Late Complications of High-Dose (≥66 Gy) Thoracic Conformal Radiation Therapy in Combined Modality Trials in Unresectable Stage III Non-small Cell Lung Cancer

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Background: Combined modality treatment is the standard of care for patients (pts) with unresectable stage III non-small cell lung cancer. Dose escalation of radiotherapy is one strategy used to improve locoregional control and survival, but it increases the risk of both early and late treatment related toxicities.

Methods: From May 1996 to August 2004, a total of 112 stage III non-small cell lung cancer pts were treated on 4 phase I/II or phase II trials to assess the safety and feasibility of high-dose (60–90 Gy) thoracic conformal radiotherapy. Patients who received ≥66 Gy ($n = 88$) were included in an analysis of late complications. Late complications were defined as complications that developed or persisted ≥90 days postradiotherapy. The classic lung toxicities of radiation pneumonitis and fibrosis were not included in this analysis.

Results: Of the 88 patients included in this analysis of late complications, 21 patients (24%) developed a late complication and a total of 28 late complications were observed. The late complications were: pulmonary ($n = 5$; bronchial stenosis [$n = 3$] and fatal pulmonary hemoptysis [$n = 2$]), esophageal ($n = 6$), cardiac ($n = 9$), osseous ($n = 6$), and second primary tumor ($n = 2$). The median survival for all patients enrolled on the 4 trials (with 95% confidence interval [CI]) was 24.7 months (18.1–30.4 months), and the 5-year overall survival (with 95% CI) was 24% (16–32%). Data to assess for radiographic evidence of local progression were available for 99 patients, and the rate of local progression was 43% (95% CI 34–53%).

Conclusions: High-dose thoracic conformal radiotherapy is feasible and results in promising survival outcomes. Late complications occur in a minority of patients.

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Lung cancer is the leading cause of cancer death among men and women, accounting for more deaths than breast, colon, and prostate cancer combined.[1] In the United States in 2007, there will be an estimated 213,000 new lung cancer diagnoses and approximately 160,000 deaths.[1] Non-small cell lung cancer (NSCLC) comprises approximately 85% of lung cancer diagnoses and of these, 30 to 40% of patients present with stage IIIA/B disease.[2] The standard of care for patients with unresectable stage III disease and a good performance status consists of systemic chemotherapy and thoracic radiation therapy (TRT). Treatment with the combination of chemotherapy and radiotherapy results in 3- and 5-year survival rates of 15 to 25% and 10 to 20%, respectively.[2] Although combined modality therapy improves survival when compared with radiotherapy alone, loco-regional and distant recurrences continue to be problematic.

A variety of different chemotherapeutic and radiation strategies have been investigated to improve outcomes in unresectable stage III NSCLC. Phase III trials revealed that concurrent chemotherapy and TRT is more efficacious than sequential.[3,4] Radiation techniques such as dose intensification and escalation have also been studied, but the current standard dose of TRT has remained unchanged for many years. The current standard radiation dose for inoperable lung cancer was established in 1987 by Radiation Therapy Oncology Group (RTOG) trials 7301 and 7302 that demonstrated improved local control with a radiation dose of 60 Gy compared with lower doses.[5] These trials used two-dimensional (2-D) treatment planning wherein the tumor volume was defined on kilovoltage radiographs. The efficacy of this dose has been questioned; evidence from Arriagada et al.[6] demonstrated a disappointing 1 year local regional tumor control rate of 17% for unresectable NSCLC patients treated with 65 Gy of TRT alone. In this same trial, those treated with chemotherapy pre- and post-TRT (65 Gy) also demonstrated a poor 1 year local regional tumor control rate (15%). This

study strongly suggests that the current standard radiation dose is inadequate.

In the interval since RTOG trials 7301 and 7302, three-dimensional thoracic conformal radiation therapy (TCRT) and modern chemotherapy have been developed. Three-dimensional TCRT has improved tumor targeting which allows for more accurate delivery of radiation to tumor and reduced radiation exposure to organs at risk within the thorax. At the University of North Carolina, we evaluated various dose escalation strategies in several Phase I and II clinical trials.[7–13] The prescribed dose of three-dimensional TCRT in these trials ranged from 60 to 90 Gy. The intensification of therapy and specifically the TCRT dose increases the risk of acute as well as late treatment-related toxicities. This analysis highlights the unclassical pulmonary toxicities and does not detail the classic lung toxicities of radiation pneumonitis and fibrosis. We herein report the long term follow-up and late complications of patients treated with high-dose three-dimensional TCRT for unresectable stage III NSCLC.

