

Carboplatin/Paclitaxel or Carboplatin/Vinorelbine Followed by Accelerated Hyperfractionated Conformal Radiation Therapy: Report of a Prospective Phase I Dose Escalation Trial From the Carolina Conformal Therapy Consortium

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A B S T R A C T

Purpose

To prospectively determine the maximum-tolerated dose of accelerated hyperfractionated conformal radiotherapy (RT; 1.6 Gy bid) for unresectable locally advanced lung cancer (IIB to IIIA/B) following induction carboplatin/paclitaxel (C/T) or carboplatin/vinorelbine (C/N).

Methods

Induction chemotherapy, C/T or C/N, was followed by escalating doses of conformally-planned RT (73.6 to 86.4 Gy in 6.4-Gy increments). Concurrent boost methods delivered 1.6 and 1.25 Gy bid to the gross and clinical target volumes, respectively.

Results

Between November 1997 and February 2002, 44 patients were enrolled (median age, 59 years; 59% male; stage III, 98%; median tumor size, 4 cm). Thirty-nine patients completed induction chemotherapy: 19 had a partial response, seven progressed, 15 had no response, and three were not assessable. Chemotherapy-associated toxicities were similar in the two chemotherapy groups. The incidence of grade ≥ 3 RT-induced toxicity was 1/13, 2/14, and 4/12 at 73.6, 80, and 86.4 Gy, respectively, thus defining the maximum tolerated dose at ≈ 80 Gy. Toxicities were in both lung and esophagus and were similar in the two chemotherapy arms. With a median followup of 34 months in the survivors, the actuarial 2-year survival was 47%, the median survival was 18 months. Fifteen patients had tumor relapse: 5 local failures in the high-dose volume, 2 regional failures outside of the high-dose volume, and 8 distant metastases.

Conclusion

High-dose conformal twice-daily radiation therapy to approximately 80 Gy appears tolerable in well-selected patients with unresectable lung cancer following either C/T or C/N. Dose-limiting toxicities are mainly pulmonary and esophageal.

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INTRODUCTION

Radiation therapy (RT) alone cures approximately 10% and 25% of patients with locally advanced and medically unresectable non-small-cell lung cancer (NSCLC), respectively.¹⁻⁵ The addition of sequent-

ial⁵⁻¹⁰ or concurrent chemotherapy^{11,12} with definitive RT modestly improves survival. Concurrent chemotherapy appears more efficacious than sequential therapy.^{13,14} High-dose^{6,15-20} and/or intensified/shortened^{21,22} RT programs have been proposed. Shortening the overall

treatment time improves outcome for NSCLC,²² small-cell lung cancer,²³ and head and neck cancer.^{24,25}

Conventional dose RT for unresectable cancer is approximately 60 to 66 Gy in a 2-Gy fraction. Three-dimensional (3D) RT planning tools provide an increased knowledge of the location of radiographically identifiable targets and normal structures. Such software facilitates better conformation of the therapeutic dose to the target. Since normal tissue complications are related to irradiated volume, there is growing interest in high-dose, 3D, conformally delivered RT.^{16,26,27} The maximum safe dose in this setting is not known.

The Carolina Consortium formulated a phase I study to deliver aggressive high-dose therapy for patients with medically unresectable and locally advanced NSCLC. Sequential chemotherapy-RT was chosen because of concerns that the severe acute reactions associated with concurrent therapy would prevent delivery of the proposed high-dose RT. During study design, there were no randomized data suggesting superiority of concurrent over sequential therapy. A previously tested, accelerated, hyperfractionated RT technique (1.6 Gy bid)^{15,28} was used to avoid excessively long treatment times. We herein report the results of our phase I study to determine the maximum-tolerated dose (MTD) of twice daily external beam RT for patients with locally advanced/unresectable NSCLC following induction chemotherapy.

METHODS

Pretreatment Evaluation and Eligibility

Adults with histologically confirmed NSCLC, medically unresectable or inoperable stage IIB, IIIA, or IIIB (1997 American Joint Committee on Cancer), Eastern Cooperative Oncology Group performance status 0 to 2, no serious illness preventing informed consent, no chemotherapy within 5 years, and no prior thoracic RT were eligible. Required initial laboratory values included granulocytes > 1,800/mL, platelets > 100,000/mL, creatinine < 2.0 mg/dL, and bilirubin < 1.5 mg/dL. A prior malignancy was not an exclusion criteria. Patients with a prior lung cancer diagnosis were eligible if their disease-free interval was ≥ 3 years. Patients with other malignancies were eligible if their disease-free interval was ≥ 5 years, with exceptions made by the principal investigator if the prior malignancy was felt unlikely to impact the patient's outcome. Prior nonmelanoma skin cancer and cervical carcinoma-in-situ were acceptable, regardless of interval from diagnosis.

Pretreatment evaluation included history, physical examination, informed consent, and evaluation of performance status. Laboratories included CBC, platelets, creatinine, liver functions, electrolytes, and pulmonary function tests including forced expiratory volume in one second (FEV1) and diffusion capacity. Radiographs included chest computed tomography (CT) scan, including the liver and adrenals, chest x-ray, bone scan, and brain CT or magnetic resonance imaging. Staging positron emission tomography (PET) was done in 13 of 44 enrolled patients. Bron-

choscopy was typically performed to assess tumor extent and obtain tissue in patients with central tumors. Mediastinoscopy was performed in 25 of 44 enrolled patients (nine, eight, and eight of the patients at each dose level, respectively), typically to confirm the extent of mediastinal nodal involvement and/or to obtain tissue for diagnosis. All patients were evaluated by a thoracic surgical oncologist, and/or a pulmonologist, and/or discussed at a multidisciplinary tumor board to deem them nonoperative candidates.

Patient eligibility was assessed before enrollment by a medical and radiation oncologist. Tumor anatomy was reviewed to assess if the RT portals/dose respected normal tissue dose/volume limits (defined in Radiation Therapy). The post-RT predicted FEV1; the pre-RT FEV1 \times percentage of lung receiving < 35 Gy had to exceed 0.8 L. This metric is based on the assumption that doses greater than ≈ 30 to 35 Gy are often associated with regional lung injury. Thus, the fraction of lung that receives less than ≈ 35 Gy may be assumed to retain its function. There is surgical data suggesting that postoperative FEV1 can be predicted using this approach (postoperative FEV1 = preoperative FEV1 [percent of lung remaining postresection]).²⁹⁻³³ Thus, an analogous approach was taken in this study, with 0.8 L used as a minimal acceptable post-RT FEV1. Patients with a predicted FEV1 less than 0.8 were permitted if there was a central tumor believed to be negatively impacting the patient's pulmonary function.³⁴ At the time that this study was initiated, there were no well-established guidelines regarding safe dose/volume parameters for the lung. Ineligibility criteria included: involved supraclavicular nodes, contralateral hilar disease, or an exudative/bloody/cytologically positive pleural effusion. Written informed consent was required. This protocol was approved by the institutional review boards of all participating institutions.

