Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non–Small-Cell Lung Cancer

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Introduction: Optimal management of clinical stage IIIA-N2 non–small-cell lung cancer (NSCLC) is controversial. This study examines whether neoadjuvant chemoradiation plus surgery improves survival rates when compared with other recommended treatment strategies.

Methods: Adult patients from the National Cancer Database, with clinical stage IIIA-N2 disease definitively treated between 1998 and 2004 at American College of Surgeons Commission on Cancer accredited facilities, were included in the study. Treatment was defined as neoadjuvant chemoradiation plus either lobectomy (NeoCRT+L) or pneumonectomy (NeoCRT+P), lobectomy plus adjuvant therapy (L+AT), pneumonectomy plus adjuvant therapy (P+AT), and concurrent chemoradiation (CRT). Median follow-up and overall survival (OS) were defined from date of diagnosis to last contact. Five-year OS was estimated using Kaplan–Meier methods. Cox proportional hazard regression was used to estimate hazard ratios and 95% confidence intervals (CIs), adjusting for sociodemographic, clinical, and facility characteristics.

Results: Median follow-up was 11.8 months for 11,242 eligible patients. Five-year OS was 33.5%, 20.7%, 20.3%, 13.35%, and 10.9% for NeoCRT+L, NeoCRT+P, L+AT, P+AT, and CRT, respectively ($p < 0.0001$). On multivariable analysis, the estimated hazard ratio was 0.51 (CI: 0.45–0.58) for NeoCRT+L; 0.77 (0.63–0.95) for NeoCRT+P; 0.66 (0.59–0.75) for L+AT; 0.69 (0.54–0.88) for P+AT; and 1.0 (reference) for the CRT group. Comorbidity did not attenuate the relationship between treatment and survival.

Conclusion: This large study demonstrates that patients with clinical stage IIIA-N2 NSCLC, who underwent neoadjuvant chemoradiation followed by lobectomy, were associated with an improved survival.

Key Words: Lung cancer, Neoadjuvant chemoradiation.

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Treating clinical stage IIIA-N2 non–small-cell lung cancer (NSCLC) is a significant challenge.[1] The high rate of local failure seen in the population treated with chemoradiation alone led investigators to examine whether neoadjuvant chemoradiation (NeoCRT) plus curative-intent surgical resection could decrease locoregional recurrence rates and improve survival. The main concern regarding this approach is the potential for increased surgical morbidity and mortality. NeoCRT can cause worsening of inflammation, which may increase the complication rates associated with subsequent surgical resection.[2]

Several phase II studies initially suggested an overall survival (OS) benefit of 10% to 20% from NeoCRT and surgery, with most trials reporting a median survival of 15 to 22 months.[3–8] However, three recent phase III randomized studies, which completed accrual, failed to confirm a clear survival benefit of neoadjuvant therapy.[9–11] Because of these results, the role of neoadjuvant chemoradiation followed by a lobectomy or pneumonectomy in stage IIIA-N2 NSCLC remains controversial.[12]

The purpose of this study was to examine whether neoadjuvant chemoradiation was associated with improved survival compared with other recommended treatment strategies among patients with clinical stage IIIA-N2 NSCLC, using observational data from the National Cancer Database (NCDB), which allows for an analysis of a much larger cohort of patients from a variety of clinical practices than previously published studies.

PATIENTS AND METHODS

The NCDB is a hospital-based cancer registry that collects data from American College of Surgeons (ACoS) Commission on Cancer (CoC) accredited facilities and is jointly sponsored by the ACoS and the American Cancer Society. It includes data on approximately 70% of all

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malignant cancers in the United States. The database contains information on patient demographics, primary tumor site, histology, stage at diagnosis, insurance status, first course of treatment, and OS.