METHODS

Eligibility

All patients were required to have histologically or cytologically confirmed unresectable stage III NSCLC and determined to be appropriate candidates for combined modality therapy. Initial staging consisted of a chest radiograph, staging computed tomography (CT) scan (including liver and adrenal glands), radionuclide bone scan and/or positron emission tomography (PET) scan, and a brain CT or magnetic resonance image. All patients were evaluated by a medical oncologist, thoracic surgeon, pulmonologist, thoracic radiologist, and radiation oncologist and discussed at a multidisciplinary thoracic oncology tumor board.

All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance of 0–1, although in our early experience a few patients with ECOG 2 were treated in this fashion. Patients could not have received prior radiation and/or chemotherapy for NSCLC or prior chest radiotherapy. Other inclusion criteria were preserved bone marrow, renal, and hepatic function. Pulmonary function test required a forced expiratory volume 1 second (FEV_1) of >800 or 1200 ml at baseline or an estimated post three-dimensional TCRT FEV_1 >800 ml. The details of the calculation of post-TRT FEV_1 have been previously published.[8] Patients with malignant involvement of the supraclavicular lymph nodes or malignant pleural effusion were excluded. In addition to meeting these inclusion criteria, patients included in the analysis of late complications were required to receive a minimum TCRT dose of 66 Gy. All of these trials were reviewed by the protocol review committee of Lineberger Comprehensive Cancer Center at the University of North Carolina, and approved by the Institutional Review Board of the participating institutions. This retrospective analysis was approved by the Institutional Review Board at the University of North Carolina.

Treatment Overview

All patients received two cycles of carboplatinum-based induction chemotherapy. The efficacy and toxicity of the induction chemotherapy regimens have been previously published.[7–13] Three of the four trials employed carboplatin and paclitaxel concurrent with radiotherapy, and one trial used hyperfractionated radiotherapy without concurrent chemotherapy. Radiation treatment planning for the three trials has been previously published.[7–13] The prescribed radiation dose ranged from 60 to 90 Gy and was delivered either in once daily fractions of 200 cGy ($n = 98$) or 125 cGy twice daily (minimum 6 hours between fractions; $n = 14$). Seventy-six patients underwent CT in the treatment position prior to chemotherapy. The remaining 36 patients underwent a planning CT after the second cycle of chemotherapy. Initial fields included the prechemotherapy gross tumor volume, ipsilateral and contralateral (elective) mediastinum as identified on CT scans with a 0.5 to 1 cm margin. The planning target volume (PTV) was the clinical target volume plus a margin added to compensate for variability in treatment setup, breathing, or motion during treatment. In general, the PTV included the clinical target volume plus a 1.0 cm expansion at all borders. The initial PTV received between 40 and 50 Gy depending on the trial and dose-escalation schema. The boost treatment volume included the postinduction tumor as defined on CT scans and regions where nodes were initially positive (size >1 cm on CT, and/or PET or mediastinoscopy positive). The quoted doses were the minimal dose to the PTV with the inhomogeneities kept within 5%. The V_{20} limitation was 35% (no more than 35% of the lung volume could receive >20 Gy). The V_{20} was calculated using the combined lung volume minus the gross tumor volume. There was no dose limit for the heart or esophagus; however, it was strongly encouraged that the entire heart (and/or left ventricle) not receive >60 Gy and that the full circumference of the esophagus for greater than a 6 cm length not receive >60 Gy. After treatment, routine clinical follow-up was scheduled every 2 months for 1 year and then every 3 months for 1 year, and then after 2 years patients were seen every 6 months for 3 years, and then yearly. A chest radiograph was done with each visit. A staging CT was done approximately 8 weeks after completion of radiotherapy, 6 months after therapy, and at the discretion of the treating physician.

