Long-Term Follow-Up of a Phase I/II Trial of Dose Escalating Three-Dimensional Conformal Thoracic Radiation Therapy with Induction and Concurrent Carboplatin and Paclitaxel in Unresectable Stage IIIA/B Non-small Cell Lung Cancer

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Background: We conducted a modified phase I/II trial investigating the incorporation of three-dimensional conformal thoracic radiation therapy (TCRT) into the treatment paradigm of induction and concurrent carboplatin and paclitaxel in patients with unresectable stage IIIA/B non-small cell lung cancer.

Methods: Patients received 2 cycles of induction carboplatin (area under the curve of 6) and paclitaxel (225 mg/m^2) on days 1, and 22. On day 43 concurrent TCRT and weekly ×6 of carboplatin (area under the curve = 2) and paclitaxel (45 mg/m^2) was initiated. The TCRT dose was escalated from 60 to 74 Gy in 4 cohorts (60, 66, 70, and 74 Gy), and the 74 Gy cohort was expanded into a phase II trial.

Results: Sixty-two patients were enrolled; the median age 57 years (range, 36–82), 39 were male (63%), 61 (98%) had a performance status of 0 or 1, 28 (45%) had stage IIIA disease, 21 (34%) had >5% weight loss, and the median forced expiratory volume 1 = 2.10 liters (range, 1.02–3.75). With a median follow-up for survivors of approximately 9 years (range, 7–11 years) the median progression-free survival, time to tumor progression, and overall survival (OS) (with 95% confidence intervals) were 10 (8.5–17), 15 (9–50), and 25 months (18–37), respectively. The 5-year progression-free survival and OS rates were 21% (12–32%) and 27% (17–39%), respectively. The 10-year OS rate was 14% (7–25%).

Conclusion: The long term survival rate compares favorably to other treatment approaches for stage III non-small cell lung cancer.

Key Words: Locally advanced non-small cell lung cancer, Combined modality therapy, Paclitaxel, Carboplatin, Conformal thoracic therapy, High dose.

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Lung cancer is the leading cause of cancer death in the United States, and it is estimated that in 2008 more patients will die of lung cancer than prostate, colorectal, and breast cancer combined.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of the cases of lung cancer and approximately 30% of patients will present with stage III disease.[2,3] The majority of patients who present with stage III disease will not be candidates for surgical resection and the standard of care for patients with a preserved performance status (PS) is a combination of chemotherapy and radiotherapy.[4] Phase III trials have revealed treatment with the concurrent systemic dose chemotherapy and radiation therapy yields an improved survival in comparison to sequential chemotherapy and radiotherapy.[5,6] Treatment with low dose chemotherapy concurrent with radiation therapy has demonstrated superior survival to radiotherapy alone, and improvement in local control could result in improved overall survival.[7] Thus, most treatment paradigms for patients with unresectable stage III disease include a combination of systemic dose chemotherapy to prevent the development of distant metastatic disease and concurrent chemoradiotherapy to obtain local control. Unfortunately, the majority of the patients experience local and/or distant disease progression.

The current standard dose of thoracic radiation therapy (TRT) for inoperable lung was established by Radiation Therapy Oncology Group (RTOG) trial 7301.[8] Patients with inoperable or unresectable stage III NSCLC who were en-

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rolled on this trial were randomized to 4 treatment arms: 40 Gy split course treatment (20 Gy in 5 fractions in 1 week, 2 weeks rest, and an additional 20 Gy in 5 fractions in 1 week), or 40, 50, 60 Gy continuous course over 5 weeks. Patients on the 50 and 60 Gy treatment arm had better tumor response and a lower rate of intrathoracic recurrence (determined by serial chest radiographs) than the lower dose arms, and based on RTOG trial 7301 alone the dose of 60 Gy was established as the current standard. This trial used 2-dimensional (2-D) treatment planning where the tumor volume is defined on radiographs which limited the accuracy of the tumor targeting and increased the radiation exposure to organs within the radiation field. Furthermore, this dose of TRT is inadequate to eradicate the intrathoracic disease in NSCLC. The 1-year local control rate observed on a phase III trial of TRT alone (65 Gy) versus chemotherapy before and after TRT (65 Gy) was 17% and 15%, respectively when patients underwent bronchoscopic evaluation for persistent disease.[9] In the interval since the RTOG trial 7301 was performed there has been the development of modern chemotherapy and three-dimensional thoracic conformal radiation therapy (three-dimensional TCRT).

