Survival impact of postoperative therapy modalities according to margin status in non−small cell lung cancer patients in the United States

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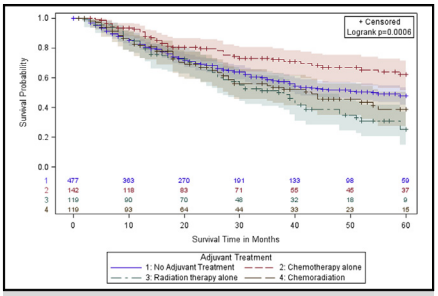
ABSTRACT

Objective: Unlike complete (R0) resection guidelines, current National Comprehensive Cancer Network (NCCN) adjuvant therapy guidelines after incomplete (R1/R2) resection of non−small cell lung cancer (NSCLC) are based on low-level evidence. We attempted to validate them.

Methods: Patients with pathologic stage I-IIIA NSCLC from 2004 to 2011 in the National Cancer Database were stratified by margin status, NCCN-specified stage groupings, and adjuvant therapy exposure (none, radiotherapy, chemotherapy, or both). Five-year overall survival (OS) and hazard ratios, adjusted for patient and institutional characteristics, were compared. We used a parallel analysis of R0 resections to validate our methodology.

Results: We analyzed 3461 R1/R2, and 78,979 R0 resections. After R0 resection, the NCCN-recommended option was associated with the best survival across all stage groups, supporting our analytic approach. Patients with R1/R2 stage IA treated with radiation had a 26% OS, compared with 58% with no treatment ($P = .003$). In patients with stage IB/IIA(N0) R1/R2, radiation was associated with a 25% OS compared with 47% with no treatment ($P = .025$) and 62% with chemotherapy ($P < .007$). Chemoradiation was not associated with a survival benefit in either group. Patients with IIA(N1)/IIB and IIIA had better survival with chemotherapy or chemoradiation. No group had a survival benefit with radiation alone.

Conclusions: NCCN adjuvant therapy guidelines after complete resection, based on high-level evidence, are validated, but not guidelines for patients with incompletely resected early-stage NSCLC, which are based on low-level evidence. Monomodality postoperative radiotherapy was not validated for any stage. Specific studies are needed to determine optimal management after incomplete resection. (J Thorac Cardiovasc Surg 2017;154:661-72)



Kaplan-Meier survival curves for margin-positive patients in stage IB (T2a, N0) and stage IIA (T2b, N0).

Central Message

NCCN guidelines for postoperative therapy after incomplete surgical resection in patients with stage I-II should be prospectively evaluated.

Perspective

NCCN guidelines for postoperative chemotherapy and radiation after complete surgical resection for NSCLC, based on high-level evidence, are validated in this analysis. Current guidelines for postoperative therapy after incomplete resection of stage I-II NSCLC, which are based on lower-level evidence, are not supported by this analysis.

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THOR

Lung cancer accounts for approximately 27% of all annual US cancer deaths.[1] Most long-term survivors are among the 29% of patients who have undergone curative-intent surgical resection.[2,3] In high-risk patients, adjuvant chemotherapy[4-6] and/or postoperative radiotherapy (PORT) may improve survival.[7] The quality of evidence for the benefit of these treatments varies by stage and margin status.[7-10]

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Abbreviations and Acronyms

HR = hazard ratio
IQR = interquartile range
NCCN = National Comprehensive Cancer Network
NCDB = National Cancer Database
NSCLC = non−small cell lung cancer
OS = overall survival
PORT = postoperative radiotherapy
R0 = complete resection (with uninvolved margins)
R1 = incomplete resection (with microscopically involved margins)
R2 = incomplete resection (with macroscopically involved margins)
RCT = randomized clinical trials

Randomized clinical trials (RCTs) and a pooled analysis have demonstrated the benefit of adjuvant chemotherapy in completely (R0) resected patients with T-category 2b or more advanced primary tumors, and those with nodal metastasis.[4-6,11] A large meta-analysis showed the harmfulness of PORT in R0-resected patients without mediastinal nodal metastasis[12,13]; a retrospective analysis of the US Surveillance, Epidemiology and End Results database and an unplanned retrospective analysis of a clinical trial suggest R0 patients with mediastinal nodal metastasis may benefit from PORT.[7,10]

Unlike the situation after complete resection, there is no RCT evidence to guide adjuvant management for the 2% to 17% of non−small cell lung cancer (NSCLC) resections with microscopic (R1)- or macroscopic (R2)-positive margins.[14-16] However, recipients of incomplete resection are at significantly high risk for early death, irrespective of stage.[16-18] Current National Comprehensive Cancer Network (NCCN) guideline recommendations for postoperative management of these patients are based on unverified expert opinion.[19] Therefore, the guidelines need validation.

