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Research paper

Risk factors for local recurrence after lobectomy and lymph node dissection in patients with non-small cell lung cancer: Implications for adjuvant therapy

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ABSTRACT

Objectives: The objective of this study was to investigate clinicopathological risk factors for local recurrence in patients who underwent either complete resection with lobectomy or more extensive resection with hilar and mediastinal lymph node dissection for non-small cell lung cancer (NSCLC). The role of adjuvant therapy was also explored.

Materials and methods: We reviewed the records of 1012 consecutive stage I–III NSCLC patients who underwent complete resection. The median follow-up time was 59 months. The risk factors for local recurrence were investigated by multivariate analysis using Cox's proportional hazards regression model.

Results: Local recurrence was identified in 9.4% of the patients. The most significant risk factor for local recurrence was lymph node metastasis (N1: hazard ratio [HR] = 2.27, $p = 0.009$; N2: HR = 6.85, $p < 0.0001$). For the subgroup of patients with lymph node metastasis (n = 289), the independent risk factors for local recurrence were N2 disease with N1 metastasis (N2 with N1; HR = 3.46, $p < 0.0001$) and non-receipt of adjuvant platinum-based chemotherapy (HR = 1.91, $p = 0.018$). The 5-year freedom from local recurrence rates were 96.1%, 84.1%, 85.0%, and 53.5% for N0, N1, skip N2, and N2 with N1 stages ($p < 0.0001$).

Conclusion: Local recurrence is significantly associated with poor overall survival. Therefore, local control is essential for radical cure of NSCLC. N2 with N1 status was the primary risk factor for local recurrence, while adjuvant chemotherapy improved local control. These data have important implications for postoperative radiotherapy and highlight the need to devise more effective eligibility criteria for this modality in patients with lymph node metastasis.

1. Introduction

Patients with stage I, II, and certain stage III non-small cell lung cancers (NSCLCs) are considered eligible for curative radical resection. The total number of surgeries for lung cancer is increasing yearly, and the procedure's 30-day mortality rate is reportedly 0.31% according to recent Japanese registry data, even when lobectomy is performed [1]. In a 2004 study, however, the overall 5-year survival rate after resection was 69.9% among 11,633 Japanese patients; the rates were 86.8% in stage IA, 73.9% in stage IB, 61.6% in stage IIA, 49.8% in stage IIB, 40.9% in stage IIIA, and 27.8% in stage IIIB patients [2]. Better survival rates are therefore desirable.

To overcome the high risk of disease recurrence after surgery, adjuvant therapies have been investigated in randomized clinical trials; cisplatin-based chemotherapy has demonstrated survival benefits in patients with stages II and IIIA disease [3,4].

Several trials demonstrated that modern postoperative radiation therapy (PORT) reduced the risk of local recurrence, and a survival benefit was observed for patients with N2 disease. However, the role of PORT remains controversial, and the therapy is not recommended for patients with N0 and N1 disease [5–8]. To date, no consistent randomized study has shown that PORT improves overall survival. Therefore, a large, multi-institutional European phase III trial, the Lung Adjuvant Radiotherapy Trial (Lung ART), is underway to compare PORT with non-PORT treatment in patients with completely resected N2 disease [9].

Radical curing of NSCLC is impossible without local control; however, the patterns of local failure ought to be better understood to be able to select patients eligible for adjuvant radiation therapy. Many studies have investigated the predictive factors associated with local

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recurrence; however, the very definition of 'local recurrence' and the criteria for patients enrolled in such studies vary widely. For example, some studies included patients who received limited pathological staging and surgical interventions, such as those who underwent sublobar resection without lymph node (LN) dissection [10–15]. Therefore, the objective of this study was to investigate clinicopathological risk factors for local recurrence in patients with NSCLC who underwent complete resection with lobectomy or more extensive resection with hilar and mediastinal LN dissection. The implications for adjuvant therapy were also explored.

2. Patients and methods

2.1. Patients

This retrospective search the Shizuoka Cancer Center database was performed in accordance with the regulations of the institutional review board, which approved our study. Between September 2002 and December 2012, 1012 consecutive patients were diagnosed with NSCLC based on the 7th edition TNM classification and underwent complete resection. In this study, we defined complete resection as either lobectomy or more extensive resection with hilar and mediastinal LN dissection, with negative surgical margins. We performed systematic mediastinal LN dissection; we also performed lobe-specific nodal dissection for patients with certain factors such as respiratory dysfunction and cardiovascular disease who were considered high-risk for more invasive surgery [16]. We excluded patients who received induction therapy (preoperative chemotherapy and/or preoperative radiation therapy) and PORT, presented with synchronous primary lung cancer, had a prior history of lung cancer, never had postoperative follow-up, or died within 30 days of surgery. Patients with stage II and IIIA disease received platinum-based adjuvant chemotherapy when possible; 88.5% of these patients received cisplatin and vinorelbine. Administration of cisplatin (80 mg/m^2) on day 1 and vinorelbine (25 mg/m^2) on days 1 and 8, every 3 weeks, was planned for 4 cycles when possible, as previously described [17]. Other adjuvant chemotherapy agents used were carboplatin and paclitaxel (4.1%), cisplatin and pemetrexed (4.1%), cisplatin and S-1 (2.5%), and cisplatin and irinotecan (0.8%). We only performed initial surgery for clinical N2-pathological N2 (cN2-pN2) patients who fulfilled our predefined specific criteria (single-station N2, non-bulky N2, N2 with regional mode of spread, and N2 without N1), as previously reported [18]. Intrapulmonary metastasis was defined as presence of additional nodules in the ipsilateral lobe, not as intrapulmonary LN metastasis by pathological investigation. Lymphovascular space invasion (LVI) was defined as the presence of tumors within the lymphatic and/or blood vessels.

