

Survival in Untreated Early Stage Non-small Cell Lung Cancer

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Abstract. *Background:* The aim of this study was to determine the survival of untreated stage I and II in non-small cell lung cancer (NSCLC) patients. *Patients and Methods:* A retrospective analysis of medical charts of all patients diagnosed with early stage NSCLC, between January 1990 and December 2001, was conducted and patients who were not treated were identified. Data on patient's age, gender, stage of the disease, pathology, reason for non-treatment and cause of death were reviewed. *Results:* Thirty-nine patients with untreated stage I and II NSCLC were identified. The median age at diagnosis was 77 years; 66.7% were men and 33.3% were women. All patients were Caucasian and 66.7% had stage I disease, 46.2% had squamous cell carcinoma, while adenocarcinoma was found in 28.2%. The major reason for non treatment was chronic obstructive pulmonary disease (64.1%) and the main cause of death was metastatic disease (48.7%). The overall mean survival was 11.9 months. The mean survival at stage I was not statistically different from the mean survival at stage II (13.7 months vs. 8.4 months) ($p < 0.12$). *Conclusion:* Patients with untreated early stages NSCLC have a very poor prognosis. Alternative therapies that are better tolerated should be investigated in these patients with early stage NSCLC who cannot be offered standard treatment.

Lung cancer is the most frequent cause of cancer death in both men and women in the world. In 1999, worldwide, there were 1.04 million (12.8%) new cases and 921,000 deaths (17.8%) due to lung cancer (1). In the United States alone, the American Cancer Society estimates that there will

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be 172,570 new cases of lung cancer and 163,510 deaths will occur from lung cancer during 2005 (2). The 5-year survival of early stage lung cancer has been reported to be between 45 to 70% (3-9). In contrast, the management of patients with early stage lung cancer who are medically inoperable is controversial. Involved-field radiotherapy is generally considered the treatment of choice for those patients who could not undergo surgery (10). The clinical course of the disease in patients with early stage NSCLC, who are not candidates for surgery or radiation therapy, is not well defined due to a relative lack of data and, as a result, the optimal treatment of these patients is unclear.

Hence, we conducted this study in patients with stages I and II NSCLC, who could not be treated with either of the current standard therapeutic interventions, in order to better define the clinical course of untreated early stage NSCLC.

Patients and Methods

We conducted a retrospective chart review of patients diagnosed with NSCLC between January 1990 and December 2001, after approval from the Institutional Review Board. The cases were identified using the International Classification of Diseases, Ninth Revision (11). Patients with stages I and II, who were not treated with curative intent, were included for further analysis in this study.

The demographic covariates analyzed included: age, gender, stage, pathology, reason for not treating the patient and the cause of death. Descriptive statistics were used to analyze patient demographics and medical characteristics. We used the Kaplan-Meier method to estimate the survival for each group (stage I and stage II). The survival distribution curves were compared using the log-rank test and a p -value ≤ 0.05 was considered statistically significant. Analyses were performed using SAS Software V8.0 (SAS Institute, Cary, NC, USA).

Results

Thirty-nine patients with untreated stage I and II NSCLC were eligible for this analysis. The patient characteristics are

Table I. Patient characteristics (N=39).

Characteristics	Number (Percent)
Gender	
Male	26 (66.7%)
Female	13 (33.3%)
Stage	
I	26 (66.7%)
II	13 (33.3%)
Pathology	
Squamous cell carcinoma	18 (46.2%)
Adenocarcinoma	11 (28.2%)
Large cell carcinoma	5 (12.8%)
Poorly-differentiated carcinoma	2 (5%)
Bronchoalveolar carcinoma	2 (5%)
Carcinoma NOS	1 (2.6%)
Reason for no treatment	
Chronic obstructive pulmonary disease	25 (64.1%)
Patient refusal	6 (15.4%)
Multiple medical problems	6 (15.4%)
Died	1 (2.6%)
Main cause of death	
Metastatic disease	19 (48.7%)
Respiratory failure/pneumonia	10 (25.6%)
Pulmonary embolism	1 (2.6%)
Myocardial infraction	2 (5.1%)
Multi-organ failure	1 (2.6%)
End stage renal disease	1 (2.6%)

shown in Table I. Of the 39 patients with (NSCLC), 26 (67.7%) were males and 13 (33.3%) were females. The median age of these patients was 77 years (range 64-93 years).

Twenty-six patients (67.7%) had stage I disease, while 13 patients (33.3%) had stage II NSCLC. Eighteen patients (46.2%) had squamous cell carcinoma, 11 patients (28.2%) had adenocarcinoma, 5 (12.8%) had large cell carcinoma while 2 patients (5%) each had poorly-differentiated carcinoma and bronchoalveolar carcinoma.

The major reason for not receiving any treatment was chronic obstructive pulmonary disease that precluded definitive therapy in 25 (64.1%) patients. Six patients (15.4%) each either refused therapy or had multiple medical conditions that made them ineligible for definitive therapy.

The overall mean survival was 11.9 months. The mean survival at stage I was not different than the mean survival at stage II (13.7 months vs. 8.4 months), *p*-value <0.12 (Figure 1). The main cause of death was metastatic disease in 19 patients (48.7%). Respiratory failure due to pneumonia was the proximate cause of death in 10 patients (25.4%).

