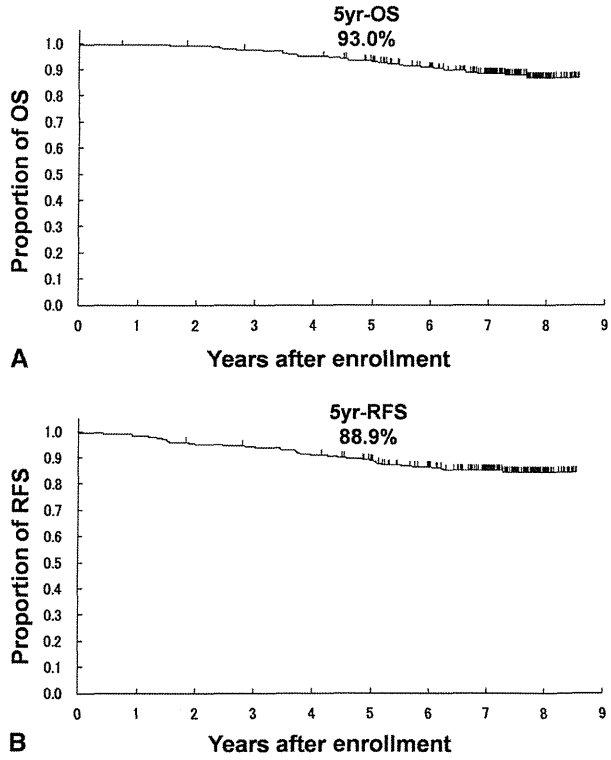

FIGURE 4. Overall (A) and relapse-free (B) survival curves for the cT1a (≤2.0 cm) group (n = 289). *OS*, Overall survival; *RFS*, relapse-free survival.

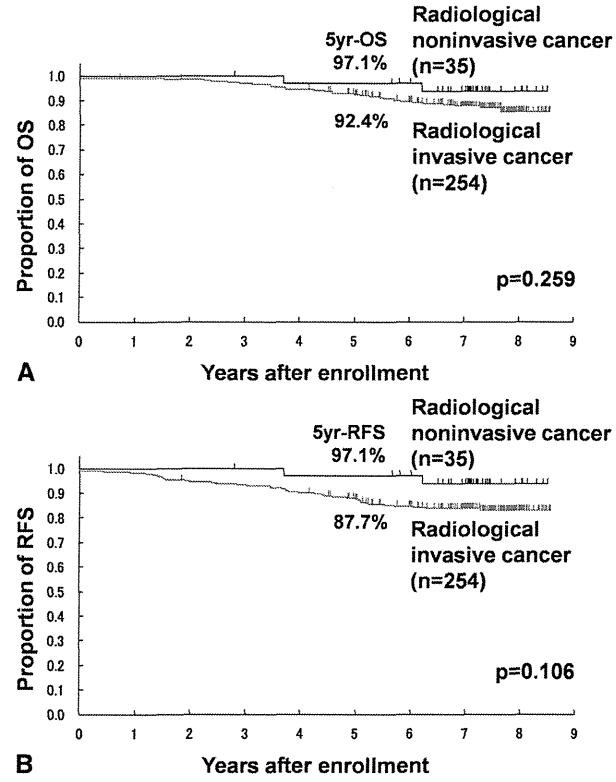

FIGURE 5. Overall (A) and relapse-free (B) survival curves for radiologically noninvasive (n = 35) and invasive (n = 254) adenocarcinomas based on a C/T ratio of 0.25 or less in cT1a (≤2.0 cm) for noninvasiveness on TSCT. The differences in overall and relapse-free survival are not statistically significant (P = .259 and .106, respectively). *OS*, Overall survival; *RFS*, relapse-free survival; *C/T*, consolidation/tumor; *TSCT*, thin-section computed tomography.

(P = .003). The relapse-free survival curves for radiologic noninvasive cancer (n = 54) and invasive cancer (n = 200) are presented in Figure 6, *B*. The 5-year relapse-free survivals for noninvasive and invasive cancer were 94.4% and 76.0%, respectively, and the difference in relapse-free survival was statistically significant (P = .003).

