

Adjuvant Chemotherapy Is Associated With Improved Survival in Locally Invasive Node Negative Non-Small Cell Lung Cancer

Usman Ahmad, MD, Traves D. Crabtree, MD, Aalok P. Patel, BS, Daniel Morgensztern, MD, Cliff G. Robinson, MD, A. Sasha Krupnick, MD, Daniel Kreisel, MD, PhD, David R. Jones, MD, G. Alexander Patterson, MD, Bryan F. Meyers, MD, MPH, and Varun Puri, MD, MSCI

Thoracic Surgery, Heart and Vascular Institute, Cleveland Clinic, Ohio; Departments of Thoracic Surgery, Medical Oncology, and Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri; and Thoracic Service, Memorial Sloan Kettering Cancer Center, New York, New York

Background. The objectives of this study are to explore factors that are associated with use of adjuvant chemotherapy and to evaluate its impact on overall survival in node-negative patients who undergo lung and chest wall resection for non-small cell lung cancer (NSCLC).

Methods. Patients who underwent concomitant lung and chest wall resection for NSCLC were abstracted from the National Cancer Database. Clinical, pathologic, treatment, and follow-up data were obtained. Patients with pathologic nodal metastases or patients who received any radiation treatment were excluded, and the cohort was dichotomized based on administration of adjuvant postoperative chemotherapy.

Results. Between 1998 and 2010, 824 patients met the inclusion criteria. This cohort exclusively consisted of pT3 N0 patients who did not receive any induction treatment or adjuvant radiation treatment. Adjuvant chemotherapy was administered to 255 patients (31%). Patients in the chemotherapy group were younger and had shorter

inpatient length of stay. Both groups had similar comorbidities, tumor size, unplanned readmission rate, and incomplete resection rate. In multivariable analysis, younger age and shorter length of stay were associated with a greater likelihood of receiving adjuvant chemotherapy. Adjuvant chemotherapy was associated with improved survival (hazard ratio 0.74, 95% CI: 0.6 to 0.9), whereas increasing age, white race, length of inpatient stay, tumor size, and residual tumor were independently associated with greater risk of death.

Conclusions. Patients who undergo lobectomy with chest wall resection for locally advanced NSCLC should be strongly considered for postoperative adjuvant chemotherapy even in the absence of nodal disease. Actual selection of patients for adjuvant chemotherapy is affected by perioperative factors.

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Chest wall invasion by non-small cell lung cancer (NSCLC) is present in 2% to 8% of patients who undergo resection [1]. This is a unique subset of locally advanced lung cancer patients who can have a higher (50% to 60%) 5-year overall survival (OS) than patients with other T3 tumors (T3 central, T3 >7 cm, T3 satellite nodule) [2–7]. The rate of lymph node involvement in T3 chest wall tumors is also lower than for other T3 tumors [8].

Traditionally, these tumors have been treated with surgical resection, and favorable OS has been noted in the absence of nodal disease. Several prognostic factors have

been identified and include completeness of resection, lack of lymph node involvement and smaller tumor size [2–8]. Adjuvant treatment has more commonly been radiation treatment after which no consistent improvement in OS has been reported [2, 9–11]. There are limited data describing the role of adjuvant chemotherapy for these tumors.

The seventh edition of TNM staging categorizes these (T3 N0) tumors as stage IIB when adjuvant chemotherapy is considered standard of care [12]. However, although data from adjuvant chemotherapy trials suggest a benefit for its use in stage IIB, none of the trials evaluated T3 N0 chest wall patients separately [13–15].

The beneficial role of chemotherapy is clear with any lymph node involvement; however, in patients with NSCLC invading chest wall who have undergone a complete resection the evidence is lacking. To study the effect of chemotherapy in these patients we used the National Cancer Database (NCDB). The objective of this study was to explore the role of adjuvant chemotherapy

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Address correspondence to Dr Puri, Division of Cardiothoracic Surgery, Washington University School of Medicine, Campus Box 8234; 660 S Euclid Ave, St. Louis, MO 63110; email: puriv@wudosis.wustl.edu.

