Split-Course Chemoradiotherapy for Locally Advanced Non-small Cell Lung Cancer

A Single-Institution Experience of 144 Patients

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Background: Concurrent chemoradiotherapy (CRT) is a standard of care in the treatment of unresectable locally advanced non-small cell lung cancer (NSCLC). At Rush University Medical Center, patients with locally advanced NSCLC are treated with split-course CRT in an attempt to maximize efficacy and tolerability. We reviewed our experience in advanced NSCLC since 1999. Subset analysis was performed on poor-risk patients.

Methods: All patients with a diagnosis of stage IIIA/IIIB NSCLC and treated with definitive split-course CRT between January 1999 and December 2008 were included in this retrospective study. The primary end point was overall survival. Poor-risk patients were defined in accordance with ongoing cooperative group trials.

Results: One hundred forty-four patients were identified, 35% stage IIIA and 65% stage IIIB. There were 52 poor-risk patients and 92 average-risk patients. Median survival for all patients was 20.4 months with an actuarial 32.1% 3-year overall survival rate. Poor-risk patients demonstrated a median survival of 22.1 months, statistically indistinguishable from the remainder of the cohort ($p = 0.21$). Acute esophagitis was mild, with a 3% rate of grade 3 esophagitis and no cases of grade 4 or 5.

Conclusions: Split-course CRT appeared effective and was delivered with a favorable toxicity profile. Poor-risk patients experienced better than expected survival. Prospective evaluation of split-course CRT must be completed before it can be considered a standard treatment option in locally advanced NSCLC.

Key Words: Treatment interruptions, Poor-risk, Locally advanced NSCLC, Split course chemoradiotherapy, Combined modality therapy

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Lung cancer is the most common source of cancer mortality in the United States, responsible for an estimated ~160,000 deaths in 2009.[1] Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer, and approximately 40% of patients with NSCLC present with locally advanced American Joint Committee on Cancer stage IIIA or IIIB disease.[2] Thoracic radiotherapy (RT) alone was the traditional standard treatment for unresectable NSCLC until evidence emerged demonstrating a benefit from the addition of chemotherapy.[3–5] Contemporary phase III trials have examined the sequencing of multimodality treatment and the value of induction chemotherapy, with evidence suggesting that concurrent chemotherapy and radiation is superior to a sequential approach.[6–8]

Median survivals ranging from 14 to 26 months have been achieved in relatively good-risk NSCLC patient cohorts.[6–12] Local and distant disease progression remains a problem afflicting the majority of patients treated with the accepted standard therapy of 60 to 63 Gy with concurrent radiosensitizing chemotherapy. Contemporary studies, such as Radiation Therapy Oncology Group (RTOG) 0617, seek to intensify treatment via an increased radiation dose, and/or by delivering more chemotherapy at a systemically active dose, but the optimal treatment regimen in good-risk patients remains uncertain.

Many patients with locally advanced disease are at higher risk, presenting with poor pulmonary reserve, poor performance status (PS), and/or pretreatment weight loss.[13] The characteristics of a "poor-risk" patient are difficult to define with precision. Classical prognostic factors associated with outcome reported by the RTOG include PS (<80 Karnofsky), pretreatment weight loss (>8%), age (>70 years), disease stage, hemoglobin level, whether or not chemotherapy was delivered, and the presence of a positive malignant effusion.[14] Poor-risk patients have not fared well when treated with concurrent chemoradiotherapy (CRT). A phase II chemoradiation trial conducted by the Southwest Oncology Group (SWOG) dedicated to the study of poor-risk patients reported disappointing results, with median progression-free survival (PFS) of 6.0 months and median overall survival (OS) of 10.2 months.[13] A Cancer and Leukemia Group B (CALGB) study in similar patients was more encouraging,

achieving a PFS and OS of 13.4 and 19.0 months respectively.[15] While treatment intensification is clearly needed to combat high rates of local and distant failure, such efforts are often hindered by the poor health of the patients. The optimal regimen for the treatment of poor-risk patients with locally advanced NSCLC remains an area of active study.

Rush University Medical Center (RUMC) has treated locally advanced NSCLC patients with a split-course CRT approach since the early 1980s in an attempt to balance treatment efficacy with morbidity in this often fragile patient population. Treatment was delivered based on the hypothesis that systemic doses of chemotherapy could mitigate the potential deleterious effects of accelerated repopulation seen with split-course RT alone. Herein, we review our experience with split-course CRT since 1999 to assess outcomes in all patients. Subset analysis was performed to specifically assess outcomes in poor-risk patients, a common patient type underrepresented in most contemporary chemoradiation trials.