DISCUSSION

During the past 80 years, the surgical mode of pulmonary resection for lung cancer has evolved from pneumonectomy to lobectomy.[10,11] Currently, resection of the entire tumor-bearing lobe is being adopted as the standard mode of surgical resection for lung cancer. During this period, attempts have been made to minimize the resection through lobectomy to limited sublobar resection. Most importantly, the North American Lung Cancer Study Group conducted a prospective, randomized trial that compared limited resection with lobectomy for stage I lung cancer.[12] The principal finding in that study was a 3-fold increase in local recurrence (17.2% vs 6.4%) in patients who had sublobar resection and a 2.4-fold increase in those with segmental resection. A 30% increase in the overall death rate and a 50% increase in the rate of death with cancer in patients with limited resection were also observed compared with those with lobectomy. Therefore, it was concluded that lobectomy should still be considered the surgical procedure of choice for peripheral T1N0 non–small cell lung cancer. However, present-day critiques of this study are arising with regard to the marginal prognostic significance, poor preoperative workup for metastasis, slow accrual rate of the study, absence of data on pulmonary function (no demonstration of superiority in pulmonary function for lesser resection), and the notion that this study is outdated.

Despite the results of the North American Lung Cancer Study Group study, many nonrandomized studies have been published, and their results suggested that an equivalent prognosis could be achieved with limited sublobar resection for selected non–small cell lung cancer as with lobectomy.[13-18] Especially for earlier forms of noninvasive or minimally invasive adenocarcinoma such as bronchioloalveolar carcinoma, it has been shown that these cases present with a GGO appearance on TSCT and could be treated with limited sublobar resections, such as wide wedge resection and segmentectomy.[13-18] Because of the accumulation of excellent prognoses by limited resection in nonrandomized studies, surgeons require a fair comparison of lobectomy

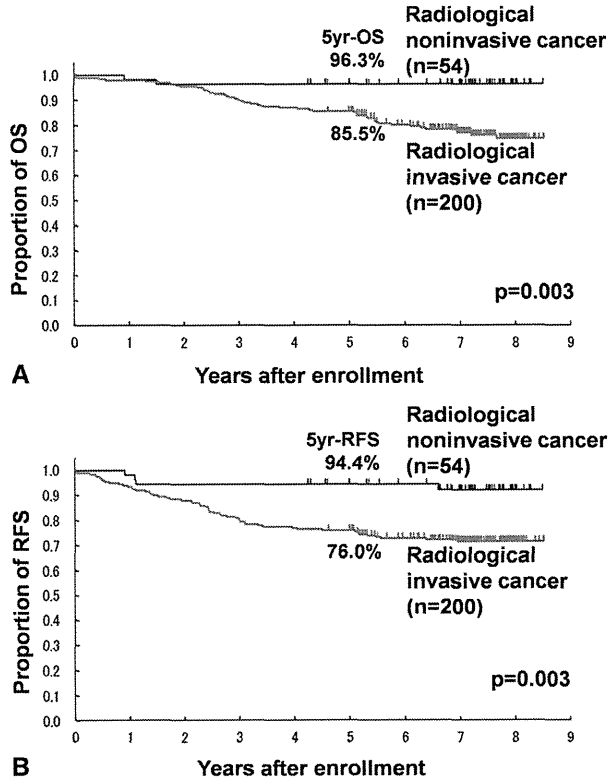

FIGURE 6. Overall (A) and relapse-free (B) survival curves for radiologically noninvasive (n = 54) and invasive (n = 200) adenocarcinomas based on a C/T ratio ≤0.5 in cT1b (>2.0-3.0 cm) for noninvasiveness on TSCT. The differences in overall and relapse-free survival are statistically significant (P = .003 and .003, respectively). *OS*, Overall survival; *RFS*, relapse-free survival; *C/T*, consolidation/tumor; *TSCT*, thin-section computed tomography.

and limited resection according to appropriate radiologic criteria for patient selection.