Treatment Overview

Patients received induction chemotherapy, either carboplatin/paclitaxel (C/T) or carboplatin/vinorelbine (C/N), followed by escalating doses of conformally planned RT (Fig 1). The first seven patients (group 1) received C/T plus 73.6 Gy. While these patients were observed for RT-associated toxicity, the next seven patients (group 2) received C/N plus 73.6 Gy. If the acute RT-associated toxicity in group 1 was acceptable (defined in Objectives and Statistics), the next cohort of seven patients (group 3) received C/T plus 80 Gy. If toxicity in group 2 was acceptable, group 4 received C/N plus 80 Gy. The induction regimen thus alternated between consecutive patient groups. In effect, two separate phase I dose escalation studies with differing induction chemotherapy were

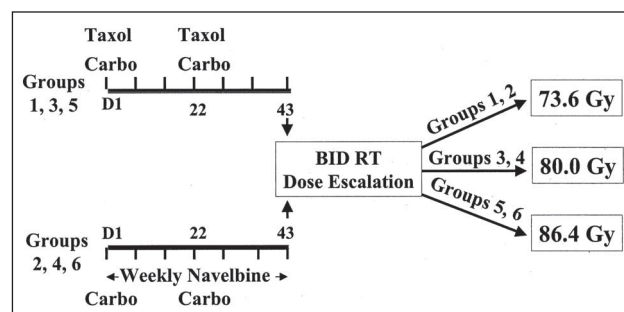


Fig 1. Overall treatment schema. Dose of carboplatin in groups 1 and 2 is area under the concentration curve (AUC) = 7; in groups 3, 4, 5, and 6, AUC = 6. Paclitaxel dose in groups 1, 3, and 5 is 225 mg/m²; vinorelbine dose in group 2 is 30 mg/m², and in groups 4 and 6, 20 mg/m².

combined into a single protocol (Table 1). By the time that one group was full, enough time had typically passed for toxicity evaluation in the prior group. Thus, the protocol usually remained open, with minimal suspensions for patient cohort maturation (eg, group 3 matured while group 4 was enrolling). This design facilitated comparison of the two chemotherapy regimens.

Induction Chemotherapy

Two cycles of either C/T or C/N were given as follows during weeks 1 to 6: carboplatin was dosed using the Calvert equation at an area under concentration curve (AUC) of 7.0 mg/mL/min dose = AUC × (glomerular filtration rate [GFR] + 25). The GFR was estimated by the Cockcroft-Gault formula: $GFR = ([140 - \text{age}] \times \text{weight in kg}) / (72 \times \text{serum creatinine})$ for males; 15% value reduction for females. The maximum allowable creatinine clearance for males and females was 150 and 130 mL/min, respectively.

Induction Carboplatin and Paclitaxel

Induction carboplatin and paclitaxel was given as follows: paclitaxel 225 mg/m² intravenously (IV) over 3 hours on days 1 and 22, and carboplatin AUC 7.0 mg/mL/min (reduced to 6.0 based on acute toxicity seen in the first 13 patients; see Results) IV over 30 minutes to 1 hour on days 1 and 22. Premedications typically included dexamethasone 20 mg orally (PO) 12 hours and 6 hours before paclitaxel, or 20 mg dexamethasone IV 30 minutes before paclitaxel; diphenhydramine 50 mg IV 30 minutes before paclitaxel, cimetidine 300 mg or ranitidine 50 mg IV 30 minutes before paclitaxel, and ondansetron 24 to 32 mg IV or granisetron 2 mg PO 30 minutes before paclitaxel, repeated as needed.

Induction Carboplatin and Vinorelbine

Induction carboplatin and vinorelbine was given as follows: vinorelbine 30 mg/m² IV push over 6 minutes on days 1, 8, 15, 22, 29, and 36, and carboplatin AUC 7.0 mg/mL/min (reduced to 6.0 based on acute toxicity seen in the first 13 patients; see Results) IV over 30 minutes for 1 hour on days 1 and 22. Granulocyte colony-stimulating factor (G-CSF) 100 µg subcutaneous beginning 24 hours after chemotherapy and administered daily (except on chemotherapy treatment days). Premedications typically included ondansetron 24 to 32 mg IV or granisetron 2 mg PO, dexamethasone 10 mg IV 30 minutes before carboplatin, and prochlorperazine 10 mg PO before vinorelbine.

A post-enrollment review of the first 13 patients revealed two of seven on the C/T and four of six on the C/N arm had chemotherapy-associated neutropenia. Therefore, the carboplatin AUC was reduced to 6 mg/mL/min, and the vinorelbine dose was reduced to 20 mg/m². With these dose reductions, the G-CSF was no longer necessary.

Radiation Therapy

Treatment planning. Patients underwent CT in the treatment position prior to chemotherapy (scan thickness ≤ 5 mm). A radiotherapy planning CT scan in a customized immobilization cradle was performed during week 6 and the chemotherapy response was assessed (see criteria in Objectives and Statistics). RT planning was performed during week 6 and treatment commenced week 7. The prechemotherapy and postchemotherapy scans were registered using image fusion tools in PLUNC (University of North Carolina, Chapel Hill, NC), based on visual inspection, to facilitate field design based on the prechemotherapy tumor volumes. If there was an obvious shift of thoracic structures due to chemotherapy response, appropriate adjustments were made as indicated by the treating physician. It was occasionally not possible to adhere strictly to the fields based solely on the prechemotherapy volumes because of anatomic changes that evolved between the two scans and inaccuracies in the image registration process. In these cases, treatment based on the postchemotherapy target volumes was considered as an alternative. In practice, the degree of tumor shrinkage was modest so these issues were not paramount. In all cases, all initially involved sites of disease were considered gross tumor volume (GTV). For parenchymal disease, the prechemotherapy volumes were included in the GTV. For nodes that responded to chemotherapy, all initially involved nodal groups were considered GTV, but the postchemotherapy nodal sizes were used in shaping the fields. The rationale for this approach is our observation that parenchymal disease assessed microscopically after chemotherapy often have multiple islands of tumor extending throughout the initially involved region. Conversely, enlarged mediastinal nodes typically displace adjacent normal structures laterally, and when they regress, the normal tissue moves back towards its normal position.