Abbreviations and Acronyms

- CI = confidence interval
- HR = hazards ratio
- NCDB = National Cancer Database
- NSCLC = non-small cell lung cancer
- OS = overall survival

in NSCLC patients who underwent lobectomy along with chest wall or diaphragm resection.

Material and Methods

The NCDB is a joint program of the American College of Surgeons and the American Cancer Society. The database captures approximately 70% of patients treated at Commission on Cancer-accredited centers and provides de-identified data. A detailed list of elements available in the database is available on the American College of Surgeons website (<http://ncdbpuf.facs.org>). The database was queried to identify NSCLC patients who underwent concomitant lobectomy and chest wall (T3) resection between 1998 and 2010. Only node negative (N0) patients were included in this study. To obtain a relatively homogenous group of patients we excluded all patients who received neoadjuvant chemotherapy or radiation. Similarly patients who received adjuvant radiation were also excluded because this may confound the effect of chemotherapy on OS. Patients who had pathologic stage other than stage II were also excluded. Because tumor size cutoff of 4 cm has been used in clinical trials previously, we chose to use this cutoff to study the relationship of size with chemotherapy administration.

Information about patient and tumor-related variables, treatment details, and short- and long-term outcomes

was extracted. With the use of information on race, income, and population size of the area from which a patient presented, we created dichotomized groups in which a patient was either white or not white, had an annual income less than or greater than \$35,000, and presented from a rural location (regional population <250,000) or an urban location, respectively. The Charlson/Deyo score was used as a measure of comorbidity. It was categorized as 0, 1, or 2 or greater. The NCDB combines patients with scores of 2 or greater into a single group, because few patients have scores greater than 2. A detailed description of the score can be found in the NCDB data dictionary (<http://ncdbpuf.facs.org>). Treatment facilities were classified as community cancer programs, comprehensive community cancer programs, and academic/research centers. For the analysis, community cancer programs and comprehensive community cancer programs were categorized as nonacademic centers.

Last known vital status and the time between diagnosis and the follow-up date were used to determine survival. According to the NCDB, date of diagnosis refers to the date of histologic confirmation of NSCLC. In patients where the diagnosis was made based on imaging and patients proceeded directly to resection without biopsy, date of diagnosis refers to the date of radiologic imaging identifying the lesion.

All analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, IL). Descriptive statistics were expressed as means ± SD unless otherwise specified. Independent samples *t* tests and one-way analysis of variance were used to compare continuous variables. χ^2 tests were used to compare categorical data. OS was estimated by the Kaplan-Meier method. Multivariate logistic regression models were fitted to evaluate variables associated with administration of chemotherapy. Factors accounted for in the multivariate analysis include age, tumor size (mm), sex, race, facility type (academic versus nonacademic), income,

Table 1. Clinical and Demographic Variables in Patients Who Underwent Lobectomy With Chest Wall Resection With or Without Adjuvant Chemotherapy

Patient Characteristics	No Chemotherapy (n = 569)	Adjuvant Chemotherapy (n = 255)	<i>p</i> Value
Age at diagnosis, years	69 ± 10	62 ± 10	<0.001
Male sex	337 (59)	154 (60)	0.76
White	503 (88)	231 (91)	0.40
Academic center	221 (39)	99 (39)	1
Annual income >\$35,000	337 (62)	154 (63)	0.94
Urban population area >250,000	367 (65)	164 (64)	1
Charlson/Deyo score			0.56
0	270 (48)	132 (52)	
1	221 (39)	92 (36)	
2	75 (13)	31 (12)	
Tumor size, mm	56 ± 35	61 ± 58	0.179
Readmission	71 (13)	23 (9)	0.19
Inpatient length of stay, days	13.0 ± 12	8.8 ± 6	<0.001
Unplanned readmission (30 days)	56 (10)	16 (7)	0.14
Residual tumor	72 (13)	29 (12)	0.65

Values are mean ± SD or n (%).

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