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Long-term outcomes of surgical resection for stage IV non-small-cell lung cancer: A national analysis

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ABSTRACT

Objective: Treatment guidelines recommend surgical resection in select cases of stage IV non-small-cell lung cancer (NSCLC) but are based on limited evidence. This study evaluated outcomes associated with surgery in stage IV disease.

Methods: Factors associated with survival of stage IV NSCLC patients treated with surgery in the National Cancer Date Base (2004–2013) were evaluated using multivariable Cox proportional hazards analyses. Outcomes of the subset of patients with cT1-2, N0-1, M1 and cT3, N0, M1 disease treated with surgery or chemoradiation were evaluated using Kaplan-Meier analyses.

Results: The five-year survival of all stage IV NSCLC patients who underwent surgical resection (n = 3098) was 21.1%. Outcomes were related to the locoregional extent of the primary tumor, as both increasing T status (T2 HR 1.30 [p < 0.001], T3 HR 1.28 [p < 0.001], and T4 HR 1.28 [p < 0.001], respectively, compared to T1) and nodal involvement (N1 HR 1.34 [p < 0.001], N2 HR 1.50 [p < 0.001], and N3 HR 1.49 [p < 0.001], respectively, compared to N0) were associated with worse survival. Outcomes were also related to the extent of surgical resection, as pneumonectomy (HR 1.58, p < 0.001), segmentectomy (HR 1.36, p = 0.009), and wedge resection (HR 1.70, p < 0.001) were all associated with decreased survival when compared to lobectomy. The five-year survival of cT1-2, N0-1, M1 and cT3, N0, M1 patients was 25.1% (95% CI: 22.8–27.5) after surgical resection (n = 1761) and 5.8% (95% CI: 5.2–6.5) after chemoradiation (n = 8180).

Conclusions: Surgery for cT1-2, N0-1, M1 or cT3, N0, M1 disease is associated with a 5-year survival of 25% and does not appear to compromise outcomes when compared to non-operative therapy, supporting guidelines that recommend surgery for very select patients with stage IV disease. However, surgery provides less benefit and should be considered much less often for stage IV patients with mediastinal nodal disease or more locally advanced tumors.

1. Introduction

The majority (~55%) of patients with non-small-cell lung cancer (NSCLC) have stage IV disease with distant metastases at the time of diagnosis [1]. The generally recommended treatment for these patients is systemic chemotherapy, but the prognosis is very poor with a 5-year survival of only 4.9% [1,2]. However, there are unusual NSCLC presentations where tumor biology is such that even patients with distant metastatic disease are potentially curable with multimodality treatment [3]. Although there is no role for local therapy of the primary tumor for most patients with stage IV disease, aggressive local therapy may be appropriate for selected patients with limited-site oligometastatic disease and otherwise early-stage local disease [3–5].

Treatment guidelines reflect the potential benefit of surgery in select stage IV patients. For patients who have single brain or adrenal metastases but a primary tumor that is otherwise T1-2, N0-1 or T3, N0, a management strategy included in the National Comprehensive Cancer Network (NCCN) guidelines is local treatment of the metastasis followed by resection of the lung lesion in combination with chemotherapy either before or after lung resection [6]. The NCCN guidelines also recommend that patients with lung cancer and a solitary contralateral lung nodule be treated as if they have two primary lung tumors if both are curable [6]. This aggressive strategy has been reported to have 5-year survival rates of 7–21% for brain metastases

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[7–12], and 12–40% for adrenal metastases [13–18].

However, published outcomes related to these management strategies are generally single-institution studies of likely highly selected patients. The nature of these unusual clinical scenarios is such that meta-analyses or large prospective studies of patients are limited or not available. The practice of resection of special instances of stage IV NSCLC is still influenced by the subjective opinion of clinicians; the NCCN guidelines mention that some NCCN Panel Members feel that local therapy for adrenal metastases is only advisable if the synchronous lung disease is stage I or possibly stage II [6]. As such, clinicians have extremely limited evidence to guide therapy or even provide a patient an estimate of their prognosis with an aggressive therapy regimen that does have some risk of treatment-related morbidity.

This study was undertaken to quantify outcomes associated with surgical therapy of the primary pulmonary tumor in patients with stage IV NSCLC using the National Cancer Database (NCDB) with the following objectives: (1) identify patient and tumor factors associated with survival for patients that underwent surgical resection to potentially improve the patient selection process and (2) test the hypothesis that surgical resection is associated with improved survival over chemoradiation in patients whose local tumor extent was stage I–II (cT1-2, N0-1 or cT3, N0).

2. Methods

2.1. National Cancer Data Base

Jointly managed by the American Cancer Society and the American College of Surgeons (ACS) Commission on Cancer (CoC), the National Cancer Data Base (NCDB) contains information on approximately 70% of all newly diagnosed cases of cancer in the United States and Puerto Rico [19]. The NCDB includes data from over 1500 cancer centers in the U.S. with records of > 30 million patients [20]. Clinical staging information is recorded in the NCDB using the American Joint Committee on Cancer (AJCC) 6th and 7th edition TNM classifications for the years of study inclusion [21,22].

