Improved Survival With Increased Time-To-Radiation and Sequential Chemotherapy After Surgery for pN2 Non–Small-cell Lung Cancer

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Abstract

Currently, the ideal timing for postoperative radiotherapy and chemotherapy is unknown for resected lung cancer. Using the National Cancer Database, we reviewed 1629 patients with resected pN2 non–small-cell lung cancer with margin-negative disease. We found that a longer time to radiation (≥ 8 weeks) was associated with better survival. Also, sequential chemotherapy was associated with better survival compared with concurrent chemoradiotherapy.

Background: Currently, the ideal timing for postoperative radiotherapy (PORT) and chemotherapy is unknown. The present study evaluated their relative timing on overall survival (OS) using the National Cancer Database (NCDB). **Materials and Methods:** The NCDB was queried for patients from 2004 to 2012 with resected non–small-cell lung cancer (NSCLC), pathologically involved N2 (pN2) nodes, and negative margins. All patients underwent adjuvant chemotherapy and external beam radiotherapy. The time to radiation (TTR) was determined from the date of surgery to the start of PORT, with the exclusion of those receiving PORT $<$ 4 weeks or $>$ 24 weeks postoperatively. Early and late TTR was dichotomized at 8 weeks after receiver operating characteristic analysis. Multivariate Cox regression analysis was conducted to predict the variables significantly associated with survival. **Results:** A total of 1629 patients were eligible for analysis. Of the 1629 patients, 703 had received PORT $<$ 8 weeks and 926 had received PORT $\geq$ 8 weeks postoperatively. The receipt of PORT after 8 weeks was associated with better OS ($P = .0044$). No significant differences were found in survival in the concurrent group comparing early and later TTR ($P = .9119$). However, a significant OS benefit was found for sequential chemotherapy with an increased TTR ($P = .0045$). Older age, male sex, shorter distance traveled, increased nodal positivity, larger tumor size, higher Charlson/Deyo comorbidity score, and early TTR were associated with inferior survival on multivariate analysis. **Conclusion:** A TTR of $\geq$ 8 weeks with sequential chemotherapy in the setting of PORT was associated with improved survival in patients with NSCLC with pN2 nodes.

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Introduction

Lung cancer affects approximately 1.6 million people worldwide annually, with a significant majority of these cases being non–small-cell lung cancer (NSCLC).[1] Although survival has improved with chemotherapy and radiation techniques, the 5-year overall survival (OS) of stage III NSCLC is 5% to 14%.[1] Selected patients with stage III NSCLC, many with subclinical N2 disease, undergo upfront surgery; however, local failure in the chest is still common.[2] Postoperative

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radiotherapy (PORT) has been used to reduce this recurrence risk; however, the timing of PORT relative to the administration of chemotherapy has not been systematically addressed.[2,3]

The use of PORT for patients with resected NSCLC remains controversial. A large meta-analysis reported in 1998 with 2128 patients concluded that PORT was associated with decreased OS, with the detriment in patients with pathologic stage N0 and N1.[4] The decline in the use of PORT has been attributed to that meta-analysis, although the meta-analysis included older treatment techniques and radiation equipment.[5] An analysis of patients treated from 1998 to 2002 in the Surveillance, Epidemiology, and End Results database found PORT to be associated with decreased OS in pN0 and pN1 patients but improved OS in pN2 patients.[6] This survival benefit for pN2 patients was also seen in a retrospective analysis of the Adjuvant Navelbine International Trialist Association (ANITA) trial.[7] Most recently, an analysis of the National Cancer Database (NCDB) found PORT to be associated with improved survival in patients with pN2 disease with negative surgical margins.[8] Therefore, the National Comprehensive Cancer Network has recommended PORT in patients with pN2 disease who have not received neoadjuvant chemotherapy.[9]

The ideal timing for PORT is unknown. In the ANITA trial, patients receiving PORT underwent irradiation either 12 to 14 weeks after surgery in the chemotherapy arm or 2 weeks after randomization in the observation group. In the observation group, the median time to randomization was 33 days (range, 7-52 days).

The purpose of the present study was to determine whether the timing of radiation and chemotherapy affected the outcomes using data from the NCDB.