METHODS

Patient Selection

Institutional Review Board approval was obtained for this retrospective study. Patients with a tissue diagnosis of NSCLC and clinical stage IIIA or IIIB who received definitive split-course CRT between January 1999 and December 2008 were identified via the RUMC tumor registry and a radiation oncology departmental database.

Pretreatment Evaluation

Before initiating the treatment, all patients were staged with chest computed tomography (CT), standard blood work, and brain imaging. A pathologic diagnosis of NSCLC was required. Mediastinal sampling and pathologic confirmation of mediastinal disease was not required for treatment or inclusion in this retrospective study. Ninety percent of patients incorporated positron emission tomography (PET) staging, and bone scans were obtained when PET imaging was unavailable. Mediastinal lymph nodes were considered involved if the standardized uptake value was greater than 2.5 or if the lymph nodes measured greater than 1 cm short-axis diameter. Thirty-five percent of patients had surgical confirmation of mediastinal disease. Patients were evaluated and managed via a multidisciplinary clinic with participating medical oncologists, radiation oncologists, and thoracic surgeons.

Treatment Regimen

The standard Rush split-course CRT regimen (Figure 1) consisted of four treatment cycles, each cycle 21 days in length. RT was delivered once daily, 180 to 200 cGy per fraction, on days 1 to 5 and 8 to 9 (or 10) to a total dose of 6000 to 6400 cGy. Chemotherapy was delivered in the form of a systemically dosed platinum doublet. Most patients received carboplatin (Paraplatin; Bristol-Myers Squibb, New York City, NY) area under the curve 4 on day 1, with either paclitaxel (Taxol; Bristol-Myers Squibb) 100 mg/m^2 on days 1 and 8 or etoposide (VePesid; Bristol-Myers Squibb) 80 mg/m^2 on days 1 to 3. After the completion of all treatment, patients underwent a chest CT approximately 4 to 6 weeks after the last fraction of RT to assess response. Patients then underwent serial imaging with chest CT every 6 to 12 weeks for the first year and every 3 to 6 months the second year.

Platinum = P
Taxol = T
RT = X

Mon	Tue	Wed	Thu	Fri
Day 1 P T X	Day 2 X	Day 3 X	Day 4 X	Day 5 X
Mon	Tue	Wed	Thu	Fri
Day 8 T X	Day 9 X	Day 10 X	Day 11 BREAK	Day 12 BREAK
Mon	Tue	Wed	Thu	Fri
Day 15 BREAK	Day 16 BREAK	Day 17 BREAK	Day 18 BREAK	Day 19 BREAK

FIGURE 1. The split-course approach illustrated. Patients receive either 7 or 8 days of radiotherapy per 3-week cycle to a total dose of 60–64 Gy.

Treatment: Radiation Techniques

Radiation technique evolved during the study period. Patients treated before 2005 received treatment with initial anterior posterior opposed fields followed by off-cord obliques, in two to four treatment phases. Most patients received elective treatment of the mediastinum during this time. Beginning in 2005, most patients were treated with at least three fields from the outset of therapy, and all fields were treated on all days. Treatment was delivered in a single phase, delivering radiation to only areas involved with disease on CT and/or PET (no elective nodal irradiation). Motion induced by respiration was assessed by fluoroscopy before 2006 and more recently by four-dimensional CT. The amount of respiratory motion was used to determine appropriate treatment margins.

Data Collection

End points included OS, defined as the interval between pathologic diagnosis and death; PFS, defined as the interval between diagnosis and evidence of any disease recurrence/progression; distant metastasis-free survival (DMFS), defined as the time between diagnosis and evidence of distant metastases; and local regional PFS (LRPFS), defined as time between diagnosis and local progression. LRPFS was deemed to have occurred when either the primary lesion or mediastinum demonstrated progressive disease on serial chest CT and/or PET. Distant failure was evidenced by imaging findings consistent with metastatic disease and/or histopathology. Clinical response was defined by Response Evaluation Criteria in Solid Tumors (RECIST).[14] Acute toxicity was assessed via review of RT on-treatment visit notes, medical oncology follow-up notes, RT completion summaries, and a review of the electronic medical record to document hematologic toxicity as well as evidence of hospital admissions during or after RT completion. Acute toxicity was scored in accordance with the Common Toxicity Criteria for Adverse