The target structures were defined by the physician, and normal structures were typically outlined by the dosimetrist, and then verified by the physician. The esophagus was contoured from the thoracic inlet through the diaphragm. Treatment planning at all centers was done using PLUNC software.^{35,36} Doses were calculated and reported to reflect tissue inhomogeneities. Quality assurance port films were taken weekly during treatment.

Volumes. The International Commission on Radiation Units definitions were used: GTV = gross radiographic disease including the primary and nodes; CTVg = GTV + 0.5 cm margin via 3D expansion; PTV2 = CTVg + 0.5 cm margin via 3D expansion = GTV plus 1 cm margin; CTVe = clinical target volume for electively irradiated nodal sites; and PTV1 = union of PTV2 + CTVe.

Mediastinal nodes were generally considered abnormal if their short axis was ≥ 1 cm, and/or if they were involved on PET scan. Nodal groups positive by mediastinoscopy were included as part of the GTV even if they were radiologically negative. The medically inoperable patients were usually node-negative and the degree of elective nodal irradiation was limited by their comorbidities, in particular, their lung function. For patients with evidence of mediastinal/hilar involvement, CTV typically included all structures located medial to the lungs and anterior to the esophagus/vertebral body. The mediastinal borders extended inferiorly to 3 cm below the carina and superiorly to the level of the inferior clavicular heads. Laterally, the superior vena cava and aorta were included. The contralateral hilum and heart were excluded.

The treated volume was the PTV + 5 mm of geometric margin for geometric penumbra, such that the PTV receives

Table 1. Definition of Treatment Groups

| Radiation Dose (Gy) | Induction Chemotherapy | |
|---------------------|------------------------|-------------------|
| | Carbo/Paclitaxel | Carbo/Vinorelbine |
| 73.6 | Group 1 | Group 2 |
| 80.0 | Group 3 | Group 4 |
| 86.4 | Group 5 | Group 6 |

Abbreviation: Carbo, carboplatin.

essentially 100% of the prescribed dose. Megavoltage \geq 6MV beams were used.

Doses. The PTV1 (gross disease + electively treated sites) received 1.25 Gy bid, minimum 6 hours between fractions. Immediately following each fraction, the PTV2 (gross disease alone) received an additional 0.35 Gy; thus, the PTV2 received 1.6 Gy bid (concurrent boost technique).

For all patients, PTV1 received 45 Gy. Dose escalation refers only to the PTV2. Typically, PTV1 was treated via anterior-posterior fields, with off-cord oblique concurrent boost fields. Following the initial 57.6 Gy to PTV2, an additional dose was delivered to PTV2 at 1.6 Gy bid to total doses as shown. This escalation scheme follows the Radiation Therapy Oncology Group (RTOG) dose escalation principles,³⁷ wherein doses are increased in \approx 10% increments.

Normal tissue dose/volume limits. The spinal cord typically received \leq 48 Gy during the initial 45 Gy prescribed to the CTV. Modest additional dose was delivered to the cord due to scatter/penumbra from the off-cord portals. The entire heart was restricted to less than 40 Gy, and no more than 50% of the heart was to receive 60 Gy. A maximum dose of 70 Gy to the chest wall was recommended. Care was taken to limit overlap of the entrance/exit regions of the oblique and anterior/posterior fields. Nonaxial beams were often helpful in this regard. The full circumference of the esophagus was not to receive beyond 73.6 Gy to a length more than 6 cm. Based on our evolving clinical experience with esophageal toxicity, attempts were made to limit the full esophageal circumference to 60 Gy in most patients. The esophageal dose restriction excluded many patients with tumors that were adjacent to, or surrounded, the esophagus.

Objectives and Statistics

The primary objective was to define the MTD of 3D-delivered twice-per-day RT in patients with locally advanced/unresectable NSCLC following induction chemotherapy. The MTD was determined separately for the two different induction chemotherapy regimens. The secondary objectives were to compare the toxicities of the two induction chemotherapies and to assess the tumor response, survival, and sites of relapse following such aggressive therapies. Local control, progression-free, and overall survival curves were generated using actuarial methods. Patients were censored from the local control analysis at the time of death. All patients who died had evidence of disease at death. No patient died of an intercurrent illness.

Grading RT toxicity. A modified Soma-Lent system³⁸ was used (Table 2). When this protocol was initiated, this toxicity system was being suggested as an alternative to the more-

commonly used systems. Although initially designed to report late effects, this scale was used to report both acute and late toxicities. Toxicities occurring during or after RT are considered in determining the MTD. Toxicities occurring within 6 weeks of completion of RT are defined as acute, versus late for others.

Definition of MTD. The MTD of radiotherapy is based on the experiences of all patients who receive radiation treatment. Patients who left the study before completing RT (other than for toxicity reasons) were not considered in MTD determination. Chemotherapy toxicity was recorded using the Cancer and Leukemia Group B toxicity scoring system. Chemotherapy toxicity was not considered in determining the MTD of radiotherapy.

The MTD was defined as the highest radiation dose at which no more than one patient developed a grade \geq 4 toxicity and no more than two patients experienced a grade \geq 3 toxicity. Patients needed to have a minimum of 6 weeks follow-up after completion of radiation treatment to be assessable. Toxicity monitoring continued beyond the initial 6-week follow-up, and any subsequent toxicity was to be used to determine the MTD. Thus, both acute and late RT-associated toxicities were considered in defining the MTD. We recognize that 6 weeks was a short interval to assess for both acute and late RT-associated toxicity. In practice, however, by requiring a minimum 6-week evaluation interval for a given cohort, all patients in that cohort were followed for more than 6 weeks. Given the rate of accrual to the protocol, most patients had been observed for many months before their cohort's toxicity was evaluated. This approach thus appears to have been reasonable, as all but one of the severe toxicities occurred within 3 months after RT. Additional severe events may be noted with longer follow-up.

Seven patients were enrolled into each group, with the hopes of having \geq five assessable patients. Only one toxicity (highest grade) was counted per patient. If a patient group included one grade 3 and one grade 4 toxicity, the protocol called for another five patients to be enrolled at that dose level. Only one grade 3 (and no grade 4 to 5) toxicities would be allowed in these five patients for that dose level to be considered acceptable.

Secondary analyses. Fisher's exact tests were used to compare the frequency of grade \geq 3 toxicities in the C/T versus C/N groups. Cox regression was used to jointly examine the effect of chemotherapy and radiation dose on survival and time to clinical failure. Survival is defined as the time between initiation of protocol and death or last follow-up. Time to clinical failure is defined as the time between initiation of protocol treatment and failure (disease progression, relapse).