The radiologic criteria for noninvasive adenocarcinoma need to be evaluated by both pathologic and prognostic aspects. The radiology-pathology correlation has been studied in detail in JCOG0201, and the results have been published.[8] Briefly, JCOG 0201 failed to demonstrate that a C/T ratio 0.5 or less in T1a-b is precisely predictive of pathologic noninvasiveness. The specificity and sensitivity for these criteria were 96.4% (95% CI, 92.3-98.7) and 30.4% (95% CI, 25.8-35.3), respectively, and they did not reach the hypotheses in the JCOG 0201 study that the lower limit for 95% CI of specificity exceeds 97%. However, according to an exploratory study, a C/T ratio 0.25 or less in cT1a (≤2.0 cm) showed a specificity of 98.7% and a sensitivity of 16.2%, which was more precise for indicating noninvasive pathologic features. On the basis of these results, we recognized that a C/T ratio 0.25 or less in cT1a (≤2.0 cm) on TSCT is a better indicator of a noninvasive histology as early adenocarcinoma than a C/T ratio 0.50 or less in cT1a-b (≤3.0 cm). In this additional study of JCOG 0201, we looked at the prognoses obtained by these 2 radiologic criteria and focused on whether noninvasive adenocarcinomas defined by these 2 criteria could indicate a good prognosis as early adenocarcinoma.

In contrast to the results regarding the radiology-pathology correlation in the JCOG 0201 study, superb prognoses were obtained for noninvasive adenocarcinomas according to both of these criteria: The 5-year overall survivals for a C/T ratio 0.50 or less in cT1a-b (≤3.0 cm) and a C/T ratio 0.25 or less in cT1a (≤2.0 cm) were 96.7% and 97.1%, respectively. Although our previous report stated that a C/T ratio 0.25 or less in cT1a (≤2.0 cm) was an appropriate indicator to select patients with noninvasive lung adenocarcinomas suitable for limited sublobar resection,[8] these results indicate that even with a generous radiologic criterion on TSCT (a C/T ratio ≤0.50 in cT1a-b), we can precisely select a group of patients with early adenocarcinomas who have an excellent prognosis. For these patients, it is considered that limited sublobar resection achieves a prognosis that is almost the same as that with lobectomy and a better preservation of the lung parenchyma. In terms of the postoperative prognosis, this analysis indicates that noninvasive adenocarcinomas can be properly selected on TSCT using radiologic criteria of a C/T ratio of 0.50 or 0.25.

There is a caution regarding the excellent prognoses of the patients with noninvasive adenocarcinomas in this study. Patients included in the JCOG 0201 study underwent lobectomy and hilar/mediastinal lymph node dissection, which is usually indicated for any type of resectable lung cancer as a radical resection. The prognoses in this study were achieved by such radical resection; therefore, the same prognoses are not warranted for these tumors if they are resected with limited sublobar resections, although this was suggested by previous studies with case series.[13-18] We should still be prudent in addressing the excellent prognoses of early adenocarcinomas with surgical resection other than lobectomy.

On the basis of these results, 2 prospective, collaborative studies between JCOG and the West Japan Oncology Group, JCOG0804/WJOG4507L (UMIN-CTR [www.umin.ac.jp/ctr/] No. UMIN000002008) and JCOG0802/WJOG4607L (UMIN-CTR No.UMIN000002317), are under way on peripherally located adenocarcinomas of the lung.[19] In these studies, a radiologic criterion of a C/T ratio 0.25 or less in cT1a is used to define noninvasive adenocarcinomas. For radiologic noninvasive adenocarcinomas with a tumor diameter of 2 cm or less, a phase II study with 1 experimental arm (JCOG0804/WJOG4507L) is under way in which tumors are resected with a wide wedge resection. As of March 2012, the target number of accrual (330 patients) was reached, and maturation of follow-up data on recurrence and prognosis is awaited. For radiologic invasive adenocarcinomas with a tumor diameter 2.0 cm or less and

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a C/T ratio greater than 0.25, a prospective, randomized phase III study (JCOG0802/WJOG4607L) between lobectomy and segmentectomy in a noninferiority setting is under way. The primary and key secondary end points are overall survival and postoperative pulmonary function, respectively. If the prognosis of those undergoing segmentectomy is not inferior to that of those undergoing lobectomy and the pulmonary function of those undergoing segmentectomy is significantly better than that of those undergoing lobectomy, we will conclude that segmentectomy should be the standard mode of pulmonary resection for a peripherally located radiologic invasive adenocarcinoma with a diameter of 2.0 cm or less and a C/T ratio greater than 0.25. The target number of patients is 1100, and accrual is under way. This study will clarify the pathologic and survival outcomes of the patients with cT1a (≤2.0 cm) tumor and a C/T ratio ranging from 0.25 to 0.5, and might validate the radiologic definition of a C/T ratio 0.5 or less for noninvasive lung adenocarcinoma among the cT1a (≤2.0 cm) group. In North America, a similar study entitled Cancer and Leukemia Group B 140503 is also under way, in which the prognosis and preservation of pulmonary function is compared between lobectomy and limited resection in a noninferiority setting.[20,21] The current survival analysis showed that noninvasive adenocarcinomas indicative of limited resection could be selected by the size of 3 cm or less and a C/T ratio 0.5 or less. Even the patients with cT1b tumors (>2-3 cm) may be candidates for limited resection if their preoperative C/T ratio is 0.5 or less. For cT1b tumors, segmentectomy but not wide wedge resection should be considered as an appropriate limited resection to obtain adequate surgical margins. Future prospective study will be needed to investigate the clinical significance of intentional segmentectomy for such a population.

