial (baseline $FEV_1 \geq 2$ L or ≥ 800 mL in the contralateral lung compared with baseline $FEV_1 \geq 1$ L on our study). An unplanned, exploratory analysis, which was recently reported, suggests that baseline pulmonary function may predict for outcomes.[11] Toxicity differences from docetaxel were not observed between the SWOG 9504 study and the current study, and the success of delivering docetaxel was also comparable.

Significant improvements in outcomes for patients with stage III NSCLC will be realized when advances in systemic therapy are discovered. This remains a challenge because NSCLC is a biologically and clinically heterogeneous disease. Local control of disease

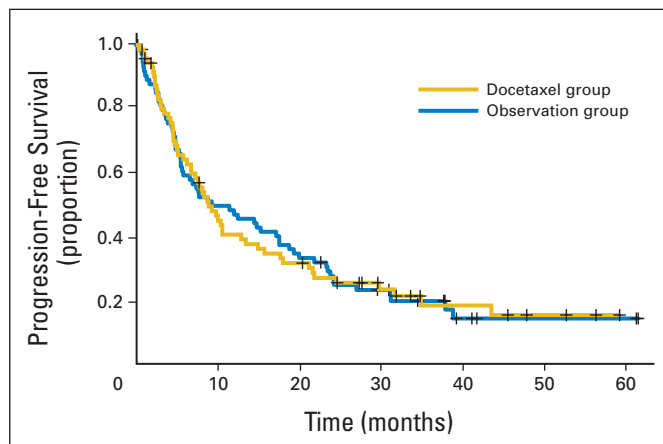Fig 2. Overall survival for all patients (n = 203).

Fig 4. Progression-free survival comparison of the two randomly assigned arms.

is necessary but not sufficient to significantly improve outcomes. The vast majority of patients with stage III NSCLC have systemic disease at diagnosis, evidenced by the poor long-term survival rates with local modalities, namely XRT or surgery, alone. This point is underscored by results from the US Intergroup trial INT 0139, in which medically operable patients with resectable stage III NSCLC did not achieve improved survival with the addition of surgery after PE/XRT (45 Gy) compared with a control arm of PE/XRT (60 Gy) alone.[12] The 5-year survival rate was only 20%, which is not substantially different from outcomes for patients with inoperable stage III NSCLC treated with chemoradiotherapy alone. Strategies to improve outcomes by applying more effective systemic treatment have generally tested the use of more chemotherapy, administered either as induction therapy before chemoradiotherapy or as consolidation therapy after chemoradiotherapy.

At least two randomized trials have compared induction chemotherapy followed by concurrent chemoradiotherapy with chemoradiotherapy alone.[13,14] Neither study demonstrated superiority with the induction regimen, and one of the studies had inferior (although not statistically significant) survival results with induction therapy.[14] In addition, median survival times for the induction arms on these two studies were only 13 and 14 months, respectively, and 3-year survival rates did not exceed 25%. Furthermore, additional randomized phase II trials testing a variety of induction regimens before chemoradiotherapy demonstrated median survival times of 13 to 18 months and 3-year survival rates of only 15% to 28%.[15-17]

In addition to our trial, one other randomized trial evaluating the role of consolidation chemotherapy has been reported.[18] In this small randomized trial (n = 104), patients received weekly P plus paclitaxel concomitantly with XRT and were then randomly assigned to either observation or three additional cycles of full-dose P plus paclitaxel; median survival times favored the observation arm (24 v 19 months, respectively). Finally, at least three randomized phase II trials have treated patients with concurrent chemoradiotherapy and evaluated induction or consolidation chemotherapy.[19-21] Only one of these studies has reported median survival times numerically better with the consolidation strategy, and none of the regimens resulted in a 3-year survival rate exceeding 25%. Collectively, these data fail to support the use of either induction chemotherapy before concurrent chemoradiotherapy or consolidation chemotherapy after chemoradiotherapy. In addition, these trials do not support the use of one chemotherapy regimen over another. Improved outcomes have been demonstrated with the incorporation of only two cycles of chemotherapy with XRT.[2-5] To date, there is insufficient evidence indicating that treatment extending beyond concurrent chemoradiotherapy alone further improves survival rates.

It seems that we have reached a plateau in survival using current chemotherapy agents against stage III NSCLC. Many questions remain unanswered in the treatment of stage III disease, including defining the optimal chemotherapy regimen and the utility of lower dose radiosensitizing chemotherapy; individualizing XRT dose and schedule based on pulmonary function, tumor volumes, and newer XRT technologies; and defining the role of prophylactic cranial irradiation. At this time, two cycles of PE administered concurrently with 59.4 Gy of XRT remains a reference regimen for the Hoosier Oncology Group for future studies.

AUTHOR CONTRIBUTIONS

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