At the University of North Carolina we performed a modified phase I/II trial investigating the incorporation of dose escalation of three-dimensional TCRT into the treatment paradigm of induction chemotherapy with concurrent chemotherapy. The modified phase I component of the trial established the ability to escalate the dose of three-dimensional TCRT,[10] and the 74 Gy cohort of the study was expanded to further assess the feasibility, toxicity, and clinical outcomes of patients at this higher dose level.[11] The hypothesis was that improved tumor targeting and higher TRT dose was possible with three-dimensional TCRT and would result in better clinical outcomes. The median survival observed on the initial publication was 26 months, and the median follow-up for survival was 31 months (range, 17–54 months).[11] However, the higher TRT may have delayed disease progression without obtaining long term disease control; poor control of systemic disease could have led to distant metastases, or the development of isolated brain metastases could have limited the long term survival of patients. We report the long term follow-up of this trial.

PATIENTS AND METHODS

Eligibility Criteria

Patients eligible for this trial were required to have a cytologic or histologic diagnosis of stage IIIA or IIIB disease as defined by the 1986 staging system[12] and be deemed appropriate candidates for combined modality therapy. Patients with T3N0–1 disease on the basis of chest wall invasion were excluded but all other patients with T3N0–1 disease were eligible.[13] All patients were reviewed by a thoracic radiologist, pulmonologist, thoracic surgeon, radiation oncologist, and medical oncologist. Initial staging consisted of a chest radiograph and a staging chest computed tomography (CT) scan which included full visualization of the liver and adrenal glands. Radionuclide bone scans were required as was either a CT or magnetic resonance imaging scan of the brain. Patients with supraclavicular adenopathy, superior sulcus tumors, or pleural effusion were excluded. Patients were required to have Eastern Cooperative Oncology Group PS of ≤ 2 and could not have received prior chemotherapy or radiotherapy to the chest. Other required parameters were as follows: absolute neutrophil count (ANC) $\geq 1500/mm^3$, platelet count $\geq 100{,}000/mm^3$, serum creatinine <1.6 mg/dl or Cockcroft calculated creatinine clearance >40 ml/min, serum bilirubin ≤ 1.5 times upper limit of institutional normal, serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times upper limit of institutional normal. Pulmonary function tests were required to document a forced expiratory volume 1 (FEV-1) second of >800 ml. Of note, there was no exclusion criteria related to weight loss. Patients with a prior malignancy who were disease free <5 years were excluded (except carcinoma in situ of the cervix or breast and nonmelanomatous skin cancer). Patients underwent a bronchoscopy, mediastinoscopy, or transthoracic fine-needle aspiration for diagnosis and staging as clinically indicated. This trial was approved by the Protocol Review Committee of the Lineberger Comprehensive Cancer Center (LCCC) and the Institutional Review Board of the University of North Carolina School of Medicine and Carolinas medical center and was labeled LCCC 9603. All patients provided informed consent before enrollment on this trial.

Treatment Administration

Chemotherapy

The treatment plan (Table 1) consisted of 2 cycles of carboplatin area under the curve (AUC) = 6 using the Calvert equation[14] and paclitaxel 225 mg/m^2 (infused over 3 hours) on days 1 and 22. Standard premedications for paclitaxel (dexamethasone 20 mg intravenously [IV], ranitidine 50 mg IV, and diphenhydramine 50 IV) were all given 30 minutes before the paclitaxel infusions. On day 43 patients received carboplatin AUC = 2 and paclitaxel 45 mg/m^2 (infused over 3 hours) weekly for 6 consecutive weeks. Standard paclitaxel premedications were used with the weekly paclitaxel infusions. Treatment on days 22 and 43 required an ANC $\geq 1500/mm^3$ and a platelet count of $\geq 100{,}000/mm^3$. During the weekly therapy with TCRT a complete blood count was monitored weekly, and the following adjustments were made based on the complete blood count on the day of treatment: for patients with an ANC $\geq 1000/mm^3$ and $\geq 75{,}000/mm^3$ the carboplatin and paclitaxel doses remained AUC = 2 and 45 mg/m^2, respectively; for patients with ANC 500 to $999/mm^3$ or platelet count 50,000 to $74{,}000/mm^3$ the carboplatin and paclitaxel doses were AUC = 1 and 45 mg/m^2, respectively; and for patients with an ANC $<500/mm^3$ and platelets $\leq 49{,}000/mm^3$ both carboplatin and paclitaxel were omitted.

