Prognostic factors for post-recurrence survival in patients with completely resected Stage I non-small-cell lung cancer

In Hag Song, Sung Won Yeom, Seohee Heo, Won Suk Choi, Hee Chul Yang, Sanghoon Jheon, Kwhamnien Kim and Sukki Cho

Abstract

OBJECTIVES: The clinical course from recurrence to cancer-related death after curative resection has not been clearly elucidated in non-small-cell lung cancer (NSCLC). This study examined the clinical outcomes after postoperative recurrence in patients with completely resected Stage I NSCLC.

METHODS: This study included patients who had recurrence after complete resection for pathological Stage I NSCLC between 2003 and 2009. Clinical data evaluated in this study included the diagnostic process of recurrence, recurrence pattern, treatment process and prognosis. A number of clinicopathological factors were analysed for post-recurrence survival by univariate and multivariate analyses.

RESULTS: Seventy-two patients experienced recurrence during a median follow-up period of 37.5 months. Thirteen patients (18%) presented symptoms at the initial recurrence. Tumour markers, computed tomography (CT) and positron emission tomography/CT were chosen as the initial diagnostic tools and detected recurrences in 1 (1%), 51 (71%) and 7 (10%) patients, respectively. The mean recurrence-free interval (RFI) was 15.4 months (≤12 months in 34, >12 months in 38 patients). The patterns of recurrence were presented as loco-regional recurrence in 36 (50%) and distant metastasis in 36 patients (50%). Types of the initial treatment included operations in 28 (39%), chemotherapy and/or radiotherapy in 38 (53%) and radiofrequency ablation in 2 patients (3%). Four patients (6%) rejected treatment. Forty-three patients (62%) presented a good response to the initial treatment. Thirty-seven patients (51%) died, and the cause of death in all of these patients was cancer-related. The median survival duration after recurrence was 43.6 (1–136) months. Univariate analysis identified no recurrence of symptoms, a good response to treatment and a longer RFI as good prognostic factors, while a good response to treatment and a longer RFI were independent prognostic factors in multivariate analysis.

CONCLUSIONS: Most postoperative recurrences were detected in an asymptomatic condition during the routine follow-up period, and a good response to initial treatment and a longer RFI were significant predictors of better post-recurrence survival in patients with completely resected Stage I NSCLC.

Keywords: Non-small-cell lung cancer • Stage I • Recurrence • Post-recurrence survival

INTRODUCTION

Despite surgical resection, which is considered to be the most appropriate choice of treatment for early-stage non-small-cell lung cancer (NSCLC) [1, 2], the recurrence rate of Stage I NSCLC is 22–38% while the 5-year survival rate is reported to be 55–80% [3–8]. Considering that ~80% of recurrence occurs within the first 2 years, many clinicians have tried to detect recurrence at a treatable stage or early signs of second primary lung cancer through postoperative surveillance to increase survival [9, 10]. As for recurrence, previous retrospective studies had endorsed only the concept of less intensive surveillance (symptom-based) because benefits in survival had not yet been demonstrated by more intensive surveillance [11–13]. However, recent studies have demonstrated that asymptomatic recurrences detected by intensive surveillance presented a better prognosis than symptomatic recurrences [14]. In general, chemotherapy, radiotherapy or concurrent chemoradiotherapy are mainly chosen as the treatment option for recurrence because the majority of recurrence has been reported to occur in a form of distant metastasis; between 7 and 15% of recurrence is loco-regional [4–6], and between 14 and 23% is distant metastasis [15–17]. However, surgical treatment has also been preferred in selective patients if they meet the criteria for surgical resection.

Recently, with the advancement of minimally invasive surgery, targeted chemotherapy, gamma knife surgery (GKS), stereotactic body radiotherapy and radiofrequency ablation (RFA), indications for treatment of recurrence and its outcomes have been extensively...
improved, and diagnosis and treatment of postoperative recurrence might have been improved in patients with pathological Stage I NSCLC as well. Hence, differences in clinical outcomes after complete surgical resection for pathological Stage I could be expected considering a variety of diagnostic tools and development of operative or non-operative treatment methods.