Statistical Methods

The Kaplan-Meier (or product limit) method was used to estimate the time to event functions of time to toxicity and overall survival. Time to toxicity was defined as the time from the date of enrollment to the date of the first late (greater than 90 days) toxicity or date of death, or of last contact. Overall survival was defined as the time from the date of enrollment to the date of death or the date of last contact. Fisher's exact test was used for data categorized into 2 by 2 contingency tables. The nonparametric Jonckheere-Terpstra method was used to test for ordered differences among categories for larger contingency tables. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. The Wilcoxon rank sum test (using Van der Waerden normal scores) was used for

two-group comparisons. Exact 95% confidence intervals were calculated for reported proportions (or percentages) of interest. Statistical analyses were performed with SAS statistical software, Versions 9.1, SAS Institute Inc., Cary, NC.

RESULTS

Patient Characteristics

From May 1996 to August 2004, 112 unresectable stage III NSCLC patients were treated on these clinical trials. The 88 patients who received ≥66 Gy were included in an analysis of late complications (Table 1). Twenty-four patients did not receive ≥66 Gy for various reasons: prescribed protocol treatment of <66 Gy ($n = 3$), withdrawal of consent ($n = 3$), interval progression of disease ($n = 8$; 3 progressed locally, 2 distant, 3 unknown), worsened medical illness ($n = 5$), hypersensitivity reaction to paclitaxel ($n = 1$), death ($n = 1$), or unknown ($n = 3$). Among those who received ≥66 Gy, the median TCRT dose was 74 Gy (range, 66–90 Gy), and 41 patients (47%) received this dose. The median age for all patients was 59 years (range, 36–82 years), 71 patients (63%) were male, 86 patients (77%) were white, and 54 (48%) had stage IIIA disease, whereas 58 (52%) had stage IIIB disease. Only six patients underwent 18-fluorodeoxyglucose-PET-CT scan as part of the initial staging workup. This is largely due to the fact that PET was not yet standard procedure for staging workup at the time several of these trials were written. All patients had an ECOG performance status of 0–1. The most common histology was adenocarcinoma (50%).

Late Toxicity

Late toxicities were defined as those that occurred or persisted ≥90 days after completion of radiotherapy. Of the 88 patients who received ≥66 Gy included in this analysis, 21 patients (24%) developed a late complication and a total of 28 late complications were observed (Table 2). Of note, the classic lung toxicities of radiation pneumonitis and fibrosis were not included in this analysis. The late complications included: bronchial stenosis ($n = 3$, 3.4%), fatal pulmonary hemoptysis ($n = 2$, 2.3%), esophageal stricture ($n = 6$, 6.8%), vertebral or rib insufficiency fracture ($n = 6$, 6.8%), pericardial effusion ($n = 3$, 3.4%) or constrictive pericarditis ($n = 2$, 2.3%), myocardial infarction ($n = 4$, 4.5%), and second primary tumor within the radiation field ($n = 2$, 2.3%; one sarcoma and one small cell lung cancer). The sarcoma was diagnosed approximately 8 years after completion of 74 Gy and the small cell lung cancer was diagnosed approximately 4 years after completion of 86 Gy. Although these malignancies occurred within the field of radiation, it is possible they were not radiation-induced. Two other patients developed a second primary malignancy outside of the radiation field (one liver carcinoid and one second primary NSCLC) that was not considered a late complication of radiotherapy.

The three patients with bronchial stenosis presented with symptoms including cough, dyspnea, and recurrent infection; lobar collapse was seen on diagnostic and therapeutic bronchoscopy. All of the patients with pericardial disease presented with shortness of breath and varying degrees of other heart failure symptoms. One of the two patients with constrictive pericarditis required a pericardial window and recovered, the other died secondary to distant relapse. Two of the three patients with pericardial effusion improved with pericardiocentesis; one improved spontaneously. The patients with esophageal stenosis presented with dysphagia and were treated with endoscopic esophageal dilation. Of the four myocardial infarctions, one was fatal. Three of four patients with MI underwent successful cardiac bypass. Although these MI's occurred postradiotherapy, it is possible that they occurred as a result of pretreatment conditions such as tobacco use and other cardiac risk factors. In total, there were 5 fatal conditions believed to be radiation induced: hemoptysis ($n = 2$), MI ($n = 1$), sarcoma ($n = 1$), and small cell lung cancer ($n = 1$).