Table 2. Toxicity Scoring System

| Site | Grade 3 | Grade 4 |
|-----------------------|---|--------------------------------|
| Lung | | |
| Symptom | | |
| Dyspnea | Breathless at rest, limits all activities | Prevents any physical activity |
| Chest pain/discomfort | Persistent and intense | Refractory and excruciating |
| Esophagus | | |
| Symptom | | |
| Dysphagia | Able to take liquids only | Totally unable to swallow |
| Pain | Persistent and intense | Refractory and excruciating |
| Stricture | \leq 1/3 normal diameter | Complete obstruction |

This protocol was developed before Response Evaluation Criteria in Solid Tumors criteria. The response to chemotherapy was assessed using two methods. First, the bi-dimensional product of the visible tumor on pre- and postchemotherapy CT images was computed. A reduction $\geq 50\%$ in this metric was termed a partial response. A more than 25% increase in this metric or the development of new lesions was considered progressive disease. A complete response was the resolution of the entire radiologic abnormality. A decrease of less than 50% or an increase less than 25% was scored as stable disease. Second, the 3D volumes of the GTV were computed in 31 patients where the tumor volume was believed readily apparent (ie, minimal associated atelectasis) on the pre- and postchemotherapy CT images. For these, the actual volumetric reductions were recorded and considered as a continuum.

RESULTS

Patients

From November 1997 through February 2002, 44 patients were enrolled on the study (Table 3). Over 50% of patients had a good performance status, and most had stage III disease as a result of mediastinal adenopathy. The demographics were similar in the C/T and C/N arms. The modest accrual rate was due to the dose/volume constraints that limited patient eligibility, competing clinical protocols, and enrollment interruptions due to protocol modifications/data review. Further, towards the end of the study period, physician enthusiasm for the study declined due to mounting data supporting concurrent, rather than sequential, chemotherapy, and recognition of the RT-associated toxicities. In fact, only one patient was enrolled between August 2001 and February 2002, during which time the investigators contemplated closure of the study.

Induction Chemotherapy

Patients were assigned to treatment cohorts as outlined in Table 1: 21 and 23 patients to the C/T and C/N arms, respectively. The acute tolerance and response rates to the induction chemotherapy regimens are outlined in Table 4. Sixty-four percent of patients experienced grade 3 to 4 chemotherapy-associated toxicity, mostly neutropenia. This included six of the first 13 patients enrolled, thus prompting an adjustment to the chemotherapy dosing (see Methods). Aside from the rates of gastrointestinal reactions, the chemotherapy-associated toxicities were similar in the two groups. All toxicities were transient and there were no chemotherapy-related deaths. The response rates and the percentage of volume reductions were similar in the two chemotherapy arms.

Radiation Therapy and MTD Determination

Of the initial 44 patients, 39 started the high-dose RT program. Of these, three patients progressed during RT, and 36 received ≥ 73.6 Gy. The incidence of grade ≥ 3 RT-associated toxicity is shown in Table 5.

Table 3. Patient Demographics

| | No. of Patients | % |
|--|-----------------|----|
| Age, years | | |
| Median | 59 | |
| Range | 39-87 | |
| Sex, male | | 59 |
| T stage | | |
| T1 | 6 | 14 |
| T2 | 18 | 41 |
| T3 | 8 | 18 |
| T4 | 8 | 18 |
| Tx | 4 | 9 |
| N stage | | |
| N0 | 5 | 11 |
| N1 | 0 | 0 |
| N2 | 32 | 73 |
| N3 | 7 | 16 |
| TNM stage | | |
| IIB | 1 | 2 |
| IIIA | 28 | 64 |
| IIIB | 15 | 34 |
| Karnofsky performance status | | |
| 90-100 (ECOG 0) | 25 | 57 |
| 70-80 (ECOG 1) | 18 | 41 |
| 50-60 (ECOG 2) | 1 | 2 |
| Pathology | | |
| Squamous cell | 15 | 34 |
| Adenocarcinoma | 14 | 32 |
| Large cell | 5 | 11 |
| Carcinoma, NOS | 10 | 23 |
| Maximum tumor size on diagnostic imaging, cm | | |
| Median* | 4 | |
| Range | 0.6-11 | |

Abbreviations: TNM, tumor-node-metastasis; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.
*Unknown in three patients.

There were two grade 4 events following C/T + 86.4 Gy, thus defining 80 Gy as the MTD. Following C/N + 86.4 Gy, there was one severe grade 4 and one grade 3 lung toxicity. These two events did not breach the protocol thresholds defining the MTD. However, the investigators elected to close the C/N arm to further enrollment due to several factors. First, the grade 4 toxicity in the C/N + 86.4 Gy arm was severe. The affected patient had dramatically reduced lung function, essentially limiting all mobility. Second, the investigators were skeptical that the type of induction chemotherapy would dramatically alter the tolerance of subsequent high-dose RT, and thus the presence of two grade 4 events in the C/T arm caused concern. Considering both chemotherapy groups together, the development of grade 4 toxicity in three of 12 patients seemed too high to warrant further treatment at that dose. Third, at about the time that these toxicities were observed, data suggesting that concurrent chemotherapy/RT might be superior to

Table 4. Induction Chemotherapy: Toxicity and Response Rates (N = 44)

| Endpoint | Regimen | |
|---|------------------------------|-------------------------------|
| | Carbo/Paclitaxel (n = 21) | Carbo/Vinorelbine (n = 23) |
| Hematologic toxicity \geq grade 3, % | | |
| Neutropenia | 48 | 52 |
| Thrombocytopenia | 5 | 4 |
| Anemia | 0 | 9 |
| Nonhematologic toxicity \geq grade 3, % | | |
| Hepatic | 5 | 0 |
| Gastrointestinal | 19 | 0 |
| Infection/fever | 10 | 13 |
| Alopecia | 5 | 4 |
| Pulmonary | 9 | 0 |
| Myalgia/arthralgia | 14 | 0 |
| Cardiac | 9 | 4 |
| Neurologic | 5 | 0 |
| Other | 14 | 13 |
| Any \geq grade 3 toxicity | 62 | 65 |
| Percent of patients with chemotherapy | | |
| Reduction | 14 | 52 |
| Delay | 14 | 30 |
| Tumor volumes/response | | |
| Initial tumor volume, cc | | |
| Median | 57.1 | 53 |
| Range* | 5-338 | 2.6-279 |
| Post-chemo volume, cc | | |
| Median | 38.5 | 23 |
| Range* | 5-291 | 2.25-200 |
| Volume reduction, % | | |
| Median | 35.2 | 36 |
| Range* | 0-72 | 0-57 |
| Off-study | | |
| No. of Patients | 1 | 4 |
| % | 5 | 17 |
| Clinical response based on bidimensional product, % | | |
| CR | 0 | 0 |
| PR | 43 | 45 |
| SD | 43 | 26 |
| PD | 14 | 22† |

Abbreviations: Carbo, carboplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*Data available in 18 and 13 patients in the carbo/paclitaxel and carbo/vinorelbine arms, respectively.