Therefore, this study aimed to evaluate prognostic factors for post-recurrence survival in patients with completely resected Stage I NSCLC.

MATERIALS AND METHODS

This study retrospectively reviewed the records of 986 patients who underwent surgery for NSCLC at Seoul National University Bundang Hospital between June 2003 and December 2009. Among them, 475 patients (48%) had pathological Stage I disease. This study excluded patients who received neoadjuvant therapy and patients who had metachronous or synchronous multiple primary lung cancer. Patients were followed up every 3 months for the first 2 years and then every 4 months for an additional 3 years. Data analysed in this study included patient's history, physical examination, chest radiograph and tumour markers such as carcinoembryonic antigen, cytokeratin fragment 21-1 and squamous cell carcinoma (SCC) antigen or neurone-specific enolase only if elevated before the operation. A contrast-enhanced chest computed tomography (CT) scan was taken every 3 months for the first 2 years and then every 6 months thereafter. If recurrence was suspected either through newly presenting symptoms or through scheduled tests, integrated positron emission tomography/CT (PET/CT) was performed. Even if patients showed no symptoms or abnormal findings in the scheduled tests, integrated PET/CT was performed ~1 year after the curative resection.

Final diagnosis of recurrence was confirmed by the histopathological examination of samples obtained from surgery or biopsy. If it was impossible to diagnose the recurrence histopathologically, recurrent malignancy was no longer suspected based on the clinical and radiological follow-up period of at least 12 months with no evidence of active malignancy. Loco-regional recurrence was defined as the recurrence in the ipsilateral hemithorax including the mediastinal lymph nodes, and distant metastasis was defined as the recurrence in the contralateral hemithorax and extrathoracic organs.

As the treatment method, surgery was performed if the patient presented a single lesion without any other lesions, if the patient was in a physically operative condition, or if complete resection was able to be performed. Otherwise, other non-operative methods were performed as the choice of treatment. In patients with pulmonary metastasis, if the lesion was a single lesion, or if it was impossible to distinguish whether it was metachronous double primary lung cancer, surgery was performed after tolerable postoperative pulmonary function was guaranteed. Especially in patients with contralateral lung metastasis, surgery was chosen not only if the patient met all those conditions but also if the patient was without lymph node metastasis.

Before the initial operation, patients were reviewed for their age, smoking history, T stage and histological type. Also, the presence of recurrence symptoms, detection methods, recurrence patterns, treatments for recurrence and responses to treatment were analysed. Regarding the responses to chemotherapy or radiotherapy, based on the Response Evaluation Criteria in Solid Tumours (RECIST) guideline, a complete response (CR) and a partial response (PR) were evaluated as a good treatment response, and stable disease (SD) and progressive disease (PD) were evaluated as a poor treatment response. However, due to the lack of a standardized method to evaluate responses to surgical treatment, in our study, complete resection was defined as a good response, and incomplete resection was defined as a poor response. When an immediate postoperative CT scan confirmed additional recurrence, it was also defined as a poor response to the treatment.

The Kaplan–Meier log-rank test was used for univariate analysis, and the Cox proportional hazards model was used for multivariate analysis. A forward stepwise selection procedure was implemented with a P-value threshold of 0.05 for inclusion in the multivariate analysis. Statistical significance was accepted when the P-value was <0.05. All data were analysed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Of 986 patients who underwent surgical resection during the study period, 259 patients experienced recurrences, and among recurrent patients, 72 patients (28%) were diagnosed with pathological Stage I lung cancer and enrolled in this study. Forty-seven patients (65%) were male, and the mean age was 64.6 ± 10.8 years (range, 34–84). Forty patients (56%) were ever smokers. The number of patients who were diagnosed with Stage T1 cancer was 22 (31%) and with Stage T2 cancer was 50 (69%). Pathological examination of the resected specimens confirmed adenocarcinoma (AC) in 46 patients (64%) and squamous cell carcinoma (SQCC) in 15 patients (21%). The median follow-up duration was 37.5 (4.4–97.5) months (Table 1).