CONCLUSIONS

Despite the finding that a noninvasive pathology is better predicted with a C/T ratio 0.25 or less on TSCT in cT1a (≤2.0 cm) than with 0.50 or less in cT1a-b (≤3.0 cm), both of these radiologic criteria could identify a group of patients with an excellent prognosis, with a 5-year overall survival of approximately 97%. These criteria can be used to select patients with peripherally located adenocarcinomas in whom a limited resection, such as wide wedge resection or segmentectomy, might be safely indicated.

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Case Report

Resection of a Second Primary Lung Cancer in a Lobe Where Small-Cell Lung Cancer was Previously Treated with Chemoradiotherapy: Report of a Case

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There are few reports of resected cases of second primary lung cancer in post-treatment survivors of small-cell lung cancer. Here, we report a surgical case of a 62-year-old female with second primary lung adenocarcinoma after chemoradiotherapy against small-cell lung cancer. She had been treated for small-cell lung cancer 2 years earlier , and achieved complete response after the treatment. A new nodular lesion was detected at a different segment in the right lower lobe. We performed a right lower lobectomy accompanied with systemic mediastinal nodal dissection. Histopathological findings revealed that the new nodular lesion was a second primary lung adenocarcinoma. No metastatic tumor was seen in the dissected lymph node; the initial tumor had disappeared completely. The postoperative course was uneventful, and she was discharged on day 10 after the operation. Ten months after the operation, she was free of recurrent tumor.

Keywords: small-cell lung cancer, second primary lung cancer, lobectomy

Introduction

Although survivors of small-cell lung cancer have increased risk for second primary lung cancers,[1] patients in whom both initial small-cell lung cancer and second primary lung cancer were resected and examined histopathologically are little reported.[2] Here, we report a case of a survivor of small-cell lung cancer with second primary lung adenocarcinoma in the same lobe. Both tumors were removed and investigated histopathologically.

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Case Report

A 62-year-old female presented to our hospital with a tumor shadow in the right lung field, shown by chest X-ray (**Fig. 1A**); followed by a mass lesion in the right lower lobe, shown by chest computed tomography scan (**Fig. 1B**); small-cell lung cancer without other histological cancer components, by transbronchial biopsy (**Fig. 1C**); and an accumulation at the primary tumor and a lobar lymph node, by fluorodeoxyglucose-positron emission tomography (FDG-PET; **Fig. 1D**). After limited-disease small-cell lung cancer was diagnosed, she was treated with four chemotherapy cycles of cisplatin plus etoposide, and a total 45 Gy of concurrent radiotherapy, and the tumor shadow disappeared (**Fig. 2A**). Two years after this treatment, a new nodular lesion appeared at a different segment in the right lower lobe, and grew progressively (**Fig. 2B**). FDG-PET revealed an accumulation at only the nodular lesion. All serum tumor maker levels