†One patient with unknown response.

sequential chemotherapy/RT was becoming available.^{13,14} Fourth, the relatively short minimum follow-up interval used in our study design mandated caution.

Detailed information regarding the incidence of RT-associated toxicity in the entire group of 39 patients is shown in Table 6. The data from the two chemotherapy arms are combined. Due to the small number of events, and the unique treatment delivered, each grade 3/4 toxicity is described (Table 7). An in-depth analysis relating toxicity to dose/volume parameters was not conducted and is beyond the

Table 5. Incidence of RT-associated Grade \geq 3 Toxicity

| Dose Level | No. of Patients Enrolled | No. of Patients Assessable for RT-Induced Toxicity | No. of Patients | |
|------------|--------------------------|--|------------------|-------------------|
| | | | Carbo/Paclitaxel | Carbo/Vinorelbine |
| 73.6 Gy | 15 | 13 | 0/7 | 1/6*§ |
| 80 Gy | 14 | 14 | 1/7*§ | 1/7*§ |
| 86.4 Gy | 15 | 12 | 2/6†‡ | 2/6† |
| Total | 44 | 39 | 3/20 | 4/19 |

Abbreviations: RT, radiation therapy; Carbo, carboplatin.

*Acute esophageal toxicity.

†Late lung toxicity.

‡Acute and late esophageal toxicity.

§The denominator represents all of the patients that initiated RT in that group. One patient in each of these groups did not reach the intended dose. The patient enrolled to the 73.6-Gy arm was the patient with the reported severe toxicity, but he only received 48 Gy (see text). The other two cases received less than the prescribed dose (69.6 and 65.2 Gy) due to general overall decline in their health without a reportable toxicity.

scope of the current work. None of the grade \geq 3 toxicities occurred in the node-negative patients (ie, those whose GTVs typically would not have included much of the mediastinum).

Patient Outcomes

The disease-related outcomes for all patients enrolled and for various subgroups are summarized in Figures 2 through 4 and Table 8.

DISCUSSION

This study demonstrates that high-dose twice-daily RT to \approx 80 Gy can be safely delivered to selected patients with locally advanced/unresectable NSCLC following induction chemotherapy. Doses of \approx 86 Gy appear to be associated with a higher rate of severe reactions. Dose-limiting toxicities were both pulmonary and esophageal. RT-induced lung injury was initially considered the primary risk for our patients. Relatively strict dose/volume limits were defined for lung, with less strict esophageal guidelines. Our three initial toxicities were esophageal. Based on our experiences with RT-induced esophageal injury here and elsewhere,³⁹ stricter dose/volume guidelines were applied to the esophagus for later patients. The later patients experienced both lung and esophageal toxicities. With careful 3D-based conformal techniques, high-dose RT can be safely delivered to many patients. However, our observations may not be widely applicable since the dose/volume constraints limited enrollment to patients with relatively favorable tumor geometries and pulmonary function.

A relatively short 6-week minimum follow-up duration was required for escalation to the next dose level in this protocol. The time between completing RT and the onset of grade 3 to 4 toxicity was 0 (developed during RT) to 5

Table 6. Number of Grade 2, 3, and 4 RT-Associated Toxicities

| Toxicity Type | 7360 (n = 13) | | | 8000 (n = 14) | | | 8640 (n = 12) | | |
|------------------|---------------|---------|---------|---------------|---------|---------|---------------|---------|---------|
| | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 |
| Acute esophageal | 3 | | 1 | 9 | 2 | | 1 | 1* | |
| Acute lung | | | | 2 | | | 2 | | |
| Skin | 1 | | | 1 | | | 1 | | |
| Other | 2 | | | 1 | | | 1 | | |
| Late dyspnea | | | | | | | | 1 | 2 |
| Late esophagus | | | | | | | | | 1* |

NOTE. Thirty-nine patients started RT, and 36 completed the planned RT. These data include the three patients who did not complete RT because of toxicity or progression during RT. Does not include five patients who progressed during chemotherapy. Patients experiencing more than one type of toxicity are listed for each toxicity.

Abbreviation: RT, radiation therapy.

*This is one patient who progressed from grade 3 acute esophagus to grade 4 late esophageal injury.

months. No patient presented with grade 3 or 4 toxicity at a time point beyond which that patient's cohort was deemed "tolerable", and thus no later toxicity altered the dose escalation. RT-associated pneumonitis typically manifests within a few months following RT.^{37,40-42} RT-induced acute esophagitis typically occurs during or immediately following RT. However, late dysphagia/stricture may occur \geq 1 year after RT.¹⁹ In a RTOG study, many patients manifest their toxicity, particularly nonpulmonary, beyond 6 to 12 months after RT.³⁷ Our surviving patients remain at risk for developing late toxicities.

We have treated patients to \geq 73 Gy in other studies and have noted some complications not typically seen at lower doses, such as a mediastinal fibrosis with recurrent laryngeal nerve dysfunction, bronchial/tracheal stenosis, broncho-esophageal fistula, and hemoptysis.^{15,43} In the present study, one patient treated with C/T and 86.4 Gy

experienced bronchiomalacia, a condition not typically reported following conventional doses of RT. Another patient with grade 4 lung toxicity after C/N + 86.4 Gy had a 10 \times 5-cm central right lung lesion and the high-dose volume was fairly limited to this region. His dyspnea was far out of proportion to that expected based on the volume of lung irradiated. A contrasted CT revealed narrowing and apparent obstruction of the right main pulmonary artery. A nuclear medicine lung perfusion scan revealed reduced perfusion throughout the right lung, not limited to the RT field. Bronchoscopy and PET were negative for recurrent disease. These findings are consistent with RT-induced fibrosis/occlusion of the right hilar vasculature, again a condition not seen with conventional dose RT. Other unexpected morbidities are likely as doses are increased further.

