Lung Cancer 117 (2018) 7–13

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Temporal and regional distribution of initial recurrence site in completely resected N1-stage II lung adenocarcinoma: The effect of postoperative adjuvant chemotherapy

Byung Jo Park[a,1], Jong Ho Cho[a,1], Jung Hee Lee[a], Sumin Shin[a], Hong Kwan Kim[a], Yong Soo Choi[a], Jae Ill Zo[a], Young Mog Shim[a], Jong-Mu Sun[b], Se-hoon Lee[b], Jin Seok Ahn[b], Myung-Ju Ahn[b], Keunchil Park[b], Jhingook Kim[b,*]

[a] Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Recurrence
Dynamics
Non-small cell lung cancer
Adenocarcinoma
N1 disease
Adjuvant chemotherapy

ABSTRACT

Objectives: Understanding the timing and pattern of cancer recurrence is essential to explain the causes of treatment failure. We investigated the recurrence pattern and rate over time in patients with completely resected N1-stage II lung adenocarcinoma.

Materials and methods: We retrospectively reviewed the medical records of 333 patients who underwent complete surgical resection for N1-stage II lung adenocarcinoma.

Results: The median recurrence-free survival (RFS) was 38.8 months and the 5-year RFS rate was 39.6%. Left-sided tumors, large tumor size, and lymph node (LN) ratio higher than 0.15 were significantly correlated with a worse RFS, whereas female sex, direct LN involvement, and adjuvant chemotherapy were significantly correlated with a better RFS. Among the 182 patients who experienced recurrences, 46 (25.3%) had only loco-regional recurrences and 136 (74.7%) had distant metastases. The organs most commonly involved in initial recurrence were the lungs (n = 89, 48.9%), followed by bone (n = 41, 22.5%) and the brain (n = 38, 20.9%). The recurrence hazard curve for the entire study population demonstrated a similarly shaped and sized initial and second peak at 15 and 23 months, and a third smaller peak during the fourth year. The recurrence hazard curve of patients who received adjuvant chemotherapy exhibited a more delayed and smaller first peak than those who did not receive adjuvant chemotherapy. The patients treated with adjuvant chemotherapy had a lower rate of distant metastasis (p = 0.037); adjuvant chemotherapy had no effect on brain metastasis (p = 0.640).

Conclusion: In the present cohort, the hazard curves suggested that bone and brain recurrences exhibited an earlier first peak, while lung recurrences presented later. Adjuvant chemotherapy not only reduced the recurrence hazard but also delayed the recurrence and altered the pattern of recurrence. However, these results need to be confirmed in a prospective study.

1. Introduction

Cases of non-small cell lung cancer (NSCLC) with N1 involvement, excluding stages T3–T4, are classified as early-stage lung cancer by definition, and surgery usually provides the best chance of a cure. Despite complete surgical resection, however, a considerable number of patients' experience recurrence and death from lung cancer [1,2]. Because distant metastasis is a leading cause of treatment failure [3–5], adjuvant systemic chemotherapy for resected N1 NSCLC has become standard in clinical practice to improve outcomes [6]. In spite of the introduction of adjuvant chemotherapy, survival is worse than expected; the 5-year overall survival (OS) rate for completely resected (R0) N1 NSCLC patients ranges between 34% and 61% [7]. In particular, adenocarcinoma has a higher prevalence of recurrence than other histologic types [8]. Therefore, more research is needed on how to improve these outcomes.

Many previous studies of N1 lung cancer were directed towards improving survival through adjuvant treatment, while studies focusing on treatment failure are rare. The timing and pattern of recurrences are useful to understand possible causes of treatment failure. An analysis of

* Corresponding author at: Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, 50 Ilwon-dong, Gangnam-gu, Seoul, 135-710, Republic of Korea.
E-mail address: jkimsmc@skku.edu (J. Kim).
[1] These authors contributed equally to this work as co-first authors.

https://doi.org/10.1016/j.lungcan.2018.01.004
Received 1 October 2017; Received in revised form 2 January 2018; Accepted 5 January 2018

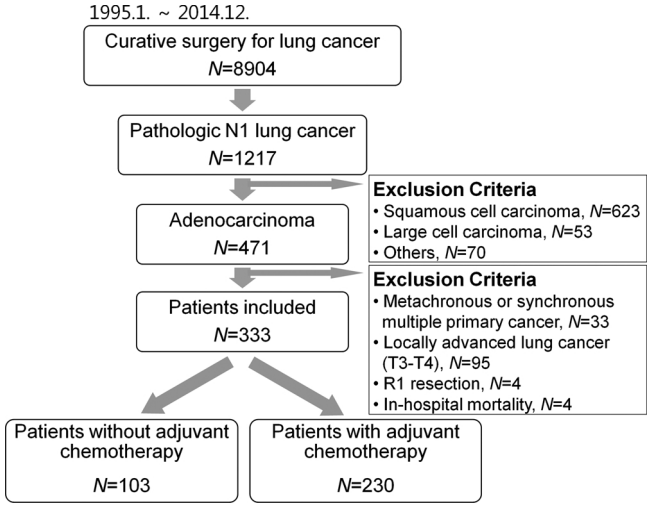

Fig. 1. Study population.

these subjects will provide insight into the actual differences among treatment strategies, clues for proper follow-up plans, and ways to overcome the limitations of current treatment options.