Recurrence

Only 13 patients (18%) discovered the recurrence via symptoms, and 59 asymptomatic patients (82%) discovered the recurrence as follows: 1 (1%) via abnormality of tumour markers, 51 (71%) via computed tomography (CT) scan was taken every 3 months for the first 2 years and then every 4 months for an additional 3 years. Data analysed in this study included patient's history, physical examination, chest radiograph and tumour markers such as carcinoembryonic antigen, cyto

<table>
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<th>Variables</th>
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<tr>
<td>Age, mean ± SD, years</td>
<td>64.6 ± 10.8</td>
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<tr>
<td>≤65</td>
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<tr>
<td>&gt;65</td>
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<tr>
<td>Female</td>
<td>25 (35)</td>
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<tr>
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<td>46 (64)</td>
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<td>Neuroendocrine carcinoma</td>
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CT and 7 patients (10%) via PET/CT. The mean recurrence-free interval (RFI) was 15.4 ± 10.7 months, and 34 patients (47%) had an RFI of 12 months or less, while 38 patients (53%) had an RFI of longer than 12 months. Although it was not statistically significant, the mean RFI was longer in asymptomatic patients (16.4 ± 10.9 months) than in symptomatic patients (10.6 ± 8.8 months) (Table 2).

Loco-regional recurrence occurred in 36 patients (50%); 28 patients (39%) experienced the recurrence without ipsilateral mediastinal lymph node (MLN) metastasis, while 8 patients (11%) experienced the loco-regional recurrence with ipsilateral MLN metastasis. In patients without ipsilateral MLN metastasis, the most common site of recurrence was the ipsilateral lung, where it presented in 20 cases (28%), and the recurrences also occurred at the stump site and pleura, where it presented in 4 cases (6%) each. Among 8 patients with ipsilateral MLN metastasis, 4 patients (6%) had LN metastasis only, 2 patients (3%) presented a poor response. Among the 28 patients with recurrence at the stump site, 2 received completion pneumonectomy, and the patient with recurrence in the pleura received pleurectomy.

Regarding distant metastasis, surgery was performed only in 15 patients with single-organ metastasis. Those 15 patients included 6 out of 8 patients with recurrence in the lung (wedge resection = 4, segmentectomy = 2), 4 out of 6 patients with recurrence in the brain (GKS = 3, craniotomy = 1), 2 patients with recurrence in the adrenal gland (adrenalectomy) and 3 out of 9 patients with others (mass excision of right atrium, nephrectomy and mediastinal LN dissection).

### Response to treatment

Having excluded the 4 patients who rejected treatment, the responses to treatment from 68 patients were evaluated. Forty-three patients (63%) presented a good response, and 25 patients (37%) presented a poor response. Among the 28 patients who received surgical treatment, 24 patients presented a good response and 4 patients presented a poor response (Table 4).

Among the 46 patients with pathological results of AC, 43 patients received tests for epidermal growth factor receptor (EGFR) mutation, and 26 of them were reported to be positive for EGFR mutation. Out of those 26 patients positive for EGFR mutation, 9 patients underwent tyrosine kinase inhibitor (TKI) treatment; 2 presented a CR, 1 presented a PR and 6 patients presented PD.
Survival

The median post-recurrence survival period was 43.6 months, and the 1- and 3-year overall survival (OS) rates were 88 and 53%, respectively. In terms of recurrence patterns, 1- and 3-year OS in those with loco-regional recurrence were 88 and 55%, respectively, and in those with distant metastasis were 86 and 46%, respectively. There was no statistically significant difference between loco-regional recurrence and distant metastasis ($P = 0.83$) (Fig. 1). Among the 36 patients with loco-regional recurrence, 21 experienced re-recurrence, and the 1-year recurrence-free survival was 43%. Among the 36 patients in the loco-regional recurrence group, 13 patients with and 23 without the surgical intervention were compared. The numbers of patients who died were 6 and 9, respectively, and the 3-year post-recurrence survival rates were 61 and 57%, respectively, where no statistical significance was observed.