2.2. Patient follow-up

Chest radiography was obtained every 3 months for the first 3 years after surgery and every 6 months for the following 2 years. Computed tomography (CT) scans of the chest and upper abdominal area were obtained every 6 months during the first 3 years after surgery and annually during the following 2 years. After 5 years, either chest radiography or CT was performed annually to check for evidence of recurrence. Some variations in this regular schedule were necessary, especially in patients with signs of recurrence or those at high risk of recurrence. Additional images were obtained at the discretion of the treating physician.

2.3. Definition of recurrence

Disease recurrence at the surgical resection margin, ipsilateral hilum, and ipsilateral or contralateral mediastinum was considered local recurrence. All other sites of failure, including the supraclavicular fossa, contralateral hilum, and ipsilateral lobe of the lung were considered distant recurrences. Only the sites of initial recurrence were recorded. Patients with simultaneous local and distant recurrences were scored as having both types of failure. Patterns of recurrence were assessed by follow-up imaging studies supplemented with invasive procedures, such as bronchoscopy and CT-guided transthoracic biopsies, as clinically indicated. Nodal failure was defined as a new or enlarging LN $\geq$1 cm on short axis CT and/or hypermetabolism on positron emission tomography that were consistent with disease progression on the patient's subsequent clinical follow-up. All cases of possible local and distant recurrences were reviewed during the thoracic oncological conferences of our institution; these conferences included thoracic surgeons, thoracic oncologists, radiation oncologists, and diagnostic radiologists. A second primary tumor was scored when a patient presented with a lesion of a different histology, or a lesion with the same histology but with a clinical presentation most consistent with a new primary tumor. Upon differential diagnosis between a second primary lung cancer and pulmonary metastasis, 21 s primary lung cancers were pathologically confirmed in 20 patients, while 16 pulmonary metastases were pathologically confirmed in 11 patients. Freedom from local recurrence (FFLR) was defined as the time from the date of surgery to the first diagnosis of local recurrence or the most recent follow-up visit. Recurrence-free survival (RFS) time was measured from the date of surgery to the date of the first occurrence of the event (recurrence [local or distant] or death). Overall survival (OS) was measured from the date of surgery to the date of death from any cause.

2.4. Statistical analysis

The associations between variables were analyzed using Fisher's exact test. The cumulative postoperative recurrence and OS rates were estimated by using the Kaplan-Meier method, with statistical significance determined by the log-rank test. Landmark analyses were performed to compare survival between patients with and without recurrence. The recurrences were divided into 3 investigative categories: local only, distant only, and simultaneous local and distant recurrences. In landmark analyses, OS rates were calculated conditional at being alive at 1, 2, and 3 years from the date of surgery. To evaluate independent risk and prognostic factors, univariate analysis was performed using the Cox proportional hazards model. The variables that were found to be significantly different on univariate analysis were subjected to multivariate analysis using Cox's proportional hazards regression model. Differences were considered statistically significant when p-values were < 0.05. Patients with simultaneous local and distant recurrences were scored as having both types of failure on univariate and multivariate analyses. Patients who developed a second primary lung cancer were censored on the date the second malignancy was diagnosed.

3. Results

The median patient follow-up period was 59 months (range: 6–139 months). The patients' characteristics are shown in Table 1. The median patient age was 65 years (range: 20–89 years). There were 625 (62%), 211 (21%), and 176 (17%) patients with pathological stages of I, II, III, respectively. Among all 1012 patients, 266 experienced recurrences (26.3%). Local recurrence occurred in 95 patients (9.4% of the entire population and 35.7% of those with any recurrences); 12 patients had recurrences in the surgical margin and 85 in the regional LNs. Of these local recurrences, 58.9% (56/95) were detected within 1 year, 90.5% (84/95) within 3 years, and 95.8% (91/95) within 5 years.

Distant recurrence was identified in 224 patients (20.8% of the population and 86.1% of all patients with recurrences of any type). Among patients with any type of recurrence, 15.8% had only local recurrence, 64.3% had only distant metastasis, and 19.9% had both local and distant recurrences. Of overall recurrences, 52.6% (140/266) were detected within 1 year, 89.1% (237/266) within 3 years, and 97.0%