Survival After Pathological Stage IA Nonsmall Cell Lung Cancer: Tumor Size Matters

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Background. **This study evaluates prognostic factors for survival in completely resected pathological stage IA nonsmall cell lung cancer with special emphasis on tumor size and assesses tumor recurrence rate by actual and actuarial analysis.**

Methods. **From January 1989 to December 2001, 130 consecutive resections for pathological stage IA nonsmall cell lung cancer were performed. Pathological tumor size was categorized into 0 to 20 mm and 21 to 30 mm. Each patient was scaled according to the Charlson Comorbidity Index. The Kaplan-Meier method was used for estimation of actuarial recurrence rate and the cumulative incidence method was used to estimate the actual recurrence rate. Risk factors for overall and disease free survival were determined by univariate and multivariate Cox regression analysis.**

Results. **Overall 5-year survival for patients with tumors 0 to 20 mm and 21 to 30 mm was 69% and 51%, respectively ($p = 0.038$). Disease-free survival at 5 years was 68% and 48%, respectively ($p = 0.015$). Only 27 patients had a recurrence and 69 patients died during follow-up. The actual 10-year recurrence rate was lower than the actuarial recurrence rate (23% vs 29%). Larger tumor size (relative risk 1.6; 95% confidence interval 1.0 to 2.7), Charlson Comorbidity Index score greater than or equal to 3 (relative risk 3.7; 95% confidence interval 1.7 to 8.0), and pneumonectomy (relative risk 2.1; 95% confidence interval 1.1 to 4.2) independently predicted adverse outcome.**

Conclusions. **Tumor size affects survival in resected stage IA nonsmall cell lung cancer. Current definition of stage IA disease should be substaged into two separate stages. In patients with early-stage lung cancer and relatively good prognosis actual recurrence rate is more realistic than the actuarial recurrence rate.**

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The incidence of nonsmall cell lung cancer (NSCLC) is increasing in the western world and still remains the leading cause of cancer-related mortality for both men and women [1]. Early-stage disease is usually treated surgically when possible and has the best prognosis. Several studies have demonstrated that tumor size is highly prognostic for survival [2, 3]. As a result stage I was subdivided into IA (tumor size $<$ 3 cm, T1N0M0), and IB (tumor size $>$ 3 cm, T2N0M0), in the current staging system in 1997 [4].

In recent years, there has been regained interest for the early screening and detection of lung cancer [5, 6]. However, more frequent chest radiographic screening has not shown to result in reduced lung cancer mortality [7]. With the widespread availability and increasing use of advanced staging techniques, such as spiral computed tomography (CT) scan, lesions smaller than 1 cm can be identified [8]. Nevertheless, if detection and treatment of smaller lesions is not associated with improved survival, early screening of lung cancer using CT scan may not result in reduced lung cancer mortality. Until now there is only limited and conflicting evidence available on the affect of tumor size on prognosis of patients with pathological stage IA NSCLC [2, 9–12].

Recurrence rate is thought to be the lowest in stage IA NSCLC patients. Patients within this stage do not always die as a result of their tumor. Currently, the Kaplan-Meier (actuarial) method [13] is generally used to estimate the recurrence rate in lung cancer patients. However, recently the cumulative incidence (actual) method proved to be a more valid method for estimating the probability of occurrence of a nonfatal time-related event because it estimates the percentage of patients who will actually have an event [14–16].

Therefore, the aims of this study were to evaluate tumor size as a prognostic factor for survival in completely resected pathologic stage IA NSCLC patients, and to estimate the actual versus actuarial risk of tumor recurrence.

Material and Methods

Retrospectively, the medical records of 139 consecutive patients who underwent complete resection for pathologic stage IA primary NSCLC at the Department of Cardio-Thoracic Surgery of the Erasmus Medical Center in Rotterdam (between January 1, 1989, and December 31, 2001) have been reviewed. Patients who had a second

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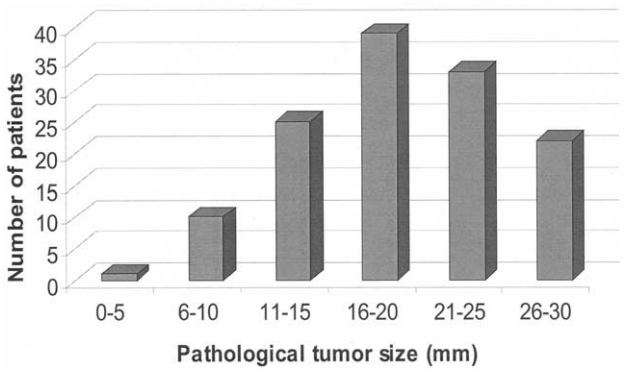

