Original Study

Risk Factors for Local and Distant Recurrence After Surgical Treatment in Patients With Non–Small-Cell Lung Cancer

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Abstract

The aim of the study was to evaluate risk factors for local and distant recurrence after surgical treatment of non–small-cell lung cancer. A total of 14,578 patients met the inclusion criteria and had complete follow-up information. Analysis indicated independent effects of the following risk factors on the risk of recurrence: age 64–90 years, histologic type of adenocarcinoma, blood vessel invasion, lymphatic vessel invasion, visceral pleural invasion, N1 or N2 disease, tumor size of 20–30 mm, 30–50 mm, 50–70 mm, and 70–100 mm, pneumonectomy, and sublobar resection.

Introduction: The purpose of this study was to identify independent perioperative and pathologic variables associated with non–small-cell lung cancer (NSCLC) recurrence after complete surgical resection. **Patients and Methods:** A retrospective examination was performed of a prospectively maintained database of patients who underwent resection for NSCLC from January 2009 to January 2014 at a multi-institution. Clinicopathologic variables were evaluated for their influence on frequency of recurrence. Cox proportional regression hazard model analysis examined the association of recurrence in NSCLC. **Results:** Of these patients, 2816 (19.3%) experienced recurrence of primary cancer. Local or distant recurrence was found in 20.5% and 79.5% of patients, respectively. Median follow-up was 27.9 months (range, 11.4–66.0 months). The analysis indicated independent effects of the following risk factors on the risk of recurrence: age 64–90 years (hazard ratio [HR], 1.136; 95% confidence interval [CI] 1.024–1.261), histologic type adenocarcinoma (HR, 1.117; 95% CI 1.005–1.24), blood vessel invasion (HR, 1.236; 95% CI, 1.124–1.359), lymphatic vessel invasion (HR, 1.287; 95% CI, 1.176–1.409), visceral pleural invasion (HR, 1.641; 95% CI, 1.215–2.218), N1 disease (HR, 1.142; 95% CI, 0.99–1.316), N2 disease (HR, 1.596; 95% CI, 1.271–1.649), tumor size of 20–30 mm (HR, 1.235; 95% CI, 1.081–1.41), 30–50 mm (HR, 1.544; 95% CI, 1.33–1.792), 50–70 mm (HR, 1.521; 95% CI, 1.275–1.815), and 70–100 mm (HR, 1.71; 95% CI, 1.385–2.11), pneumonectomy (HR, 1.08; 95% CI, 0.97–1.203), and sublobar resection (HR, 1.762; 95% CI, 1.537–2.019). **Conclusion:** In the largest series reported to date on postresection recurrence of NSCLC, increasing pathologic stage, advanced age, pneumonectomy, sublobar resection, lymphatic and blood vessel invasion, and visceral pleural invasion were independently associated with local and distant recurrence.

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Introduction

Worldwide, lung cancer is the most common cancer among men in terms of both incidence and mortality; among women, it has the third highest incidence and is second after breast cancer in mortality. In 2012, there were 1.82 million new cases globally; 1.56 million deaths occurred as a result of lung cancer, representing 19.4% of all deaths from cancer.[1] In Eastern Europe, lung cancer is the greatest cause of cancer-related deaths among men, while in northern Europe and Poland, it causes the highest mortality among

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women.[1] On the basis of a new tumor, node, metastasis classification system (TNM), 5-year survival for IA, IB, IIA, IIB, IIIA, IIIB, and IV stage disease is 73%, 58%, 46%, 36%, 24%, 9%, and 13%, respectively.[2-4] Local recurrence and distant metastases (with a rate up to 33.9%) are the most common reasons for treatment failure.[4] The purpose of this study was to identify the prognostic factors associated with recurrence and survival after complete resection of non−small-cell lung cancer.

Material and Methods

Material was collected retrospectively from an online-survey-based database of the Polish Lung Cancer Group that included information on patients with non−small-cell lung cancer operated on in 30 thoracic surgery centers in Poland. The 7th edition of the 2009 TNM classification system was used to determine staging.[3] The database of the Polish Lung Cancer Group is conducted voluntarily with the consent of all thoracic surgery centers in Poland. Each center has a coordinator responsible for collecting detailed data about each patient operated on for lung cancer. The data are collected in the form of electronic forms, including demographics, surgical and histologic data, and information from follow-up visits after surgery. All data are transferred electronically to a central registry, where the information is stored, managed, updated, and analyzed. The database covers all lung cancer patients operated on in Poland and includes detailed demographic, epidemiologic, and clinical data. In the "preoperative assessment" section, the results of imaging and invasive procedures can be found, on which diagnosis, staging, and qualification for surgical treatment are based (bronchoscopy, endobronchial ultrasound transbronchial needle aspiration, endoscopic ultrasound fine needle aspiration, mediastinoscopy, mediastinotomy, videothoracoscopy, thoracotomy). The "operating treatment" section lists information about the type of procedure, size and location of tumor, number of mediastinal lymph nodes collected from lymph node stations, and details about the operation method. The "postoperative" section provides histologic details, including the exact number of metastatic mediastinal lymph nodes as well as tumor characteristics.