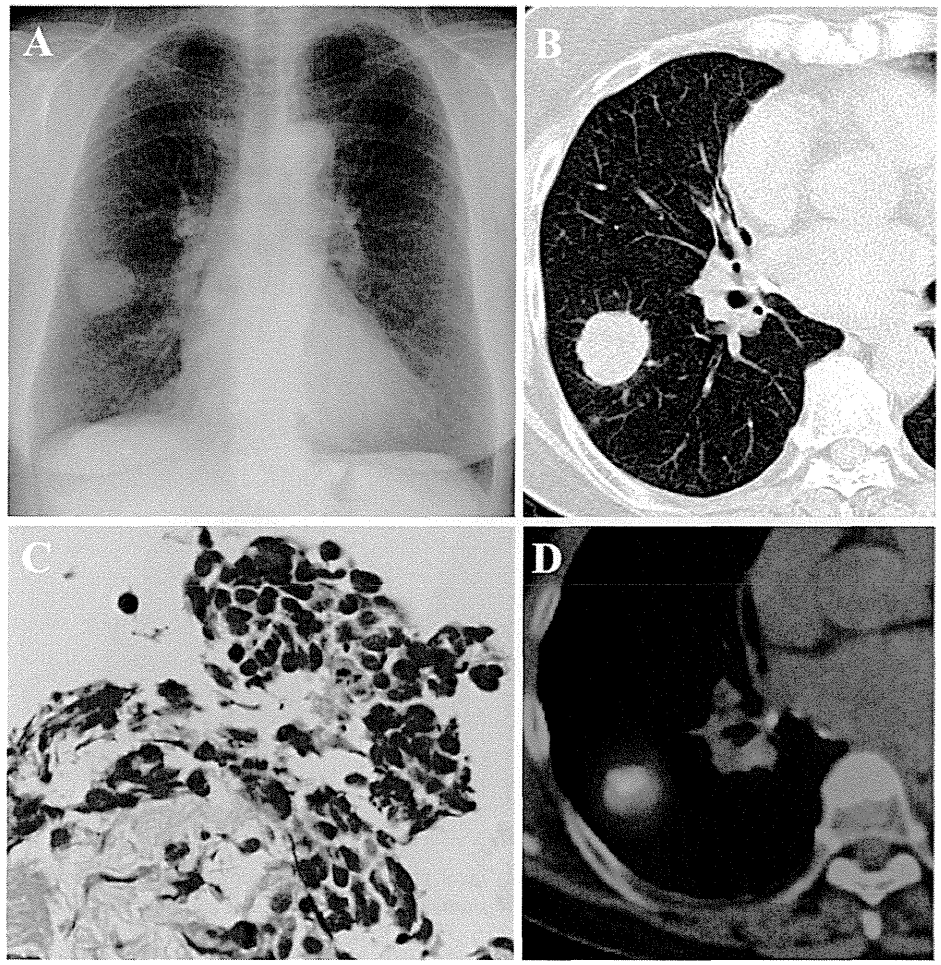

Fig. 1 (**A**) Chest X-ray showed a tumor shadow in right lung field. (**B**) Chest computed tomography (CT) showed a tumor shadow in the right lower lobe. (**C**) Transbronchial biopsy for an initial tumor revealed small-cell lung cancer without other histological cancer components (×200). (**D**) Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed an accumulation at the primary tumor and lobar lymph node.

were within normal range throughout the therapeutic course.

We supposed that the nodular lesion was a recurrence of initial small-cell lung cancer or second primary lung cancer. We diagnosed and treated the new lesion using surgery. A tumor with pleural indentation was found close to the right inferior pulmonary vein in the right lower lobe. Intra-operative aspiration cytology from the nodule revealed lung adenocarcinoma. Because the initial tumor was a small-cell lung cancer without other histological cancer components, the new lesion was diagnosed as a second primary lung cancer. The tumor was completely removed with a right lower lobectomy, as it was located near the right lower pulmonary vein. Lymph node dissection was also performed. Histopathological findings revealed adenocarcinoma and no metastatic tumor in the dissected lymph node (p-T1aN0M0 stage1A; **Fig. 3**). The initial tumor had completely disappeared, both macroscopically and histopathologically.

Her postoperative course was good, and she was discharged from the hospital on day 10. Ten months after the operation, she has no signs of recurrent tumor.

Discussion

In the present case, preoperative differential diagnoses were intrapulmonary recurrence, pulmonary ligament lymph node recurrence, and second primary lung cancer. We performed right lower lobectomy to completely remove the tumor, and arrived at a correct diagnosis.