Discussion

Surgical resection is the standard of care for early stage NSCLC. Adjuvant chemotherapy with a platinum-based regimen has recently been shown to offer a survival advantage over surgery alone (12). Radiation therapy is the current standard therapy for patients with early stage NSCLC who are not surgical candidates (10, 13-16). Patient who receive only radiation therapy in this setting have 5-year survival rates ranging from 13-23% (17, 18), as opposed to 50-70% following surgical resection for stages I and II (3-9, 19). However, patients, who are not candidates for either surgery or radiation, pose a therapeutic dilemma. This group of patients has not been well studied but their prognosis seems to be dismal (20-22).

Vrdoljak *et al.* studied 130 patients with untreated NSCLC and found no significant differences in survival between various TNM combinations classified into stage groups II, IIIa, IIIb and IV, as proposed by Mountain in 1989 (20, 23). In this series, they found that patients with T1 and 2, N0, M0 had a better outcome than the others. In another study, Kyasa and Jazieh studied 97 patients with unresected stage I and II and found that a majority of them (72%) did not receive any treatment for their disease. The patients who received treatment had a median overall survival time of 22 months, as compared to 11 months for the untreated group (*p*=0.008) (21). In a similar study, McGarry *et al.* studied 129 patients with stage I and II NSCLC treated with various treatment modalities. In their study, the median survival following surgery was 46.2 months, as compared to 14.2 months in patients who received no treatment and 19.9 months for those who received radiotherapy alone (22).

The median survival of 11.9 months in our series of untreated patients is similar to that seen for the untreated patients in the above studies. Our data certainly seems to re-emphasize the poor prognosis of untreated NSCLC, as the cause of death in almost half of our patients was progressive disease.

Smoking is the most common cause of lung cancer and, naturally, most patients with lung cancer will also have other, often more than one, smoking-attributable conditions. According to a recent CDC report, in 2000, an estimated 8.6 million persons in the United States had an estimated 12.6 million smoking-attributable conditions, namely chronic bronchitis, emphysema and coronary artery disease (24). Since the most common cause for non-treatment in our series was chronic obstructive pulmonary disease, with recognition of increased need for screening for early stage NSCLC, the number of patients with early stage, resectable, NSCLC who are medically unfit for standard surgical treatment will be substantial (25).

Given the dismal prognosis of these patients, if not treated, we believe that every effort should be made to

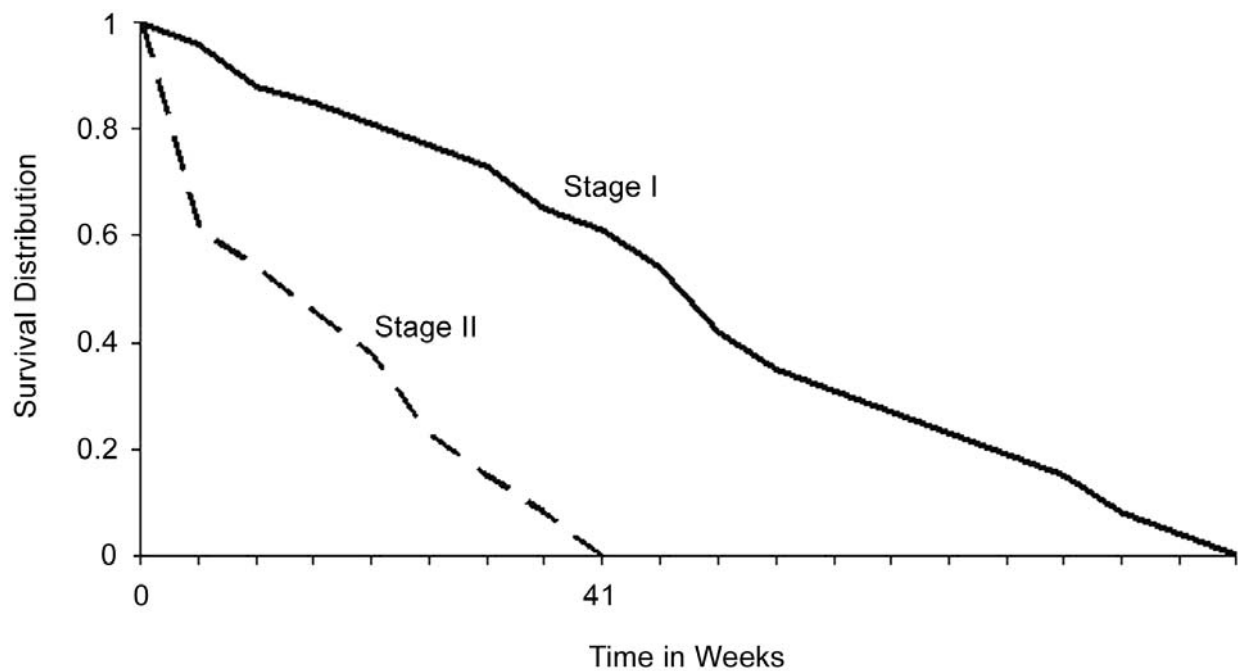


Figure 1. Survival in patients with untreated early stage NSCLC.

encourage these patients with early stage (NSCLC) who are not candidates for curative therapy to be enrolled in clinical trials using systemic chemotherapy, advanced radiation techniques with lesser radiation exposure to normal tissues and less invasive surgical procedures and newer targeted therapies. There is also an urgent need for less toxic and novel agents to be introduced, either alone or in conjunction with systemic chemotherapy, for this subgroup of unfortunate patients with early stage NSCLC.

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