Materials and Methods

The present project was exempt from institutional review board review, which is the case for all NCDB analyses from our institution. The present analysis used the NCDB from 2004 to 2012 to examine receipt of PORT in patients with pathologic stage N2 NSCLC with negative margins. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society.

Patient Selection and Demographic Data

Patients were required to have pN2 NSCLC and to have received adjuvant chemotherapy and external beam radiotherapy. Those who had received neoadjuvant chemotherapy or neoadjuvant radiotherapy, had metastatic disease or positive or unknown surgical margins, had received other systemic therapies, including palliative care, immunotherapy, and hormonal therapy, had died within 90 days of surgery, had undergone evaluations at multiple hospitals, or had a history of multiple cancers were excluded. Patients were included in the present analysis if they had undergone PORT 4 to 24 weeks postoperatively and were excluded if the radiation treatment doses or start dates were unknown. This period was selected to mirror that of the Lung ART trial (phase III study comparing postoperative conformal radiotherapy to no postoperative radiotherapy in patients with completely resected non-small cell lung cancer and mediastinal N2 Involvement).[10]

Patient demographic data and facility covariates included age, sex, race (white, black, and other), Charlson/Deyo comorbidity score (0 vs. 1 vs. $\geq$ 2), primary health insurance (private vs. government vs. no insurance), median income in zip code area by quartile, distance from residence to treatment facility ($\leq$ 50 vs. $>$ 50 miles), facility type (academic vs. nonacademic), and location (metropolitan vs. urban/other). The clinicopathologic characteristics assessed included year of diagnosis, laterality, type of surgery, histologic features, tumor size, number of positive lymph nodes, and number of lymph nodes removed.

Sequential versus concurrent chemotherapy was defined by the timing of chemotherapy and PORT. Concurrent chemotherapy was defined as chemotherapy starting during RT or within 2 weeks before the start of RT. Additional chemotherapy data such as the duration and type of chemotherapy were not available from the database.

Statistical Analysis

A cutoff point analysis was conducted using a receiver operating characteristic analysis. Treatment time was dichotomized at the most significant cutpoint, which was 8 weeks. For simplicity, the groups were divided into an early time to radiation (TTR; $<$ 8-week TTR) for those receiving PORT within 8 weeks and late TTR ($\geq$ 8-week TTR) for those undergoing PORT after $\geq$ 8 weeks.

The demographic, clinicopathologic, and treatment details were compared between the groups using Wilcoxon rank sum tests for continuous variables and the χ^2 test for categorical variables. OS was defined from the date of diagnosis until the last contact. The last follow-up point was the end of 2013.

Propensity matching was used to decrease selection bias. A logistic regression was run using $<$ 8 weeks versus $\geq$ 8 weeks TTR as the dependent variable. The following factors were included in the propensity match: age, sex, distance, facility type, urban/rural, histologic features, tumor size, positive lymph node, and Charlson/Deyo score. A match was done based on the propensity score from the logistic regression. The value of the match tolerance was set at 0.05.

A 2-sided $P < .05$ was used to determine statistical significance. SPSS, version 23 (IBM, Armonk, NY), and MedCalc Statistical Software, version 15.11.3 (MedCalc Software BVBA, Ostend, Belgium; available at: https://www.medcalc.org; 2015) were used to perform all statistical analyses.

Results

Patient Characteristics

We identified 1629 patients who met the inclusion and exclusion criteria. The CONSORT (consolidated standards of reporting trials) diagram showing patient selection is summarized in Figure 1. Of the 1629 patients, 703 were in the early TTR group and 926 were in the late TTR group. The median age was 63 years (range, 19-90 years; Table 1). The median number of weeks between surgery and PORT in the early TTR group was 6 weeks compared with 18 weeks in the late TTR group ($P < .001$).

Survival Stratified by TTR

The median survival time from diagnosis was 45.9 months (95% confidence interval [CI], 41.1-51.7 months) in the late TTR group compared with 38.0 months (95% CI, 33.2-42.2 months) in the early TTR group ($P = .0044$; Figure 2A). The 5-year unadjusted survival rate was 42.6% $\pm$ 1.9% in the late TTR group versus 37.7% $\pm$ 2.0% in the early TTR group.

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