As N1 NSCLC is a complex and heterogeneous disease, an analysis of all patients with N1 lung cancer is not only difficult to perform but also hard to interpret. To analyze a relatively homogeneous group, we focused on adenocarcinoma, the most common type of lung cancer with a higher prevalence of recurrence than other histologic types [8,9]. In this study, we investigated the recurrence pattern and event rate over time in patients with completely resected N1-stage II lung adenocarcinoma.

2. Patients and methods

2.1. Study population

The study population is shown in Fig. 1. This study was a retrospective review of a prospective lung cancer database at our institution using data collected between January 1995 and December 2014. The inclusion criteria for this study required patients to have the following: (1) histologically proven lung adenocarcinoma, (2) a histologic confirmation of regional lymph node (N1) metastasis, and (3) undergo curative-intent surgical resection. Patients (1) who had metachronous or synchronous multiple primary cancer, (2) with locally advanced lung cancer (T3-T4), (3) with positive microscopic resection margins (R1), or (4) who died in the immediate postoperative period (within 30 days of surgery or during the initial hospitalization) were excluded. The study was reviewed and approved by the Institutional Review Board of Samsung Medical Center.

2.2. Staging workup and treatment protocol

Details of the staging workup and operative procedures are described in our previous study [10]. Pulmonary resection included segmentectomy, lobectomy, bilobectomy, sleeve resection, or pneumonectomy, as indicated. We reviewed the pathology reports to restage the cases according to the 7th lung cancer TNM classification and staging system, and described the anatomic location of LN metastases according to the Regional Lymph Node Classification for Lung Cancer Staging [11]. Our pathologists defined direct invasion of LNs as an infiltrative extension of viable tumor cells without loss of continuity from the primary tumor mass to the lymphatic tissue of an adjacent node. Postoperative thoracic radiation therapy and/or chemotherapy were optionally added for multiple N1 nodes with extracapsular invasion or close (less than 5 mm from the stump to tumor) resection margins. As a result of changing treatment guidelines on adjuvant chemotherapy, postoperative adjuvant chemotherapy has been routinely recommended since 2005.

2.3. Definition of recurrence and follow-up strategy

Disease recurrence within the surgical field such as those at the bronchial stump, pleural seeding, or regional LNs were defined as locoregional recurrences. All other sites of failure, including the contralateral lung or outside the hemithorax and mediastinum, were defined as sites of distant metastases. All patients who were diagnosed with secondary primary lung cancer with a histological type and clinical features consistent with a new primary tumor were excluded from the present study. However, for patients with multiple lung cancers of the same histological types and for those without histological confirmation, our study was limited to distinguishing the metastatic disease from a secondary malignancy.

Patterns of recurrence were assessed primarily using imaging techniques. Patients were evaluated regularly by physical examination, blood tests, chest computed tomography (CT), and/or positron emission-CT (or bone scans before 2002) every 3 months for the first 2 years after surgery, every 6 months over the next 3 years, and once per year thereafter. Whole-brain CT or magnetic resonance imaging and other imaging techniques were performed if indicated by symptoms or biochemistry. For cases requiring a pathological diagnosis to support the clinical diagnosis and the decision to initiate treatment, we performed invasive procedures including CT-guided needle biopsy, mediastinoscopy, and bronchoscopy. Late outcome data on patients who were lost to follow-up were collected by conducting telephone interviews or by examining data from the office for national statistics.

2.4. Statistical analysis

Descriptive statistics were used to illustrate patient characteristics and outcomes. Student's *t*-tests or Mann-Whitney tests, depending on the normality of distribution, and the χ^2 test or Fisher's exact tests were used to compare continuous and categorical variables, respectively. We calculated the lymph node ratio (LNR) as the ratio between the number of positive N1 nodes and the number of LNs removed from all nodal stations during surgery. Based on prior studies and on the distribution of the LNR in present data, patients were classified into two LNR groups: ≤ 0.15 and > 0.15 [12–14]. Recurrence-free survival (RFS) was defined as the time from surgery to the earliest occurrence of relapse or death. Overall survival (OS) was defined as the time from surgery to death from any cause. Patients who were lost to follow-up were censored at the time of last contact. Survival curves were prepared using the Kaplan-Meier method and were compared univariately using the log-rank test. To determine which factors were significantly associated with recurrence, univariate and multivariate analyses were performed by means of the Cox proportional hazards model. On multivariate analysis, we used the variables extracted from univariate analysis ($p < 0.1$). Estimates for the hazard function were made from right-censored data using kernel-based methods [15]. A discretization of the time axis in 6-month units was applied. All statistical tests were two-sided with a significance level set at 0.05 and were performed using SPSS software (version 18.0; SPSS, Chicago, Illinois, USA) and R software (version 3.3.0) with the "muhaz" package (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

The clinicopathological characteristics of the 333 patients are listed in Table 1. All patients were rigorously followed up, with a median follow-up time of 40.8 months.