Two cases of fatal hemoptysis were observed. One patient was a 41-year-old man with stage IIIB (T4N1) poorly differentiated NSCLC who initially presented with hemoptysis and received 90 Gy TRT. One hundred and ten days after completion of the TRT, an episode of massive fatal hemop-

TABLE 1. Patient Characteristics

Characteristic	Entire Sample ($n = 112$) No. of Patients	TCRT ≥66 Gy ($n = 88$) No. of Patients
Age (yr), median (range)	58.8 (36–82)	58.5 (36–82)
Gender (male:female)	71:41	56:32
Race (white:non-white)	86:26	67:21
Stage (IIIA:IIIB)	54:58	42:46
ECOG PS (0:1)	51:61	46:42
Histology (%)		
Adenocarcinoma	50% (56/112)	47% (41/88)
Squamous	36% (40/112)	38% (33/88)
Other	14% (16/112)	16% (14/88)

n, number; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TCRT, thoracic conformal radiation therapy.

TABLE 2. Late Complications in Patients Receiving ≥66 Gy

	Cases ($n = 88$)	% of Total Late Complications ($n = 28$)	Onset (mo)
Pulmonary			
Bronchial stenosis	3	11	2, 6, 7
Fatal hemoptysis	2	7	4, 13
Esophageal			
Stricture	6	21	3, 3, 3, 10, 40, 65
Osseous			
Vertebral/rib fracture	6	21	2, 8, 16, 17, 21, 36
Cardiac			
Pericardial disease[a]	5	18	2, 15, 33, 41, 90
Myocardial Infarction	4	14	21, 33, 33, 65
Oncologic			
Second primary	2	7	48, 95

[a] Pericardial effusion ($n = 3$) and constrictive pericarditis ($n = 2$).
n, number.

tysis occurred in the emergency department. An autopsy was performed and did not reveal an identifiable origin of bleed and no local residual tumor was identified. The second patient was a 39-year-old man with stage IIIA (T2N2) NSCLC (squamous cell) who initially presented without hemoptysis, and received 82 Gy in 41 fractions over 80 days rather than the expected 57 days, due to grade 3 esophagitis. Four hundred days after completion of TRT, he experienced massive fatal hemoptysis, observed in the medical intensive care unit. An autopsy was performed, and revealed severe left upper lobe pulmonary fibrosis with chronic radiation-induced vasculopathy; no residual tumor was identified.

When comparing those who did not experience a late complication to those who did experience a late complication, both groups received a median TCRT dose of 74 Gy, but those who had a late complication had a significantly higher interquartile range (IQR) (74 Gy, IQR 74–86 versus 74 Gy, IQR 74–78, respectively; $p = 0.03$) (Table 3 and Figure 1). Those who had a late complication also had a trend toward younger median age (53 years versus 59 years, respectively; $p = 0.07$). The other patient characteristics were quite similar (Table 3). Pulmonary and esophageal complications tended to occur earlier after completion of radiotherapy, whereas cardiac, osseous, and second primary tumors tended to occur later (Table 2).

Overall Response and Survival

Overall survival analysis was performed based on intent to treat and included all patients enrolled on the 4 clinical trials ($n = 112$). Of a total of 112 patients, 92 have died and 20 were still alive at the time of analysis (Figure 2). The median follow-up time for survivors was 7.5 years, and 9 survivors were alive more than 8 years from date of enrollment. The median survival (with 95% CI) was 24.7 months (18.1, 30.4), and the 1-, 3-, and 5-year overall survival (with 95% CI) was 70% (60, 77%), 35% (27, 44%), and 24% (16, 32%), respectively.