Prognostic factors for significantly poor post-recurrence OS were identified by the univariate analysis as follows: presence of symptoms ($P = 0.01$), recurrence within 12 months of surgery ($P = 0.02$), not having received any treatment ($P = 0.04$) and a poor response to treatment ($P < 0.01$). The multivariate analysis revealed that recurrence within 12 months of surgery [odd ratio (OR): 2.11, 95% confidence interval (CI): 1.03–4.31, $P = 0.04$] and a poor response to treatment (OR: 2.62, 95% CI: 1.26–5.45, $P = 0.01$) were the independent prognostic factors for significantly poor post-recurrence OS (Table 5).

DISCUSSION

Because most of the patients with recurrences are seen by medical oncologists, for thoracic surgeons, relatively little is known about the clinical course of post-recurrence and the prognostic factors influencing post-recurrence survival in early-stage NSCLC. In the present study, there were 72 patients with pathological Stage I NSCLC who experienced recurrences postoperatively, which was 28% out of 259 patients with recurrences in all stages. Among those 72 patients, there were 59 asymptomatic patients, which was over 80%. Due to the increasing number of patients with early-stage lung cancer, the number of recurrence in patients who are diagnosed with pathological Stage I disease has also been growing. With the help of intensive postoperative surveillance and the advancement of diagnostic methods, the numbers of patients with recurrences and their early detections have been increasing, which makes this study more noteworthy.

Analysis of recurrence patterns provides information on which part to focus on during the postoperative follow-ups in patients with pathological Stage I lung cancer. Most of the recurrences in patients with pathological Stage I lung cancer occur within 2 years, and distant metastasis has been known to occur more frequently than loco-regional recurrence [4–10]. In this study, the mean RFI was 15.4 months, and similar to the results from other studies, 57 patients (79%) experienced recurrences within 2 years of surgery. Also in this study, recurrence within 12 months of surgery was revealed to be an independent prognostic factor for significantly poor post-recurrence OS.

By adopting the intensive surveillance protocol, more asymptomatic patients (82%) in this study were able to be detected than in other studies. Although there could be a controversy over the cost-effectiveness or survival benefits in terms of routine postoperative PET/CT on asymptomatic patients, this particular test allows the detection of recurrence or other primary cancer in
asymptomatic patients at once [18, 19]. In general, as a choice of treatment for recurrence of lung cancer, non-surgical treatment has been selected in most cases where systemic chemotherapy combined with radiotherapy was implemented [17, 20] However, recently, surgical resection has also been performed in localized local or distant recurrences [15–17]. Diagnosing and treating the recurrence before symptoms arise allows more aggressive treatment since asymptomatic patients are in better condition than patients with symptoms. Since asymptomatic patients are in better condition than patients with symptoms, they more likely meet the physical condition to endure more aggressive treatment, which proves the benefit of diagnosing and treating the recurrence before symptoms arise.

Walsh et al. [12] reported that complete surgical resection and high-dose radiotherapy with curative intent significantly increased the post-recurrence survival. Also, Sugimura et al. [15] and Yoshino et al. [20] reported that surgical resection and a combination of chemotherapy and radiation therapy significantly increased the survival rate as well. Such an improved prognosis could be explained by the recent development of various treatment methods and the enhancement of their effects, which enabled the personalized treatment designed based on the degree of recurrence and the recurrence patterns.

In terms of surgery as a treatment option, previously, open thoracotomy was the only choice even in limited resection, and this caused surgeons to be hesitant about aggressive surgical intervention for recurrences considering patients’ condition. However, the recent adoption of video-assisted thoracic surgery (VATS) has contributed to the advancement of minimally invasive surgery, and the number of patients who receive surgical treatment for recurrences has been increasing. In this study, among the 28 patients who underwent pulmonary resection, 7 patients received surgery via VATS.

Regarding chemotherapy, with the help of targeted therapy, proper chemotherapeutic agents could be chosen depending on the types of cancer, and this influences positively and extensively patients’ responses to the treatment of recurrences.