2.2. Study design

All patients in the NCDB diagnosed with stage IV NSCLC (2004–2013) were identified using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology (adenocarcinoma, squamous, adenosquamous, and large cell carcinoma) and topography codes. Patients were excluded if they exhibited non-malignant pathology, had history of previous unrelated malignancy, or received only palliative treatment. From this patient group, we created two patient cohorts for analysis.

2.3. Cohort of all surgical patients

The first cohort was all patients with stage IV disease who underwent surgical resection with or without chemotherapy and with or without radiation. All patients with T1-4, N-3 disease were included in this analysis to assess the impact of disease stage on survival of surgery patients. A multivariable Cox proportional hazards model was performed using this cohort to assess factors associated with survival. The factors that were adjusted in the model included: age, sex, race, CDCC score, clinical T status, clinical N status, facility type, histology, tumor location, insurance type, type of adjuvant or neoadjuvant therapy (chemotherapy, radiation, chemoradiation, or none), and extent of resection (wedge resection, segmentectomy, lobectomy, or pneumonectomy).

2.4. Cohort of cT1-2, N0-1 and cT3, N0 patients

The second cohort were those patients with clinical T1-2, N0-1, M1 and T3, N0, M1 disease who received the following: 1) surgery with or without chemotherapy and with or without radiation, 2) chemotherapy alone, 3) radiation alone, or 4) chemoradiation. Patients were divided into four groups by the type of primary treatment described above. The Kruskal-Wallis test for continuous variables and Pearson's chi-square test for discrete variables were used to compare baseline characteristics and unadjusted outcomes. A multivariable logistic regression was performed to evaluate predictors of use of surgery (vs no surgery) and included the following covariates: age, sex, race, Charlson Deyo comorbidity (CDCC) score, tumor location, histology, clinical T status, clinical N status, facility type, and insurance type. The Kaplan-Meier product limit approach was used to estimate median survival and 5-year survival for each subgroup of patients. Within the surgery group, we calculated the survival stratified by each substage of stage IV NSCLC and stratified by type of operation. The primary outcome of overall survival was compared between groups using the log-rank test.

To address the possibility of selection bias where patients who underwent surgery may simply be the healthiest patients with the most indolent of stage IV disease, we performed an exploratory analysis by comparing the overall survival of 1761 patients who underwent surgery with the 1761 patients who had the longest survival after being treated with chemotherapy and radiation using Kaplan Meier analysis. We also performed a propensity-score-matched analysis to create a cohort of patients who underwent surgery with similar baseline characteristics to patients who received chemotherapy and radiation, and to attempt to control for imbalance between the two groups. A logistic regression model was fitted to calculate the propensity score for the probability of a patient receiving surgical treatment. The following were adjusted as independent variables in the model: age, sex, race, CDCC, clinical T&N stages, histology type, treating facility type, and insurance status. Using a greedy 1:1 matching algorithm [23,24], 3512 patients were matched by propensity score.

All of the above-mentioned analyses were repeated in a sensitivity analysis that focused only on patients who were diagnosed as having stage IV disease from years 2010–2013 in accordance to the AJCC 7th edition. We did this analysis because multiple tumors in the same lung were originally classified in the 6th edition as being M1 disease [21]. In AJCC 7th edition, this is now considered T4 disease [22]. In the 7th edition, malignant pleural and pericardial effusions now have been reclassified from T4 to M1a [22]. In these sensitivity analysis, the variable "site of metastasis" was added to the modeling because metastasis site data (data on contralateral lung, pericardial and pleural effusion, brain, bone and liver) became available from 2010 onwards.

All statistical analyses were performed using SAS for Windows, Version 9.4; SAS Institute Inc.; Cary, NC. A 2-sided p-value of 0.05 was used to define the statistical significance.

3. Results

3.1. Outcomes associated with surgery

Between 2004 and 2013, surgery was utilized in 3098 patients with clinical M1 NSCLC in the NCDB (Fig. 1). Characteristics of these patients are detailed in Table 1. Overall 5-year survival of this cohort was 21.1% (Fig. 2A). Factors associated with increased survival in these patients who underwent surgery are detailed in Table 2 and were consistent in the sensitivity analysis using only patients staged by AJCC 7th edition (Table A.6). Survival stratified by different sub-stages are shown in Fig. 2B.

3.2. Impact of surgery for patients with cT1-2, N0-1 or cT3, N0 disease

Of the 94,672 patients from Fig. 1 who had cM1 disease and received some combination of chemotherapy, radiation, or surgery, there were 21,108 cT1-2, N0-1 or cT3, N0 patients who received treatment.

Baseline characteristics stratified by the different treatments for this