The University of Michigan (Ann Arbor, MI) reported on 81 patients treated to 63 to 102.9 Gy at 2.1 Gy fractions.¹⁶

Table 7. Details of Patients With Toxicity

| Patient No. | Treatment Arm | Toxicity | Outcome |
|-------------|---------------|---|--|
| 1 | 73.6 Gy C/N | Progressive grade 4 esophagitis during RT. Treatment stopped at 48 Gy. Subsequent CT scan with progressive subcarinal adenopathy and might have been exacerbating the symptoms. | Dead of disease 3 months after RT |
| 2 | 80.0 Gy C/T | Dysphagia by the end of RT (grade 3). Persisted for \geq 18 months. Barium swallow with 80% narrowing of esophagus, but patient able to eat solids. | Alive, NED 4 years after Tx |
| 3 | 80.0 Gy C/N | Esophagitis (grade 3) at the end of RT. Resolved symptoms by 1 month post-RT. | Alive, NED, no symptoms 3.5 years after Tx |
| 4 | 86.4 Gy C/T | Progressive dyspnea starting 3 months post-RT (grade 3). Progressed to grade 4 at 5 months. Bronchoscopy revealed narrowed bronchus without evidence of tumor. | Received brain RT for metastases 8 months post-RT; alive 3 years after Tx; resolved pulmonary symptoms |
| 5 | 86.4 Gy C/T | Pain with swallowing starting 1 month post-RT (grade 3), progressed to grade 4 at 5 months. | Developed metastases and died 10 months post-RT |
| 6 | 86.4 Gy C/N | Dyspnea starting 5 months post-RT (grade 3), then progressing to grade 4 at 8 months. | Alive with persistent dyspnea 18 months post-RT |
| 7 | 86.4 Gy C/N | Grade 3 pneumonitis 3 months post-RT. Better with steroids by 7 months. | Alive with mild chronic dyspnea 12 months post-RT |

Abbreviations: C/N, carboplatin/vinorelbine; RT, radiation therapy; CT, computed tomography; C/T, carboplatin/paclitaxel; NED, no evidence of disease; TX, treatment.

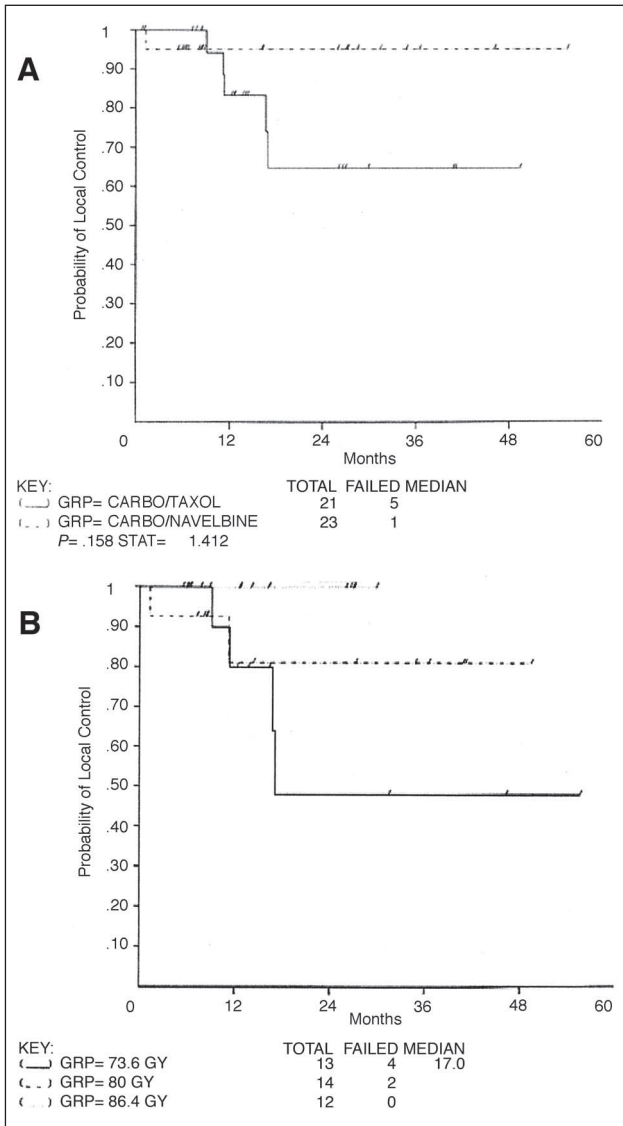


Fig 2. Actuarial local/regional control for patients enrolled onto the (A) carboplatin/paclitaxel (Taxol) and carboplatin/vinorelbine (Navelbine) arms and (B) assigned to the different dose levels.

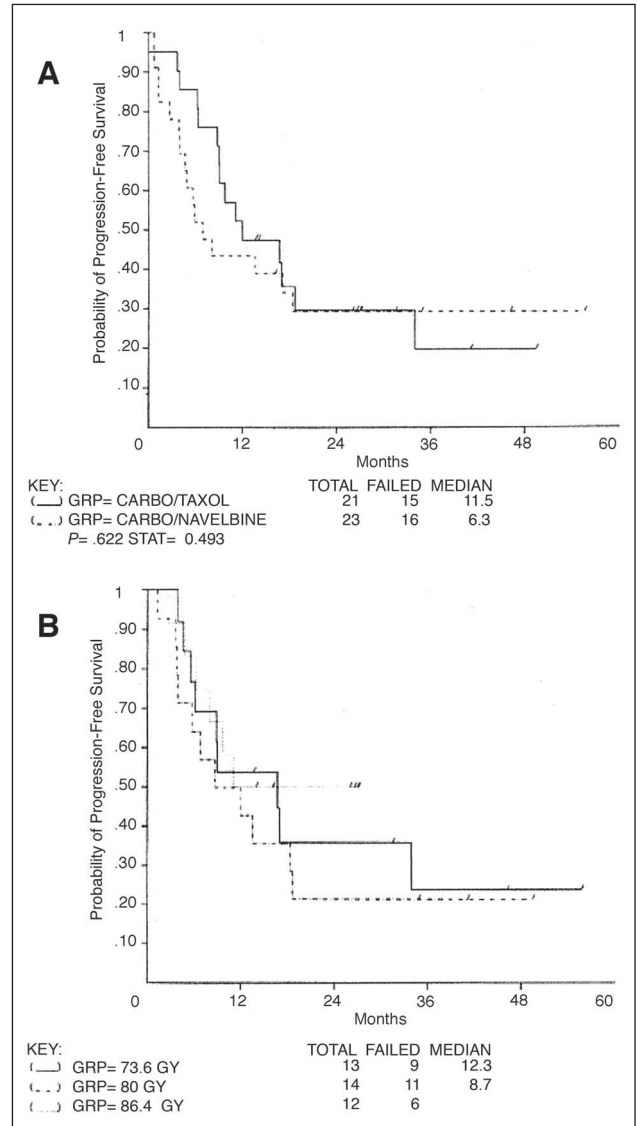


Fig 3. Progression-free survival for patients enrolled onto the (A) carboplatin/paclitaxel (Taxol) and carboplatin/vinorelbine (Navelbine) arms and (B) assigned to the different dose levels.