TCRT

TCRT was initiated on day 43 with concurrent weekly carboplatin and paclitaxel. Patients underwent a planning CT scan after the second cycle of induction chemotherapy. Details of the TCRT treatment planning have been published previously.[15] The lungs, esophagus, heart (left ventricle), spinal cord, primary tumor, and radiographically positive

TABLE 1. Patient Characteristics

Characteristic	No. of Patients	
Total no. of patients	62	
Age (yr), median (range)	57	(36–82 yr)
Gender (male:female)	39:23	
Race (white:non-white)	49:13	
Stage (IIIA:IIIB)	28:34	
Stage IIIA		
T3N0–1	2	
T1–2N2	19	
T3N2	7	
Stage IIIB		
T1–2N3	11	
T4N0	9	
T4N2–3	14	
Weight loss (>5%:≤5%)	21:41	
PS (0–1:2)	61:1	
Histology (%)		
Adenocarcinoma	36	(58%)
Squamous	23	(37%)
Other	3	(5%)
Pulmonary function tests, median (range)		
FEV_1, l (range)	2.10	(1.02–3.75)
FVC, l (range)	3.27	(1.69–5.64)
DLCO (range) (ml/min/mmHg)	14.5	(4.8–32.7)

FVC, forced vital capacity; FEV, forced expiratory volume; DLCO, diffusing capacity of the lung for carbon monoxide.

lymph nodes were contoured. The prechemotherapy CT scan then was registered spatially with the planning CT scan, and the initial treatment was designed from it. The macroscopic tumor volume (GTV) included the primary tumor and any radiographically positive lymph nodes (all lymph nodes >1.0 cm). The clinical target volume (CTV) included the GTV, the entire uninvolved mediastinum, and 1.0 to 2.0 cm margin around the GTV; then 50 Gy was delivered to the prechemotherapy CTV. Respiratory variation (planning target volume) was taken into account only in that the inferior and superior margins were usually extended to 2.0 cm. The boost volumes included only the GTV and a 1.0 to 2.0 cm margin. The treatment was given with a standard daily fractionation of 2.0 Gy per fraction 5 days a week. All quoted doses have incorporated inhomogeneity corrections. Patients were treated supine with the arms over the head but were not immobilized otherwise, and port films of all fields were taken at least once a week. The quoted doses are at the isocenter, but variations over a 3D expanded CTV (1.0 cm) were within 5%. Radiation fields tended to follow standard practice using anterioroposterior-posterioroanterior to spinal cord tolerance and then obliques. In some patients, nonaxial fields were used when they would significantly reduce the volume of the normal lung treated. Radiation plans were developed from historic experience and were not inverse planned. The spinal cord dose was limited to 50 Gy anywhere within the cord, including the dose under the blocks, the total left ventricle dose was limited to 40 Gy, and the maximal dose to the brachial plexus was kept to <66 Gy. While not specifically required the length of the esophagus receiving full dose radiation was kept as short as possible. When data on the association between pneumonitis rates and the dose-volume histograms became available[16] attempts were made to limit the lung volume receiving >20 Gy (V_{20}) to <35%.

Patient Evaluation and Follow-Up

All patients had a CT scan performed 2 months after the completion of TCRT. Routine clinical evaluation with a chest radiograph was every 2 months for the first year, then every 3 months for 1 year, and then after 2 years every 6 months, and then after 5 years patients were evaluated annually. If patients had signs on physical examination (e.g., palpable lymphadenopathy) or symptoms concerning for disease progression, they underwent the additional testing including repeat CT scans of the chest/abdomen, imaging of the brain and bone scans as clinically indicated.