Data and Study Population

Eligible patients had histologically confirmed first primary invasive NSCLC and received all or part of their first course of treatment at ACoS CoC accredited facilities.[13] We restricted the analysis to patients aged 19 years and older, with pretreatment clinical stage IIIA-N2 (T1–T3) disease, treated between 1998 and 2004, to allow for a minimum of 5 years of follow-up (n = 39,359). Patients were not required to have histologic confirmation of clinical N2 disease because this information was unavailable in the database. The treatment categories were selected a priori according to a review of the literature. The five recommended treatment strategies in this population, which were consistent with curative therapy, according to evidence-based guidelines released by various oncologic societies for positive clinical N2 nodal status included neoadjuvant chemoradiation plus a lobectomy (NeoCRT+L), neoadjuvant chemoradiation plus a pneumonectomy (NeoCRT+P), lobectomy plus adjuvant therapy (L+AT), pneumonectomy plus adjuvant therapy (P+AT), and concurrent chemoradiation (CRT) alone.[14–18] Adjuvant therapy included chemotherapy alone, radiation alone, and chemoradiation. Patients with missing demographic data (n = 126), missing treatment data (n = 7755), those who did not receive treatment (n = 4358), those who received chemotherapy or radiation therapy alone (n = 9431), or who received treatment that did not meet criteria established for the three categories as mentioned above, such as sequential chemotherapy and radiation, were excluded (n = 6447). All patients were retrospectively classified into each category, based on the actual treatment they received.

The ACoS CoC requires accredited programs to update vital status and other information in 5-year cycles; for example, patients first diagnosed with cancer in 1998 (1998 incident cases) would be initially reported in 2000 and would have their vital status updated in 2005 (which would be the same year when the 2003 incident cases would be reported). After the initial 5-year follow-up, the vital status of the case and follow-up time are updated on an annual basis. The NCDB does not have cause of death data. Therefore, for this study, overall follow-up time was defined as the time from diagnosis to date of death from any cause, or the time from diagnosis to date of last contact for those who were alive at last contact. Patient risk factors that were part of the statistical analysis included histology, T-stage (according to the 6th edition of the American Joint Committee on Cancer Stage), laterality, age at diagnosis, sex, insurance type, race/ethnicity, and geographic region.[19] The variables and categorizations were based on previously published data sets examining prognostic factors in lung cancer patients.[20,21] Among patients who underwent surgery, the surgical margin status of the pulmonary resection was recorded. From 2003, the NCDB began collecting data on comorbidities from the hospital face sheet. A modified version of the 17-item Charlson–Deyo Index (eliminating solid tumors and leukemia) was computed to permit adjustment for comorbidities.[22] The 15-item modified index measured conditions such as diabetes, myocardial infarction, and kidney failure.

Facility-level characteristics included the volume of patients who received care for NSCLC at an ACoS CoC facility during the study period and treatment facility type. Four types of treatment facilities were included in the classification scheme used by the CoC accreditation program, (1) community cancer programs, (2) comprehensive community cancer programs, (3) teaching or research centers, and (4) National Cancer Institute–designated cancer centers. Community cancer centers treat at least 300 cancer patients a year and have a full range of services for cancer care. Comprehensive community cancer centers offer the same range of services as the community hospitals but treat at least 650 cancer patients annually. Teaching/research facilities are affiliated with medical schools, have residency programs, conduct ongoing cancer research, and have no minimum caseload requirement.

Statistical Analysis

Median follow-up was calculated among individuals with censored data.[23] Estimates of OS, stratified by the treatment received, were calculated using Kaplan–Meier survival estimates. The log-rank test was used to estimate whether there were differences in OS rate by treatment type. Differences in treatment type by patient, facility, and area-level characteristics were estimated using χ^2 tests. All statistical tests were two sided, and a 0.05 level of significance was used.

Multivariable Cox proportional hazards (PHs) regression models were used to assess the importance of treatment received as an independent predictor of OS. All statistically significant (at the 0.05 level) data on patient, facility, and area-level variables from the aforementioned bivariate analysis were included in the multivariate Cox PH analysis. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated in models adjusted for the aforementioned covariates of interest. A test for PHs in initial survival models revealed time interactions among several factors, including histopathology, sex, clinical T-stage, laterality, diagnosis year, and age at diagnosis. Because of the violation of PH for these variables, we controlled for these variables by stratification. Stratification allows for different stratum to have different baseline hazard functions and ultimately results in an HR being weighted over the different strata. This procedure allows for simultaneous calculation of HR for those variables that do not violate the PH assumption, but it does preclude the generation of HR estimates for variables that do violate the PH assumption.[24,25] Furthermore, the treatment category violated the PH assumption within the first 4 months of follow-up. The Cox proportional hazards model relies on the hazards to be proportional, meaning that the effect of a given covariate does not change over time. The treatment category violated PH in the first 4 months of follow-up. To correct this, we performed multivariate analysis on patients who survived a minimum of 4 months, after which the treatment variable did not violate the PH assumption (n = 10,058). Use of the 4-month cutoff in the multivariate analysis also reduced potential time biases from differences in the duration of therapy.[26–28]