The total dose was determined based on the volume of normal lung that was to be irradiated. They do not report unusual complications. Several factors may explain the differences between their observations and ours. First, they treated patients with single daily fractions of 2.1 Gy versus 1.25 to 1.6 Gy bid as used in our study. The latter will clearly increase acute normal tissue reactions and may increase consequential late reactions resulting from a severe acute reaction. The shorter interfraction interval (6 and 18 hours) leaves less time for repair of sublethal damage and will increase normal tissue effects. Chemotherapy was used in all of our patients, but in only a minority of the Michigan patients; however, they did not note an increased rate of toxicity in their patients receiving chemotherapy. Lastly,

only one of our patients had stage I to II disease, versus 27% with early stage disease in the Michigan study. Since the prescribed dose in the Michigan study was based on the irradiated lung volume, many of the patients in the very high-dose groups had small/peripheral tumors (J. Hayman, personal communication, November 2003).

Toxicities following high-dose/accelerated RT for NSCLC have been reported (Table 9). Methodologic differences between the studies make comparisons problematic. Nevertheless, all studies report that most patients do not suffer a severe toxicity. Given the poor prognosis of unresectable disease with conventional therapies, the modest rate of severe toxicities supports the continued study of dose escalation. However, the reported toxicity rates are typically

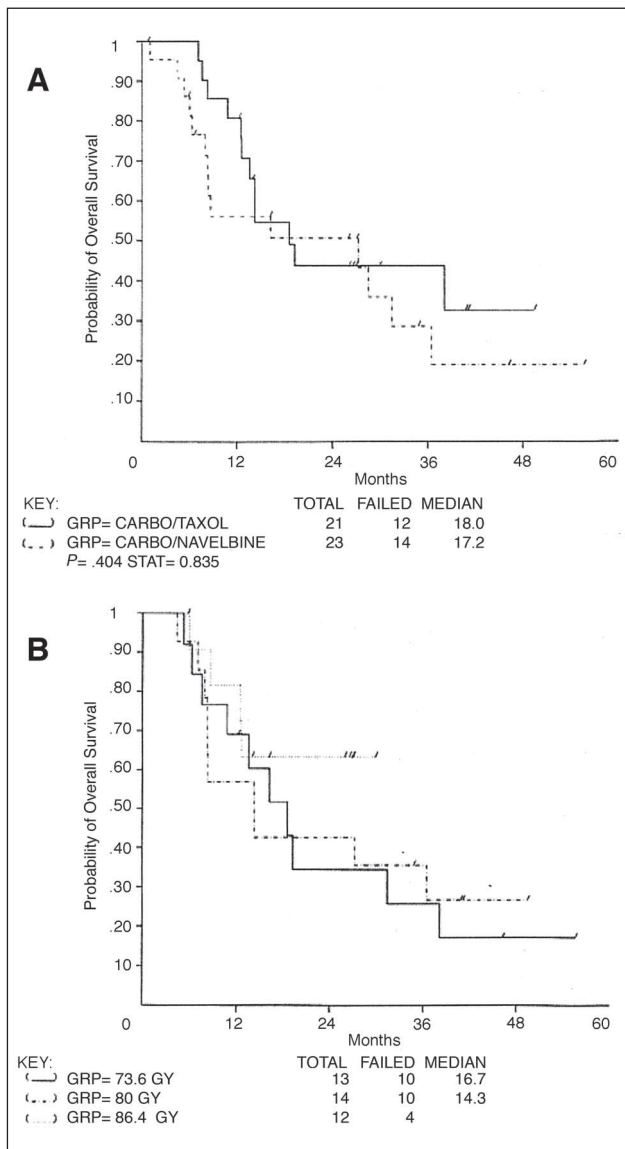


Fig 4. Overall survival for patients enrolled onto the (A) carboplatin/paclitaxel (Taxol) and carboplatin/naavelbine (Navelbine) arms and (B) assigned to the different dose levels.

crude and actuarial calculations would certainly yield higher rates.

We used twice-daily fractionation to reduce the impact of tumor growth during RT. Several randomized studies demonstrate that shortening the overall treatment time improves outcome for rapidly proliferating tumors such as lung and head/neck cancers.²¹⁻²⁴ These approaches, however, tend to increase the toxicity associated with acutely responding tissues, such as the esophagus. Thus, the studies in Table 9 using multiple fractions per day^{15,16,18,19,22,26,37,43-45} generally report higher rates of esophagitis than do the studies using once-per-day fractionation.

The volume of esophagus irradiated markedly affects the risk of esophagitis.⁴⁶ This, in turn, is greatly influenced

by the decision to electively treat, or not to treat, the radiologically normal mediastinal lymph nodes. Studies in Table 9, which include elective nodal irradiation (references^{22,39} and present study), typically have higher rates of esophagitis than do studies that omit elective nodal RT.^{16,19,26} The Memorial Sloan-Kettering Cancer Center (New York, NY) study¹⁸ initially included, and then omitted, elective nodal RT. We have been using elective nodal irradiation because of the high risk of microscopic spread to regional nodes in patients with locally advanced disease. As our ability to image targets improves, as a result of tools such as PET, the rationale for elective nodal irradiation is certainly reduced. The risk of isolated nodal failures in patients not receiving elective nodal RT has been reported to be low.^{16,26,47} While this observation is encouraging, it likely is possible for tumor deposits in regional nodes to remain subclinical, yet still be a source of distant dissemination. The majority of patients die of systemic disease, often before their local/regional recurrence is grossly evident. In practice, we find that portions of the radiologically normal node-bearing areas are frequently incidentally included within RT beams designed only to treat the gross target volume. As we gain additional flexibility in distributing incidental doses to surrounding nontarget tissues with tools such as intensity modulated radiotherapy (IMRT), it would seem logical, all other things being equal, to purposefully direct this incidental dose to the nodal areas at risk. A formal analysis of the toxicities and dose/volume parameters in our patients was not performed. This is beyond the scope of this study and will be addressed in the future.