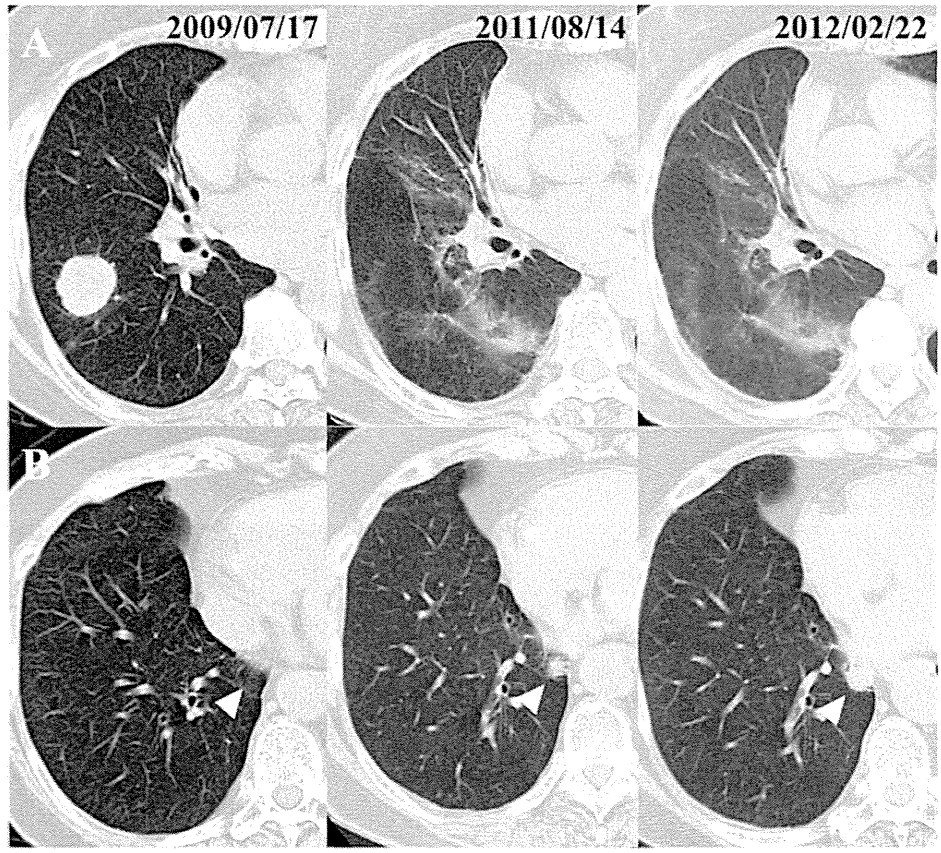

Fig. 2 (**A**) After treatment for small-cell lung cancer, an initial tumor shadow in the right lower lobe had disappeared. (**B**) A new nodular lesion appeared at a different area in the right lower lobe, and grew progressively larger.

An increased risk of second primary lung cancers has been reported in survivors of small-cell lung cancer. Johnson, et al., reported that six of 40 patients with small-cell lung cancer, who had been cancer-free for 2 years, had second lung cancers; they reported the distribution of second tumors to be three in the contralateral lung, one in a different lobe in the ipsilateral lung, and two in the same lobe as the initial small-cell lung cancer, respectively.[1] Compared with the general population, the risk of all second cancers among these patients was increased 3.5-fold. Moreover, in survivors of small-cell lung cancer, risk of a second lung cancer increased 7-fold.[2] Reportedly, cumulative risk of a second primary lung cancer was 32% after 12 years, and did not appear to reach a plateau.[2] Several articles show that continuing to smoke is a risk factor for second primary lung cancer in survivors of small-cell lung cancer.[1–3] Only one article discussed the relationship between second primary lung cancers and chemotherapy against initial small-cell lung cancers,[2] suggesting that chemotherapy, particularly alkylating agents, contributes to the second cancer risk. These reports indicate that survivors of small-cell lung cancer are at high risk for second primary lung cancers. Long-term follow-up with careful attention to second primary lung cancer may be necessary for survivors of small-cell lung cancer.

Few reports have been published in which the initial tumor was removed and investigated histopathologically. Inoue, et al., reported a case of second primary lung cancer in the same lobe as initial small-cell lung cancer.[4] Because the initial small-cell lung cancer was located in the left S^{1+2} area and the second primary adenocarcinoma was located in left S^4 area, they treated the case with an left upper lobectomy. The site of the initial cancer was scarred and did not contain any neoplastic cells. In the present case, however, the initial tumor disappeared completely, without even fibrous scar tissue. This difference may have been affected by whether the initial