Statistical Design

The primary objective of the modified phase I part of the trial was to determine if the dose of TCRT could be escalated from 60 to 74 Gy when delivered with concurrent carboplatin and paclitaxel. The Cancer and Leukemia Group B (CALGB) Expanded Toxicity Criteria were used to assess toxicity on this study with the exception of the grading of acute esophageal toxicity for which the RTOG grading system was used. Once dose escalation to 74 Gy was completed additional patients were enrolled at that dose level as the phase II portion of the trial. The decision to expand the 74 Gy cohort to a phase II trial and not investigate further dose escalation was part of the initial trial design.[10] This trial design was employed to obtain additional information about the efficacy of high-dose TCRT before pursuing further dose escalation.[10] A Simon two-stage minimax design was used for the phase II portion of the trial.[17] The six evaluable patients from the phase I trial were included in the first stage of the phase II trial. Details of the modified phase I and II study design have been published previously.[10,11]

Statistical Methods

The Kaplan-Meier (or product limit) method was used to estimate the three 'time to event' functions of: time to tumor progression (TTP), progression free survival (PFS), and overall survival (OS). TTP has been defined as the time from the date of diagnosis until the date of disease progression (the event) or date of death or last contact (death censored). PFS has been defined as the time from the date of the diagnosis to the date of disease progression or death (two events, whichever occurred first) or the date of last contact. The date of progression has been defined as the documented date of either pathologic confirmation of disease progression, or the date when radiologic exams determined disease progression. OS has been defined as the time from the date of the diagnosis to the date of death (the event) or the date of last contact. Median follow-up time for survivors has been defined as the median amount of the time that survivors have been followed. Exact binomial confidence intervals have

been calculated for the percentages of interest. Statistical analyzes were performed using SAS statistical software, Versions 9.1, SAS Institute Inc., Cary, NC.

RESULTS

Patient Characteristics

Between June 1996 and July 1999 62 patients were enrolled on this trial (Table 2). The median age was 57 years (range, 36–82). Thirty-nine (63%) were male, 28 (45%) had stage IIIA and 34 (55%) had stage IIIB disease. Twenty-one patients (34%) had >5% weight loss, and 61 patients (98%) had a CALGB PS of 0 or 1 with only one patient having a PS of 2. Adenocarcinoma was the most common histology (58%) followed by squamous cell (37%) and non-small cell lung cancer not otherwise specified (5%). The median FEV-1 was 2.10 L (range, 1.02–3.75). The median tumor volume was 135 ml (range, 8–602 ml). Forty-eight of the 62 patients initiated the concurrent chemoradiotherapy on day 43. The reasons for not starting the protocol treatment on day 43 were: progressive disease ($n = 8$, 13%) early death ($n = 2$, 3%), and decline in PS due to intercurrent illness ($n = 1$, 2%), voluntary withdrawal ($n = 2$, 3%) and paclitaxel hypersensitivity reaction ($n = 1$, 2%). The radiation dose patients received on protocol during the phase I part of the trial were: 60 Gy ($n = 3$, 5%), 64.6 ($n = 1$, 2%), 66 Gy ($n = 5$, 8%), 70 Gy ($n = 6$, 10%); 39 patients were enrolled on the phase II part of the trial, 32 patients initiated the concurrent chemoradiotherapy, and 31 (97%) completed treatment to 74 Gy.

Long Term Efficacy of Therapy

Patients were followed until death except those surviving who were followed from 7 to 11 years (median follow-up 9 years Table 3). Fifty-three of the patients have died; 33 patients died with evidence of disease progression, and 20 patients died without evidence of disease progression. Three patients are alive with evidence of disease progression, and 6 patients are alive without evidence of disease progression. The median survival time and the 5-year overall survival rate observed were 25 months (95% confidence interval [CI], 18–37 months) and 27% (95% CI, 17–39%), respectively (Figure 1). The 10-year survival rate was 14% (95% CI, 7–25%). The median PFS and 5-year progression-free survival rate observed were 10 months (95% CI, 8–17 months) and 21% (95% CI, 12–32%), respectively (Figure 2). The median TTP and 5-year tumor progression rate were 15 months (95% CI, 9–50 months) and 64% (95% CI, 51–77%), respectively (Figure 3). Data were available to assess for isolated brain relapse on 60 patients; 9 patients experienced isolated brain metastatic disease and the rate of for isolated brain metastatic disease was 15% (95% CI, 7–27%). Data to

TABLE 2. Treatment Schema

Induction Chemotherapy	Concurrent Chemotherapy
Carboplatin AUC = 6	Carboplatin AUC = 2 weekly × 6
Paclitaxel 225 mg/m^2 on days 1, 22	Paclitaxel 45 mg/m^2 weekly × 6
	Thoracic conformal radiation therapy
	Cohort / Dose level
	1 / 60 Gy
	2 / 66 Gy
	3 / 70 Gy
	4 / 74 Gy

AUC, area under the curve.