For the 112 patients treated on these trials, data on response were available for 94 patients; the overall response rate after combined modality therapy was 56% (95% confidence interval [CI] 46%, 66%); complete response 5%, partial response 51%. The disease control rate (complete response, partial response, and stable disease combined) was 89% (95% CI 83–96%). Data to assess for radiographic evidence of local progression were available for 99 patients, and the rate of local progression was 43% (95% CI 34–53%). Data on distant recur-

TABLE 3. Comparisons of Patients Who Had a Late Toxicity to Those Who Did Not

	Had a Late Toxicity	Did Not Have a Late Toxicity	*P*
Gender (male)	14/21 63%	42/67 62%	0.79
Race (Caucasian)	15/21 71%	52/67 78%	0.77
Stage (III-B)	8/21 38%	38/67 57%	0.21
ECOG (1)	7/21 33%	35/67 54%	0.14
Con-Chemo (yes)	2/19 11%	10/59 17%	0.72
Age (median, range)	53 (36–81)	59 (39–82)	0.07[a]
XRT (median, IQR)	74 (IQR 74–86)	74 (IQR 74–78)	0.03[b]
Response			0.78
CR	1 (5%)	4 (6%)	
PR	10 (50%)	36 (55%)	
SD	8 (40%)	20 (30%)	
PD	1 (5%)	6 (9%)	
Histology			0.84
Adenocarcinoma	9 (44%)	32 (48%)	
Squamous	9 (43%)	24 (36%)	
All others	3 (14%)	11 (16%)	

[a] Borderline significant.
[b] Significant at $\alpha = 0.05$.
ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; XRT, concurrent chest radiation; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

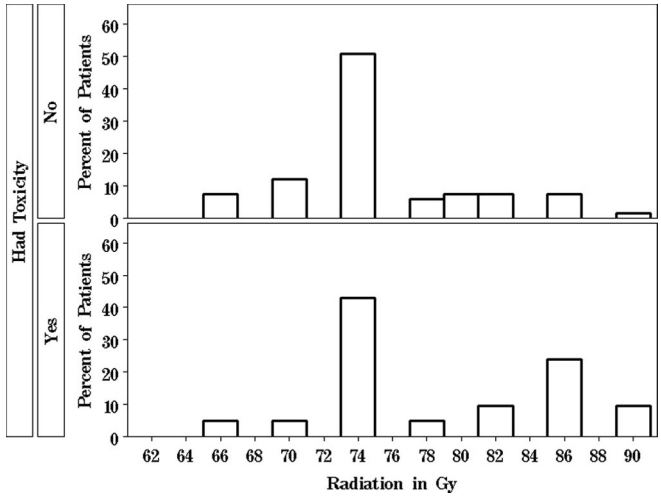

FIGURE 1. Histogram that compares the distribution of patients who had late toxicities to those who did not by radiation dose. The distributions are similar (with the same minimum, median, and maximum doses) except more patients who received 82, 86, and 90 Gy dose levels in the 'Yes' 'Had Toxicity' group ($p = 0.02$).

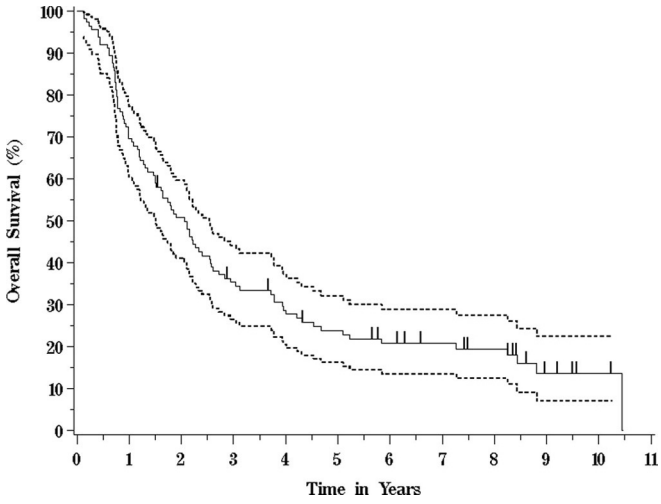

FIGURE 2. Overall survival including 95% confidence bands for all patients (n = 112).