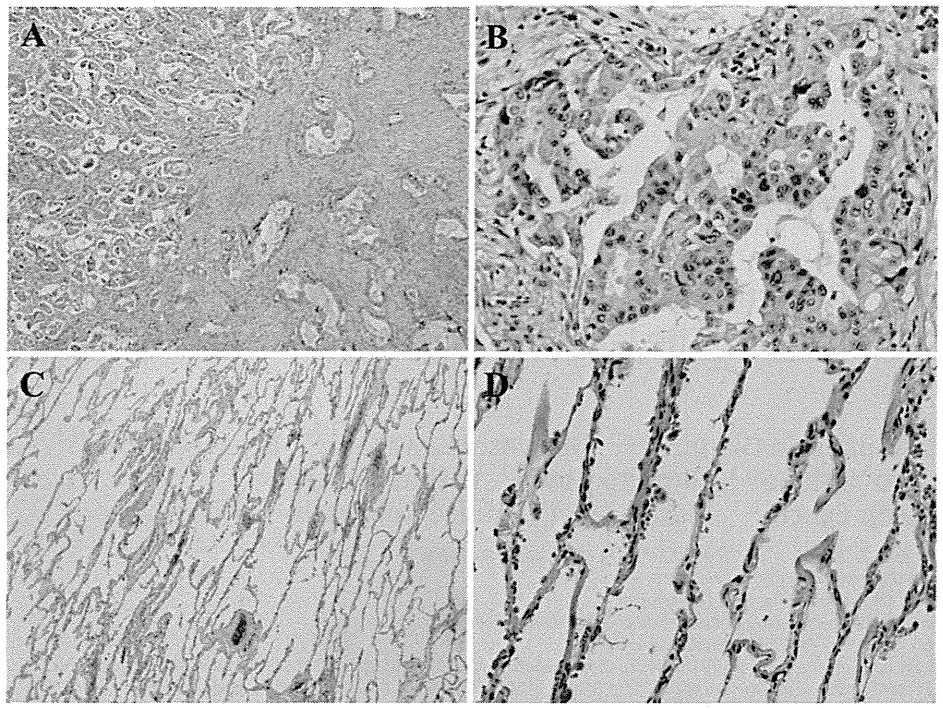

Fig. 3 **(A), (B)** Histopathological findings of a new nodular lesion revealed adenocarcinoma with mixed subtype (A, ×40; B, ×200). **(C), (D)** There was normal lung tissue in the area of the initial tumor (C, ×40; D, ×200).

small-cell lung cancer contains other histological components. Tumors of pulmonary adenocarcinoma or squamous cell carcinoma are reportedly likely to contain scar and interstitial tissues. Whereas tumor cells disappeared after chemoradiotherapy, interstitial tissue developed scars and remained.[5] Accordingly, tumor shadow of pulmonary adenocarcinoma or squamous cell carcinoma remained after chemoradiotherapy. In the present case, the initial lung cancer was diagnosed by transbronchial biopsy as pure small-cell carcinoma. Because collected tissue via transbronchial biopsy was small, complete histological picture might not be investigated. However, the initial tumor tissue might be more likely to contain no scar or interstitial tissue.

Conclusion

We report a case of a survivor of small-cell lung cancer with a second primary lung adenocarcinoma in the same lobe. Both initial and second primary lung cancers were removed and investigated histopathologically. As the initial tumor might contain no scar or interstitial tissue, the initial cancer tissue had apparently completely disappeared after chemoradiotherapy.

Disclosure Statement

Takuma Tsukioka and other co-authors have no conflict of interest.

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Clinicopathological characteristics and surgical results of lung cancer patients aged up to 50 years: The Japanese Lung Cancer Registry Study 2004