We previously described chest wall/soft-tissue injury following 1.6 Gy bid to 76.3 Gy through a common skin portal.¹⁵ This problem was not seen in this study as care was taken to distribute the entrance/exit dose on the patient's skin. Significant RT-associated cardiotoxicity was not identified. However, routine cardiac assessments were not done. Such heart dysfunction⁴⁸ and resultant symptoms may have been ascribed to pulmonary dysfunction.

The number of patients in the two chemotherapy groups in our study is small, making comparisons difficult. In broad terms, the acute tolerance of the two regimens, the RT-associated toxicities, and the tumor response rates are similar in the two groups. The ideal induction chemotherapy regimen remains unclear. With regard to RT-associated toxicity, the Michigan study did not note differences in toxicity between those patients with and without induction chemotherapy.¹⁶ Anscher reported the MTD of twice-daily RT, using the same regimen used in the present study, to be 86 Gy. There was a suggestion that the use of induction chemotherapy increased the risk of toxicity, though the number of events was small and the use of chemotherapy was nonrandomized.⁴⁹

A recently published randomized trial from Japan suggests that chemotherapy concurrent with 56 Gy was modestly better than induction chemotherapy followed by

Table 8. Outcomes and Failure Patterns for Eligible Patients

| Patient/Failure Status | 7360 (n = 13) | 8000 (n = 14) | 8640 (n = 12) | Total (n = 39) |
|-----------------------------------|------------------|------------------|------------------|-------------------|
| Alive, no evidence of progression | 2 | 3 | 6 | 11 |
| Alive, local progression | 0 | 1 | 0 | 1 |
| Alive, with metastases | 1 | 0 | 2 | 3 |
| Dead, with disease, no metastases | 3 | 2 | 1 | 6 |
| Dead with metastases | 7 | 8 | 3 | 18 |
| High-dose volume | | | | |
| CR | 1 | 1 | 2 | 4 |
| PR | 5 | 1 | 1 | 7 |
| NR | 1 | 4 | 2 | 7 |
| Fibrosis | 1 | 1 | 3 | 5 |
| Progression | 5 | 6 | 2 | 13 |
| Unknown | | 1 | 2 | 3 |
| Subclinical volume | | | | |
| Failures | 4 | 2 | 0 | 6 |
| Untreated nodal volume | | | | |
| Failures | 2 | 0 | 0 | 2 |
| Distant metastases | | | | |
| Failures | 8 | 8 | 5 | 21 |

Abbreviations: CR, complete response; PR, partial response; NR, no response.

similar RT.¹³ Similarly, the RTOG reported improved outcomes following concurrent chemotherapy and once per day (qd) 60 Gy RT versus sequential chemotherapy and qd 60 Gy RT. Among concurrently treated patients, 1.2 Gy bid to 69.6 Gy was no better than qd 2 Gy to 60 Gy.¹⁴ Thus, patients who can tolerate the increased acute morbidity of concurrent therapy should receive exactly that. It is not clear if very high doses of RT can be safely delivered concurrently with chemotherapy, especially if an accelerated fractionation scheme is used. Acute morbidity appears acceptable with qd RT to 78 to 90 Gy with concurrent carboplatin, irino-

tecan, and paclitaxel.⁴³ If high-dose RT is better than conventional-dose RT, and if the use of concurrent chemotherapy limits the dose of RT that can be delivered, one would need to assess the relative benefits of these two approaches.

Additional studies are needed to better clarify the tolerance of this RT regimen. With improved understanding of the dosimetric predictors of both radiation-induced lung⁵⁰⁻⁵² and esophageal injury,⁴⁶ doses in excess of 80 Gy likely can be safely delivered to many patients with lung cancer. Newer RT delivery techniques, such as IMRT, will better enable the therapeutic dose volume to conform to the

Table 9. Incidence of Esophageal and Pulmonary Toxicity After High-Dose Radiotherapy in Non-Small-Cell Lung Cancer

| Author | Dose (Gy) | Fractionation | Elective Mediastinal Irradiation | No. of Patients | Esophageal Toxicity (%) | | Pulmonary Toxicity (%) | | |
|---------------------------|-----------|---------------|----------------------------------|-----------------|-------------------------|---------------------------|------------------------|-----------------------|---------------------|
| | | | | | Grade \geq 3, Acute | Stricture/Dysphagia, Late | Grade \geq 2, Acute | Grade \geq 3, Acute | Lung Fibrosis, Late |
| Rosenman ¹⁹ | 70-74 | 2/qd | Yes | 39 | 8 | 6 | | | |
| | 60-74 | 2/qd | Yes | 62 | 8 | | 2 | | |
| Sanders ²² | 54 | 1.5/tid | Yes | 338 | 19 | 7 | 10 | | 16† |
| Rosenzweig ^{18*} | 70.2-75.6 | 2/qd | Variable | 46 | 4 | 0 | | 15 | 9 |
| Maguire ^{15*} | ≈ 73.6 | 1.25-1.6/bid | Yes | 94 | 15 | 3 | | 3 | 17 |
| Belderbos ^{26*} | 61-87.8 | 2.25/qd | No | 55 | 0 | 0 | 13 | 5 | |
| Hayman ¹⁶ | 63-102.9 | 2/qd | Mostly no | 81 | 9 | | 6 | | 1 |
| Cox ³⁷ | 69.6-79.2 | 1.2/bid | | 638 | | | | 7 | |
| Singh ^{43*} | 60-74 | 2/qd | | 207 | 5 | 6 | | | |
| Byhardt ^{45*} | 69.6 | 1.2/bid | | 158 | 34 | 8 | | 7 | 20 |
| Current study | 73.6-86.4 | 1.25-1.6/bid | Yes | 44 | 9 | 2 | 9 | 0 | 7 |

NOTE. Some data estimated from information included in reference.
Abbreviation: qd, once per day.
*Toxicity scored by Radiation Therapy Oncology Group criteria.
†Of evaluated 2-year survivors.

GTV, thus sparing adjacent normal structures. However, IMRT may not typically reduce the average dose to the surrounding normal tissues, rather, it primarily redistributes this dose.⁵³ Thus, reducing the dose to the esophagus will likely increase dose to the lung or adjacent soft tissues (for example). Nevertheless, IMRT should provide increased flexibility and hopefully improve the therapeutic ratio of RT.

Our tumor response rates and overall survival are similar to prior reports.^{15,22} While our patient numbers are small, local control rates appear higher in the high-dose groups. However, follow-up is short and patients did not undergo bronchoscopy to assess local control. Thus, the control rates are undoubtedly overstated. Additional work is needed to better understand the utility of high-dose RT for unresectable lung cancer.

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Authors' Disclosures of Potential Conflicts of Interest

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