TABLE 3. Long-Term Follow-Up of Efficacy of Combined Modality Therapy

Parameter	Median Time (95% CI)	5-yr Rate (95% CI)
Progression-free survival	10 (8.5–17) mo	21% (12–32%)
Time to tumor progression	15 (9–50) mo	64% (51–77%)
Overall survival	25 (18–37) mo	27% (17–39%)

CI, confidence interval.

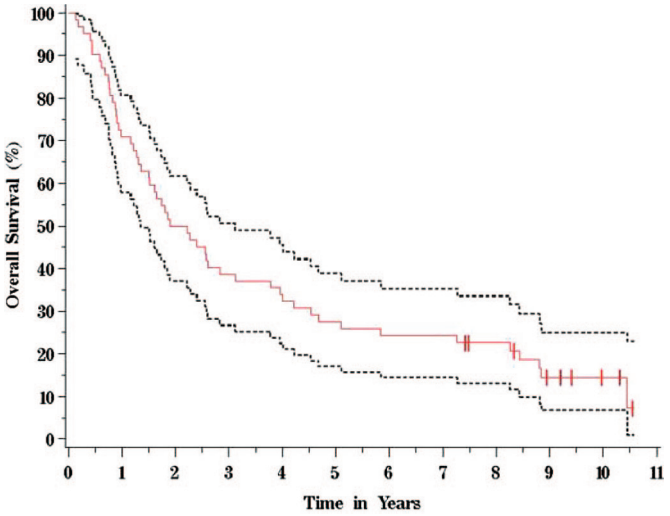

FIGURE 1. Overall survival with 95% confidence intervals.

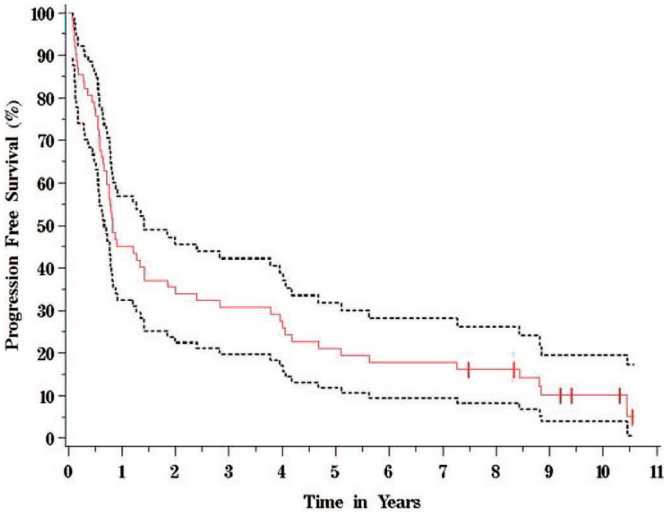

FIGURE 2. Progression-free survival with 95% confidence intervals.

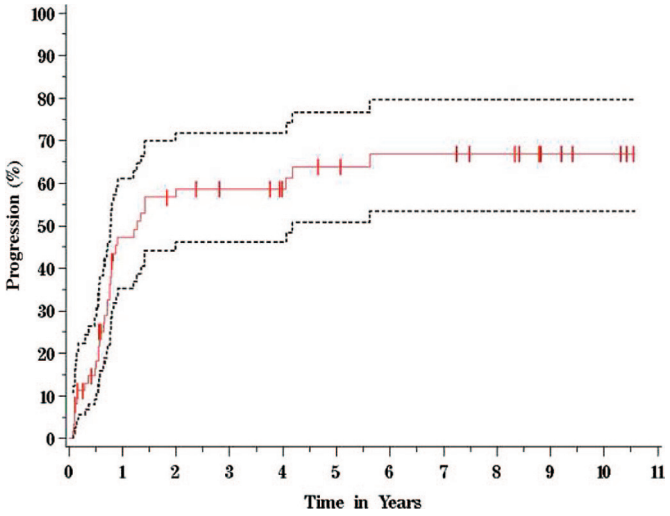

FIGURE 3. Time to tumor progression with95% confidence intervals.

assess for radiographic evidence of local progression were available on 53 patients and the rate of local progression was 34% (95% CI, 22–48%). Of note, one patient developed and died as a result of a treatment related radiation-induced sarcoma 8 years after completion of radiotherapy.[18] No other fatal treatment related complications were observed.

