

# Role of Adjuvant Therapy for Node-Negative Lung Cancer Invading the Chest Wall

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## Abstract

**The use of adjuvant therapy in T3N0 non–small cell lung cancer chest wall tumors is unclear. The results of the present retrospective analysis of 759 patients suggest that those with tumors  $\leq 4$  cm will benefit from adjuvant chemotherapy and those with tumors  $> 4$  cm will benefit from adjuvant chemoradiation, implying that the treatment for these patients should be different from that of other stage IIB patients.**

**Introduction:** The present study investigated the effect of adjuvant chemotherapy and radiation on survival among patients undergoing chest wall resection for T3N0 non–small cell lung cancer (NSCLC). **Materials and Methods:** Patients with T3N0 NSCLC who underwent chest wall resection were identified in the National Cancer Data Base in 2004 to 2012. The cohort was divided into patients who had received adjuvant chemotherapy, radiation therapy, chemoradiation therapy, or no adjuvant treatment. Kaplan-Meier and log-rank tests were used to compare overall survival, and a bootstrapped Cox proportional hazards model was used to determine the significant contributors to survival. A subset analysis was performed with stratification by margin status and tumor size. **Results:** Of 759 patients identified, 42.0% underwent surgery alone, 23.3% underwent surgery followed by chemotherapy, 22.3% underwent surgery followed by chemoradiation therapy, and 12.3% underwent surgery followed by radiotherapy alone. Tumors  $> 4$  cm benefited from adjuvant chemotherapy and radiation therapy in the multivariable analysis, and those  $\leq 4$  cm benefited only from adjuvant chemotherapy. The subgroup analysis by margin status identified that margin-positive patients with tumors  $> 4$  cm benefited significantly from either adjuvant chemoradiation therapy or radiation therapy alone. **Conclusion:** T3N0 NSCLC with chest wall invasion requires unique management compared with other stage IIB tumors. An important determinant of management is tumor size, with tumors  $\leq 4$  cm benefiting from adjuvant chemotherapy and tumors  $> 4$  cm benefiting from adjuvant chemotherapy if margin negative and adjuvant chemoradiation therapy or radiotherapy if margin positive.

*Clinical Lung Cancer*, Vol. ■, No. ■, 1-9 © 2016 Elsevier Inc. All rights reserved.

**Keywords:** Chemoradiation, Chemotherapy, Margins, NSCLC, Tumor size

## Introduction

Locally advanced, node-negative, non–small cell lung cancer (NSCLC) with invasion of the chest wall poses a difficult therapeutic challenge. These tumors are staged as T3N0 disease, along with tumors  $> 7$  cm, tumors within 2 cm of the carina, and tumors with additional nodules in the same lobe.<sup>1-4</sup> T3N0 tumors are

classified under stage IIB with T2bN1 tumors.<sup>4</sup> Although surgical resection is a widely accepted mainstay of treatment, the optimal postoperative treatment is poorly defined.<sup>5,6</sup> Various strategies have been used, including neoadjuvant chemoradiation (CRT) and adjuvant chemotherapy (CT) and radiation therapy (RT).<sup>7,8</sup> Nonetheless, the outcomes have remained poor, with 5-year overall survival (OS) rates for T3N0 NSCLC tumors involving the chest wall remaining at 40% to 50% for  $> 1$  decade.<sup>7,9,10</sup>

The current guidelines suggest that operable stage IIB patients should undergo surgical resection with lymph node evaluation followed by postoperative RT if margin positive or adjuvant CT if margin negative.<sup>11,12</sup> Despite this recommendation, no randomized clinical trials have compared adjuvant treatment regimens for T3N0 tumors invading the chest wall. A recent National Cancer Data Base (NCDB) study by Liu et al<sup>13</sup> showed that T3N0 NSCLC tumors  $> 7$  cm were optimally treated with surgical resection followed by

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Submitted: Apr 18, 2016; Revised: Jul 19, 2016; Accepted: Aug 23, 2016

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adjuvant CT. However, their study focused on tumor size and did not specifically analyze adjuvant therapy for tumors with chest wall involvement.

The Cancer and Leukemia Group B (CALGB) 9633 trial also revealed a statistically significant survival advantage for NSCLC patients with node-negative tumors  $\geq 4$  cm who had undergone adjuvant CT.<sup>14</sup> That study also did not specifically define the role of tumor size in the selection of adjuvant therapy for tumors with chest wall invasion.

Considering that tumors staged as T3N0 are a heterogeneous group, it would likely be advantageous to evaluate tumors with chest wall invasion separately. This is especially important considering that traditionally this subgroup has a poorer prognosis than those with other T3N0 tumors.<sup>15,16</sup> However, data on the optimal treatment of NSCLC with chest wall invasion are sparse. The primary objectives of the present study were (1) to investigate whether adjuvant CT, CRT, or RT alone prolongs the survival of patients with T3N0 chest wall tumors compared with surgery alone (SA); and (2) to understand the role of tumor size in the selection of adjuvant CT, RT, or combined treatment. We hypothesized that T3N0 chest wall tumors might respond differently to adjuvant treatment than other stage IIB tumors and even other T3N0 tumors.