Fig 1. Distribution of pathological tumor size.

primary lung tumor were included in this study. Patients were followed with regular visits to the outpatient clinic. Civil administrations were consulted to assess late mortality. Follow-up was completed in all patients through July 2003. Median follow-up was 6.8 years. Overall survival time was defined as the difference between the date of surgery and the date of last follow-up. Disease-free survival was defined as the difference between the date of surgery and the date of local or distant recurrence of disease or the date of last follow-up in case of no recurrence. Hospital mortality was defined as death occurring within 30 days of surgery or any death later during the same postoperative hospital stay.

In all patients diagnostic work-up included a complete medical history, physical examination, plain chest radiography, electrocardiography, routine laboratory tests, lung function tests, and CT of the chest and upper abdomen. Patients were found to have positive mediastinal lymph nodes if mediastinal lymph nodes on computed tomography scan were more than 10 mm in diameter. Additional staging procedures, ie, mediastinoscopy, liver, bone, and brain scans were selectively performed to aid in treatment planning according to best clinical practice at the time of presentation. Each patient was scaled preoperatively according to the Charlson Comorbidity Index [17–19]. The index can be divided into four comorbidity grades: 0, 1 to 2, 3 to 4, and 5 or more.

Histologic typing occurred according to the World Health Organization Histologic Typing of Lung Tumors [20]. Pathologic staging of the patients occurred according to the international TNM classification for lung cancer [4]. Staging was based on pathological assessment of the primary tumor and lymph node assessment was carried out with preoperative mediastinoscopy or surgical sampling of bronchopulmonary, hilar, and mediastinal lymph nodes. The surgical-pathologic size of the primary tumor was obtained by measuring the greatest diameter of the fresh surgical specimen by the pathologist. Patients were categorized as patients with pathologic tumors of 0 to 20 mm in diameter (n = 75) and 21 to 30 mm in diameter (n = 55).

The following risk factors for overall and disease-free survival were evaluated: sex, age, type of surgery, histologic cell type, tumor size, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, forced expiratory volume in 1 second (unknown in 9 patients), and Charlson Comorbidity Index.

Table 1. Patient Characteristics

Characteristic	Number of Patients (n = 130) (%)
Sex	
Male	94 (72)
Female	36 (28)
Age (years)	
≤ 70	97 (75)
> 70	33 (25)
Mean ± SD	64 ± 9
Median follow-up (years)	6.8
Histology	
Squamous cell carcinoma	56 (43)
Adenocarcinoma	53 (41)
Large cell carcinoma	16 (12)
Bronchoalveolar cell carcinoma	5 (4)
Tumor size	
0–20 mm	75 (58)
21–30 mm	55 (42)
Smoking habits	
Nonsmoker	28 (22)
Current or former smoker	108 (78)
FEV1%[a]	
< 70	32 (26)
≥ 70	89 (74)
Charlson Comorbidity Index	
0	28 (22)
1–2	71 (55)
3–4	29 (22)
≥ 5	2 (2)

[a] FEV1% was unknown in 9 patients.

FEV1% = forced expiratory volume in 1 second, expressed as a percent of predicted; SD = standard deviation.

Discrete variables are displayed as proportions, continuous variables as means ± standard deviations unless specified otherwise. The χ^2 or Fisher exact test was used to analyze the categorical data. Continuous variables were analyzed using the Student's t test. Long-term survival curves were estimated by the Kaplan-Meier method, and the resulting survival curves were compared with the Breslow test. The Kaplan-Meier method was used for estimation of actuarial recurrence rate and the cumulative incidence method was used to estimate the actual recurrence rate. Univariate and multivariate Cox proportional hazard analysis within different time intervals determined risk factors for long-term survival. The Cox proportional multivariate analyses were performed with a stepwise forward regression model in which each variable with a p-value of less than 0.20 in the univariate analysis was entered in the model. Relative risks are reported with 95% confidence intervals.