GKS for brain metastasis, RFA on patients whose condition is not good enough for surgery and photodynamic therapy can also be implemented as the treatment options.

Examining the appropriateness of the various treatment methods for the recurrence described in this study, it can certainly be expected that good treatment responses could yield good prognoses as well. Therefore, this study focused on the relationship between the various responses to the different treatment methods and the prognosis of the recurrence. For evaluating the treatment responses to chemotherapy or radiotherapy, the RECIST guideline was used to classify SD and PD as the poor treatment response. However, because there was no standardized way available to evaluate responses to surgical treatment, in our study, complete resection was defined as a good response and incomplete resection was defined as a poor response. Among the 43 patients who presented a good treatment response, the number of patients who underwent surgery was 24 (86%), and the number of patients who received chemotherapy and radiation therapy was 19 (50%). The higher rate of a good response in patients who underwent surgery was explained by the strict selection of the patients in whom surgical intervention was made only of those who had localized recurrences or those who were in a good enough condition to undergo surgery. Responses to chemotherapy are expected to improve further with targeted therapy. EGFR-TKI has been known to be a very effective chemotherapeutic agent in some patients, and it is a very important tool in recurrence treatment because it allows postoperative evaluation for mutations, which could be used to predict the response. In this study, a poor response to treatment was revealed to be an independent prognostic factor for significantly poor post-recurrence OS. One- and 3-year post-recurrence OS were 88 and 53%, respectively. Also, the 1- and 3-year survival rates in loco-regional recurrence were 88 and 55%, respectively, and those in distant metastasis were 86 and 46%, respectively.

However, Hung et al. [9, 10] reported that the 1- and 2-year post-recurrence survival in patients with local recurrence were 48.7 and 17.6%, respectively, and those in patients with single-organ metastasis were 30.2 and 15.1%, respectively. Also, Yoshino et al. [20] reported 15.7% as the 2-year survival after distant organ metastasis. The reasons for so much lower rates in these studies than in our study could include, first, the recent advancement of chemotherapy and radiation therapy along with surgery, and second, and most importantly, the higher rate of surgical intervention in our study. In case of pulmonary resection, double primary lung cancer could have been a possibility, but it is highly unlikely since the pathologists in our study performed an immunohistochemical staining or mutation profile in the resected specimen and reported different clonal origins from the initial surgery.

Among the prognostic factors that were reported to be significant by univariate analysis, presence of symptoms has been known as the conventional prognostic factor. However, lead time bias could exist in this factor and could have been asserted in the past when the outdated therapy was implemented. However, our research confirmed a shorter recurrence-free time in the symptomatic patients than in the asymptomatic patients. Whether or not the patients present symptoms, early detection with the proper treatment would have a more positive influence on the survival period.

The disease-free interval (DFI) has also been known to be a prognostic factor for post-recurrence OS [12, 15, 17]. Even though it has not been applied to the TNM staging system, DFI is a direct measure of tumour biology. With a short DFI, there might be systemic micrometastasis that could not be discovered before or during surgery. Therefore, this study carefully compared the preoperative CT with the CT results after the recurrence in patients who presented MLN metastasis to check whether pre-existing lung cancer was misdiagnosed with the recurrence.

There could be limitations in this study. Since it was a retrospective review at a single centre, unintentional selection or referral bias could exist. Also, because there is no standardized evaluation system at this time, responses to surgical treatment were arbitrarily defined.

In conclusion, this study confirmed post-recurrence survival in 72 patients with Stage I NSCLC. In most of them, the recurrence was detected during routine follow-ups in an asymptomatic condition. Contrary to other studies, which reported the rate of distant metastasis to be twice as high as the rate of loco-regional recurrence, this study showed similar rates of loco-regional recurrence and distant metastasis. Multivariate analysis revealed that the RFI of 12 months or longer and the good response at initial treatment were the significant predictors for better recurrence survival.

Conflict of interest: none declared.
REFERENCES