### Materials and Methods

#### Data Source

The present study was a retrospective analysis of data from the NCDB, a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB integrates cancer registry records from > 1500 accredited hospitals and captures approximately 70% of newly diagnosed cancer cases in the United States.<sup>17</sup> The variables recorded in the database include patient demographics, Charlson-Deyo comorbidity score, socioeconomic status, tumor characteristics and

histologic features, stage, and the first course of therapy (defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence). Treatments delivered or withheld because of progressive disease and other treatment modifications are not recorded. Although the details of anatomic treatment location, dose, number of fractions, and radiation technique are recorded, the details regarding CT drug names, dose, treatment duration, and performance status are not recorded. The American College of Surgeons and the Commission on Cancer have not verified and are neither responsible for the analytic or statistical method used nor the conclusions drawn from these data by the investigators. The present study was granted an exemption by the Yale human investigation committee.

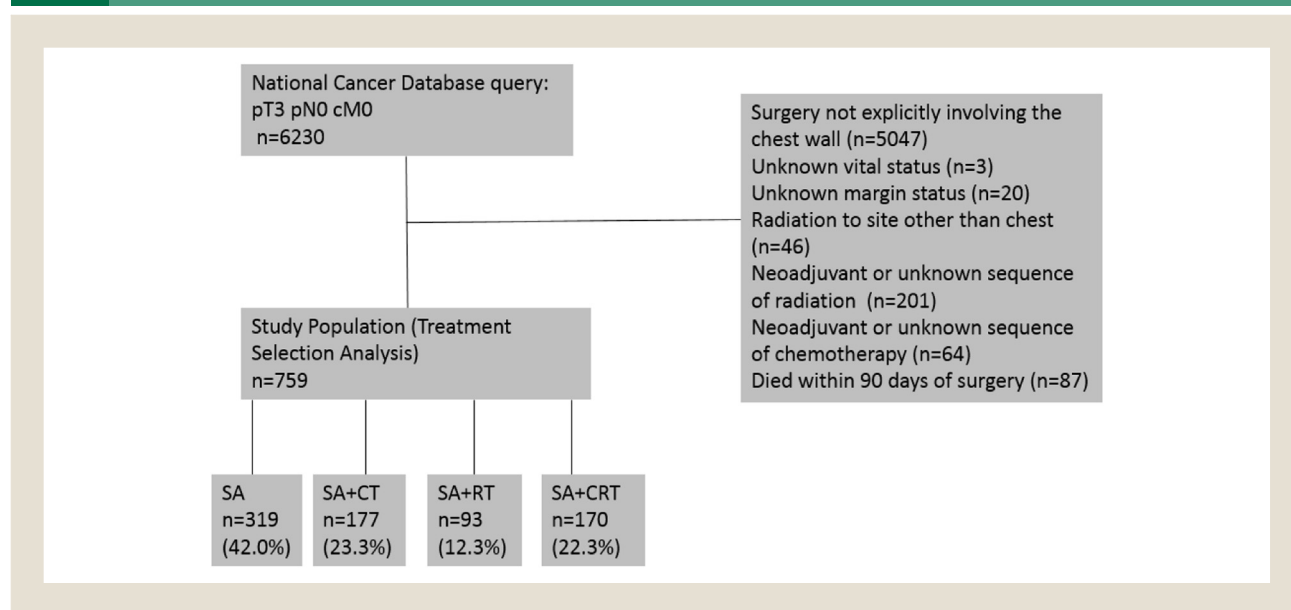
#### Study Cohort

The records for patients diagnosed with pathologic T3N0 NSCLC with no clinical evidence of metastatic disease (cM0) from 2004 to 2012 were obtained from the NCDB participant user file. The inclusion and exclusion criteria are summarized in Figure 1. Only patients who had undergone chest wall resection were included, which restricted the present analysis to patients who had undergone lobectomy or bilobectomy (Facility Oncology Registry Data Standards [FORDS] code 46). Patients with unknown vital status, unknown margin status, receipt of neoadjuvant therapy, or an unknown treatment sequence with respect to surgery or who had died within 90 days of surgery were excluded. For patients who received radiation therapy, this cohort was limited to patients receiving thoracic RT, without constraints on the total dosage; thus, the patients who could not complete their course of RT were included.

#### Variables

The patients were dichotomized as living in an urban location (population > 250,000) or nonurban location

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) Diagram



Abbreviations: CRT = chemoradiotherapy; CT = chemotherapy; RT = radiotherapy; SA = surgery alone.

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