DISCUSSION

The median survival time of 25 months and 5-year overall survival rate of 27% (95% CI, 17–39%) observed on this trial are promising. The high TCRT may have contributed to the increased survival observed on this trial. The rate of local progression as assessed by radiographic evaluation was 34% (95% CI, 22–48%) but this rate probably would have been higher if patients had undergone bronchoscopic evaluation for tumor assessment and thus this rate should not be compared with the local control rate observed on the trial be Le Chevalier et al.[9] The 10-year overall survival rate was 14% (95% CI, 7–25%). Unfortunately, there are limited data to compare the 10-year overall survival rate observed on this trial with other trials due to the fact that the majority of the patients with stage III disease die of disease progression within the first 3 years. Of note some patients died without clinical or radiographic evidence of disease progression (n = 20) from causes other than their NSCLC. As a result of this observation the TTP was calculated in addition to the progression-free survival. This revealed that the majority of the patients who experienced disease progression did in the first 18 months. Nevertheless, the TTP should be interpreted cautiously since there can be significant variability in the investigation of disease progression depending on the clinical circumstances, and the physician's and patient's preferences. This parameter (or a similar parameter such as disease-specific mortality) may be of value in future larger studies as the prognosis of patients with stage III disease improves the impact of deaths from comorbidities, subsequent illnesses, or late treatment related adverse events may need to be considered.

Although the current data are encouraging there is a reasonable concern about patient selection bias. However, the eligibility criteria in regard to PS, staging requirements, and organ function were similar to other trials performed in this patient population. In fact there was no exclusion criteria for weight loss which is a known poor prognostic factor,[19] and the FEV-1 requirement was more lenient than other trials[20,21] and similar to another trial.[22] This trial was also performed before the routine use of staging positron emission tomography (PET) scan, and approximately 25% of patients with stage III disease will have metastatic disease detected on PET scan staging, and PET scan staging has been associated with improved survival in stage III patients in comparison to patients staged with conventional methods.[23,24] The dose and volume constraints of high dose three-dimensional TCRT in the trial did restrict enrollment based on tumor volume, anatomic location (e.g., superior sulcus tumors were excluded due to the potential harm of high dose radiotherapy on the brachial plexus), and to patients without supraclavicular lymph node involvement.

The rate of isolated brain metastases observed on trial was 15% (95% CI, 7–27%), and is similar to the rate observed after combined modality therapy by other investigators. Of 422 patients treated on combined modality protocols performed by the Southwest Oncology Group a total of 268 patients (64%) had experience disease progression; 54 (20%) developed isolated brain metastases, 17 (6.5%) developed metastases at the brain and other sites, 197 (63.5%) developed metastases at other sites.[25] A similar review of 177 patients with stage III disease who were treated with combined modality therapy revealed that 34% of patients recurred in the brain as their first site of failure, and 40% of patients developed brain metastases as some point in their course.[26] To investigate the role of prophylactic cranial radiation (PCI) in patients with stage III NSCLC the RTOG initiated a phase III trial (RTOG 0214) of PCI versus observation after completion of definitive therapy for stage III NSCLC.[27] Unfortunately the trial closed early due to poor accrual, and the role of PCI therapy in stage III NSCLC is unknown at this time.