After surgery, patients are followed for 2 to 3 weeks, then every 3 to 5 months for 5 years. Follow-up examinations include computed tomography (CT) and, in justified specific cases, positron emission tomography (PET)-CT. In case of abnormal imaging studies, further invasive diagnostic methods for confirmation of relapse are performed, including diagnostic operations. Each follow-up visit is entered into the database, from which dates of relapse and death can be determined. Only patients who had received radical treatment (R0) were included in the present study. Patients who received surgical treatment were assessed by a surgeon within 2 to 3 weeks; then they underwent follow-up tests every 3 to 5 months for period of 5 years. As part of the follow-up tests, chest x-ray, CT, and/or PET-CT in justified cases were performed. Hilar and/or mediastinal lymph node failures were defined as a new or enlarging lymph node measuring > 1 cm on the short axis on CT and/or hypermetabolic on PET imaging, which in the patient's subsequent clinical follow-up was consistent with disease progression.

Patterns of failure were assessed by follow-up imaging studies and by data obtained from procedures such as bronchoscopy, endobronchial ultrasound transbronchial needle aspiration, endoscopic ultrasound fine needle aspiration, mediastinoscopy, and mediastinotomy. Cancer recurrence was carefully divided according to the site of the initial relapse into 2 categories: local and distant recurrence. Local recurrence was defined as any recurrent disease within the ipsilateral hemithorax, mediastinum, or supraclavicular lymph nodes. All other sites of recurrence were considered distant metastases. The following factors were included in an analysis of risk factors: age, sex, histologic type, staging, tumor size, metastases to lymph nodes, extent of resection, lymphatic and blood vessel invasion, and visceral pleural invasion. Age groups were classified as follows: 15−59, 59−64, 64−70, and 70−90 years.

Statistical analysis was performed by R 3.0.2 (http://www.R-project.org/). The distribution of continuous variables was first analyzed by the Shapiro-Wilk test of normality; then, according to the results, the Student t test or the Mann-Whitney test was used. Categorical variables were compared by Fisher's exact test. In assessing statistical significance, we compared the group of patients with relapse to the control group. The significance level was set at .05. The impact of clinical and pathologic factors on overall survival (OS), relapse-free survival, and time from relapse to death were analyzed by the Kaplan-Meier method, and log-rank tests were used to compare categories in univariate analysis. To identify prognostic factors for relapse, univariate and multivariate Cox proportional hazard models were used. The multivariate model was chosen by AIC (Akaike information criterion) in a stepwise algorithm. Cox models for relapse and relapse-free survival analyses were performed for relapse, defined as above, and time from relapse to death was analyzed for patients with disease recurrence.

Results

Material covered the period between January 2009 and January 2014. The study was conducted in a group of 14,578 patients aged 15 to 90 years (mean, 62.9 years; median, 63 years). A total of 9865 male patients (67.7%) and 4713 female patients (32.3%) were operated on (M/F ratio, 2.1:1). In the group of patients without recurrence, 1324 patients (11.3%) died of reasons unrelated to cancer, and 10,438 patients (88.7%) were still alive without recurrence. In the group of patients with recurrence, 619 patients (22%) were still alive at the time of data analysis.

Recurrence was observed in 2816 patients (19.3%), with local recurrence in 578 (20.5%) and distant metastases in 2238 (79.5%). The highest rates of distant metastases were observed in lung ($n = 945$, 42.2%), brain ($n = 512$, 22.9%), and bone ($n = 158$, 7.1%). Both types of recurrence were present at the same time in 103 patients (3.7%). Recurrence was confirmed by cytologic or histologic examination in 54% of patients. In the initial period (2009−2010), PET-CT was not performed as a standard procedure; the recurrence rate in these subjects was 36%. CT was the basic imaging modality used to confirm recurrence. In the later period (2011−2014), the rate of patients who had a PET-CT performed increased to 77%. In this group, the examination efficacy was 88%. Adenocarcinoma was diagnosed in 1201 patients (42.6%) and squamous cell carcinoma in 1093 patients (38.9%). Other types of cancer were diagnosed in 534 patients (19%).