We evaluated the survival impact of 4 different adjuvant therapy options, after incomplete resection, in the National Cancer Database (NCDB) to determine which options seemed best for patients grouped into stage clusters as in the NCCN guidelines.[19]

METHODS

Cohort Selection

We used the NCDB, an oncology database sourced from Commission on Cancer-accredited Facilities, which covers approximately 70% of newly diagnosed US cancer cases.[20,21] We selected patients with surgically resected pathologic stage I-IIIA NSCLC from 2004 to 2011 (International Classification of Disease for Oncology, 3rd version site codes C34.0-C34.9), excluding patients with missing information on last date of contact, administration (or date of administration) of radiation or chemotherapy, facility, or patient location. We also excluded patients with more than 1 surgical procedure, neoadjuvant radiation or chemotherapy, no (or unknown) nodal examination, adjuvant therapy more than 180 days past date of surgery, government insurance, and death within 60 days of surgery.

Objectives

The primary objective of this analysis was to compare stage-specific survival between postoperative therapy modalities in patients with incomplete surgical resection (R1/R2) who did not undergo re-resection. We used a parallel analysis of R0 patients to evaluate whether our data and methodology produced results congruent with existing high-level evidence for treatment of R0 patients.

Adjuvant Therapy Options

We classified postoperative therapy modalities as chemotherapy, radiotherapy, chemoradiation, or no treatment. Therapy administered within 6 months after surgery, at any dose level, was included as postoperative therapy. The median time from surgery to onset of treatment, by modality, is reported in Table E1. For combined-modality chemoradiation therapy, the second modality had to begin within 2 months of the end of the first. The time from surgery to initiation of adjuvant therapy was evaluated to verify that adjuvant modalities were not typically used for the purpose of salvage therapy in this cohort.

NCCN Stage Groups and Adjuvant Therapy Guidelines

NCCN recommendations for adjuvant therapy are based on pathologic stage, categorized into the following 4 groups: (1) stage IA (T1ab, N0); (2) stage IB (T2a, N0) and stage IIA (T2b, N0); (3) stage IIA (T1ab-T2a, N1) and stage IIB (T3, N0; T2b N1); and (4) stage IIIA (T1-3, N2; T3, N1). The NCCN-recommended nonsurgical adjuvant therapy for group 1 is PORT; for group 2, PORT with or without chemotherapy; for groups 3 and 4, chemoradiation (sequential or concurrent) for R1 and concurrent chemoradiation for R2.[19]

Variables

Margin status was evaluated as negative (R0) or positive (R1, R2, or positive not otherwise specified), and in subsequent analyses R1 and R2 were evaluated individually. Covariates (detailed in Table 1 and Table E2) in the analysis included patient demographics (age, sex, race, insurance status, income, rural/urban residence, census region), and clinical characteristics (comorbidity score [0, 1, or ≥2], histology, tumor grade, tumor size, primary site, type of surgery), as well as institutional characteristics (facility type).

Statistical Analysis

Overall survival (OS) times were taken from the date of surgery until the date of death or last follow-up. Survival analyses were conducted to compare the 4 postoperative treatment modalities within each of the 4 stage groups. OS was estimated using the Kaplan-Meier method and postoperative treatment groups were compared using the log-rank test.

OS comparisons also were evaluated using univariate and multiple variable Cox proportional hazards models to adjust for covariates. Model-based hazard ratio estimates are reported with 95% confidence intervals. For each model, we present unadjusted hazard ratios and hazard ratios adjusted for demographic, clinical, surgical, and institutional characteristics. The proportional hazards assumption was evaluated graphically, using log(−log) survival plots by treatment group. We used "no adjuvant treatment" as the reference adjuvant therapy option, because there is no clinical trial evidence to support adjuvant therapy after