The chemotherapy paradigm used in this trial may be considered suboptimal by some investigators based on the results of trials that have been completed and published since the time this trial was initiated. The phase III trials that have revealed a survival benefit to concurrent chemoradiotherapy have used systemic dose cisplatin-based chemotherapy rather than low dose carboplatin and paclitaxel therapy.[5,6] There is also evidence from the metastatic setting that cisplatin-based treatments provide superior survival than carboplatin-based therapies, but with greater toxicity.[28,29] These data raises the question of whether cisplatin is a better agent in NSCLC, particularly when the intent of the treatment is curative. Furthermore, phase III trials that have compared the treatment strategy of induction chemotherapy followed by concurrent chemotherapy versus concurrent chemoradiotherapy have not revealed a statistically significant survival benefit with the addition of induction chemotherapy.[19,30] It is possi-

ble that modification of the chemotherapy platform or the addition of a targeted agent may have greater efficacy provided that the combination had acceptable toxicity and did not compromise the delivery of the high dose TCRT.

Other investigators have also performed trials that have investigated dose escalation of TCRT in NSCLC. RTOG trial 0117 was a phase I/II trial that investigated dose escalation of TCRT in combination with concurrent carboplatin and paclitaxel in patients with stage I-III NSCLC with a PS of 0–1 and ≤10% weight loss.[31] The dose constraints employed on this trial included: a V_{20} ≤30% and for the esophagus a mean dose ≤34 Gy and V_{55} ≤30%. The phase I part of the trial enrolled 17 patients, and the maximum-tolerated dose of TCRT with concurrent chemotherapy, was determined to be 74 Gy. The phase II portion of the trial is currently enrolling patients.[31] The North Central Cancer Treatment Group (NCCTG) also performed a phase I/II trial that investigated dose escalation of TCRT in combination with concurrent carboplatin and paclitaxel in patients with unresectable stage I–III NSCLC, a PS of 0–1, and weight loss <10%.[32] This trial employed the following dose constraints: no part of the spinal cord could receive greater than 48 Gy, a V_{20} of ≤40%, the full circumference of esophagus could not receive ≥60 Gy, the entire brachial plexus could not receive ≥60 Gy, and one-third the heart could not receive ≥60 Gy, two-thirds could not receive ≥50 Gy, and the entire heart could ≥40 Gy. The phase I portion of the trial included 15 patients and the maximum-tolerated dose of TCRT with concurrent carboplatin and paclitaxel was 74 Gy. The phase II portion of the trial is currently enrolling patients.[32] These trials provide additional evidence of the safety of TCRT to 74 Gy with concurrent carboplatin and paclitaxel.

Recently this treatment paradigm was investigated in CALGB trial 30105. This trial was a two arm phase II trial that investigated induction therapy with carboplatin with either gemcitabine or paclitaxel for two cycles followed bi-weekly gemcitabine (arm A) with concurrent TCRT or weekly carboplatin and paclitaxel with concurrent TCRT (74 Gy) (arm B).[33] The trial enrolled (n = 69); arm A was closed after 26 patients had been enrolled due to the fact that 3 patients experienced grade 5 pulmonary events and arm B enrolled 43 patients. The median progression-free and median survival times observed on arm B were 14.9 months and 24.3 months (95% CI, 12.3–36.4), respectively. The median survival time observed on this trial was higher than the median survival time observed on the previous CALGB trials, 9431 and 39801.[19,34] The major therapeutic difference between CALGB 30105 and LCCC 9603 and the other CALGB trials was the higher total dose of 74 Gy.

Based on the safety and efficacy of our modified phase I/II trial, CALGB trial 30105, and the safety data and preliminary efficacy results of the phase I/II RTOG 0117 and the NCCTG trials a phase III trial (RTOG 0617) comparing TCRT at the standard dose of 60 Gy versus a higher dose of 74 Gy with concurrent chemotherapy was recently initiated.[35] In this trial, patients will be treated with concurrent chemotherapy (weekly carboplatin AUC = 2 and paclitaxel 45 mg/m^2) in combination with TCRT. After completion of the concurrent chemoradiotherapy, all patients will then be treated with 2 cycles of systemic chemotherapy (carboplatin AUC = 6 and paclitaxel 200 mg/m^2) every 3 weeks. This randomized phase III trial, performed in cooperation by CALGB, RTOG, and the NCCTG will provide additional information about the efficacy, as well as acute and late toxicities of high dose three-dimensional TCRT. Until the results of this phase III trial are available the treatment strategy of low dose concurrent carboplatin and paclitaxel with high dose TCRT and systemic dose carboplatin and paclitaxel should be considered investigational.

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