TABLE 4. Grade 3–5 Late Complications of Dose Escalation Trials

First Author	No. of Patients	Radiation Dose (Gy)	Type of Complication (n = Number of Patients)				
			Pulmonary	Esophageal	Cardiac	Bone	Other
Maguire[17]	94	≥73.6	15[a]	3	2	0	6[b]
Bradley[15]							
Cohort 1[c]	113	70.9–90.3	12	5	2	1	0
Cohort 2[d]	45	70.9–77.4	7	1	0	0	0
Hayman[16]	104	63–102.9	1	0	0	0	0
Belderbos[14]	55	74.3–87.8	0	0	0	0	1[e]

[a] Grade 3 (n = 11), grade 4 (n = 1), and grade 5 (n = 3).
[b] Dermatologic toxicity (n = 5), vocal paralysis (n = 1).
[c] V_{20} <25%.
[d] V_{20} 25–36%.
[e] Dermatologic toxicities (n = 1).

rence were available for 103 patients, and 12.6% (n = 13) developed recurrent disease in the brain only.

DISCUSSION

This analysis demonstrates that high-dose thoracic conformal radiotherapy (TCRT) is feasible in patients with unresectable stage III NSCLC, and late complications occurred in a minority (24%) of patients. Other groups have investigated the toxicity of high dose three-dimensional TCRT in Phase I and II trials (Table 4), and the incidence of late complications seen on this study is consistent with previous studies.[14–17] The cumulative data from these trials indicate that the primary late toxicities of high dose TRT are pulmonary and esophageal.

In unresectable stage III NSCLC, the goal of TRT is to control local disease and subsequently prolong survival. More aggressive TCRT may be beneficial; however, it is clear that dose escalation alone is not sufficient to eliminate the problem of local recurrence, and its effect on long term survival.[8] Local failures, observed in 43% of the patients in this analysis, will continue to be problematic. Radiation resistance, faulty tumor localization, and treatment precision could all be factors contributing to the problem of local recurrence. Technologic advances in treatment planning and tumor targeting such as the use of intensity modulated radiotherapy will aid in optimal delivery of radiation with minimal risk to vital structures. Improved tumor imaging, using techniques such as PET scan, will improve staging and better localize malignant tissue within the thorax. PET imaging may also better exclude patients who have occult metastatic disease. These technologic advances alone may lead to improvements in overall survival on future combined modality clinical trials.

In our opinion, this rate of late toxicities is acceptable given the poor prognosis for patients with unresectable stage III NSCLC, and the promising median survival (24.7 months) and 5-year overall survival rate (24%) observed in this analysis. However, this cohort of patients may represent a select group of patients with unresectable stage III disease who received their treatment on a clinical trial in a multidisciplinary thoracic oncology clinic. The dose and volume constraints of the high dose three-dimensional TCRT in our cohort limited enrollment based on tumor volume, anatomic location (e.g., superior sulcus tumors were excluded) and to patients without supraclavicular lymph node involvement. However, other eligibility criteria used in our trials such as performance status, staging requirements, and organ function were similar to other trials performed in this patient population.[18–21] The high dose TCRT investigated in these trials may have a higher rate of toxicity in different clinical settings or a more heterogeneous patient population.

An ongoing phase III trial is comparing TCRT at the standard dose of 60 Gy to treatment at a higher dose of 74 Gy with concurrent chemotherapy. Patients enrolled on this trial will receive concurrent chemotherapy (weekly carboplatin area under curve = 2 and paclitaxel 45 mg/m^2) and TRT to either 60 or 74 Gy. After completion of the concurrent chemoradiotherapy, all patients will then receive 2 cycles of systemic chemotherapy (carboplatin area under curve = 6 and paclitaxel 200 mg/m^2) every 3 weeks. This phase III trial is being performed in cooperation by Cancer and Leukemia Group B, RTOG, and the North Central Cancer Treatment Group. This trial will provide additional information about the efficacy, as well as the acute and late toxicities of high dose three-dimensional TCRT Until the results of this trial available this treatment approach should be considered investigational.

In conclusion, higher TCRT doses are accompanied by the risk of late complications, but this strategy appears to be tolerable and result in promising survival outcomes. Unfortunately, the majority of patients with unresectable stage III disease will die of progressive disease within 3 years of diagnosis. A combination of strategies that optimize the selection of patients for combined modality therapy and maximize the therapeutic benefit of radiation, chemotherapy, and potentially targeted therapies are needed.

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