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ABSTRACT

Objective: The clinicopathological characteristics and surgical results of young lung cancer patients were investigated.
Materials and methods: Seven hundred and four (6.0%) patients with lung cancer, aged up to 50 years, were enrolled from among the 11,663 patients registered in the Japanese Lung Cancer Registry Study 2004, and their clinical data were compared with those of 10,959 patients older than 50 years. This epidemiological study is based on the single year registration of surgically treated patients in the major institutes in Japan.
Results: The 5-year overall survival rate (5Y-OS) and the 5-year lung cancer-related survival rate was 79.2%/69.0% ($p < 0.001$) and 81.3%/76.6% ($p = 0.005$) in the young/old groups, respectively. In the young/old groups, lobectomy and pneumonectomy was performed in 76.9%/78.0% and 5.7%/3.2%, respectively; adjuvant therapies were given preoperatively in 10.4%/4.7% ($p < 0.001$) and postoperatively in 31.4%/24.5% ($p < 0.001$). The proportions of patients with p-stage IIIA (18.2%) and adenocarcinoma histology (78.7%) were higher in the young group. The 5Y-OS was 94.8%/86.2% for p-stage IA ($p < 0.001$), 87.0%/73.2% for p-stage IB ($p = 0.001$), 61.0%/61.6% for p-stage IIA ($p = 0.595$), 71.0%/48.4% for p-stage IIB ($p = 0.003$), 49.6%/39.4% for p-stage IIIA ($p = 0.020$), and 80.0%/24.8% for p-stage IIIB ($p = 0.012$); it was 83.5%/80.7% for females ($p = 0.106$) and 75.1%/62.3% for males ($p < 0.001$) in the young/old groups. The postoperative survival was significantly better with all operative procedures in the young group. The 5Y-OS after recurrence was 17.9%/13.4% in the young/old groups ($p = 0.016$). In the young group, the 5Y-OS was better in females (83.5%) than in males (75.1%, $p = 0.002$), and for patients with adenocarcinoma (80.3%) than for those with squamous cell carcinoma (68.5%, $p = 0.013$). Age up to 50 years was identified as an independent better prognostic factor on multivariate analysis.
Conclusions: The postoperative survival in lung cancer patients aged up to 50 years was better than that in patients older than 50 years.

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[1] For the Japanese Joint Committee of Lung Cancer Registry.

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1. Introduction

Lung cancer is a leading cause of malignancy-related death. The American Cancer Society estimates that 226,160 people will be diagnosed and 160,340 patients will die of lung cancer in the United States in 2012 [1]. Lung cancer occurs mainly in older people, and fewer than 2% of all cases are found in people younger than 45 years in the USA [1]. The Ministry of Health, Labor, and Welfare, Japan, reported that 69,813 people died of lung cancer in 2010 in Japan, and the number is still increasing. According to the Japanese Lung Cancer Registry Study, the number of patients younger than 50 years ranged from 5.0% to 8.2% of all resected cases since 1994 [2]. Because of the small size of the young population, the clinical features of young lung cancer patients remain unclear.

Better survival of lung cancer patients in the middle-aged group (45–60 years) as compared to the young (<45 years) or old group (>60 years) was reported by a multicenter study [3]. Several previous studies also revealed better postoperative survival rate in the young lung cancer patients [4–6], while other reports showed equivalent survival outcome to the old patients [7,8]. So, the survival superiority of the young patients is still controversial in lung cancer. Active treatment with multiple modalities was recommended in young patients in association with these results, while the study cohort included all lung cancer patients treated with surgery, chemotherapy, and irradiation [3]. However, the clinicopathological characteristics and surgical results of young patients with lung cancer have not yet been identified. Recent developments in chemotherapy and molecular targeted therapy might contribute to prolonged survival and improvement of results with multimodality management, especially in young patients, who are expected to be able to tolerate active treatments.

Patients aged up to 50 years extracted from the Japanese Lung Cancer Registry Study 2004 who underwent surgical resection were evaluated in order to clarify their clinicopathological characteristics and the results of surgical intervention in the present study [2].

2. Materials and methods

2.1. Patients

A total of 704 lung cancer patients aged up to 50 years were extracted from among the 11,663 patients listed in the Japanese Lung Cancer Registry Study 2004, which was conducted as a multicenter surveillance study of patients who underwent surgery by the Japanese Joint Committee of the Lung Cancer Registry (JJCLCR) [2]. JJCLCR is officially authorized by The Japan Lung Cancer Society, The Japanese Association for Chest Surgery, The Japanese Respiration Society, and The Japan Society for Respiratory Endoscopy. Of the 605 teaching hospitals certified by the Japanese Board of General Thoracic Surgery, 253 participated in this registry. All patients analyzed in the present study underwent surgery in 2004 and the single year registration included the following data: (1) demographic background (age and sex), (2) preoperative status (Eastern Cooperative Oncology Group performance status (ECOG PS), preoperative comorbidity, smoking status, tumor markers), (3) clinical TNM, (4) induction therapy, (5) operative procedure, (6) postoperative morbidity, (7) tumor histology, (8) adjuvant therapy, (9) pathological TNM. The clinicopathological characteristics and the results of surgical intervention in patients aged up to 50 years were analyzed in detail and compared to those of 10,959 patients older than 50 years. The data collected using the UICC-TNM staging system (version 6) were converted to the UICC-TNM staging system (version 7) to assess the extent of lung cancer [9].

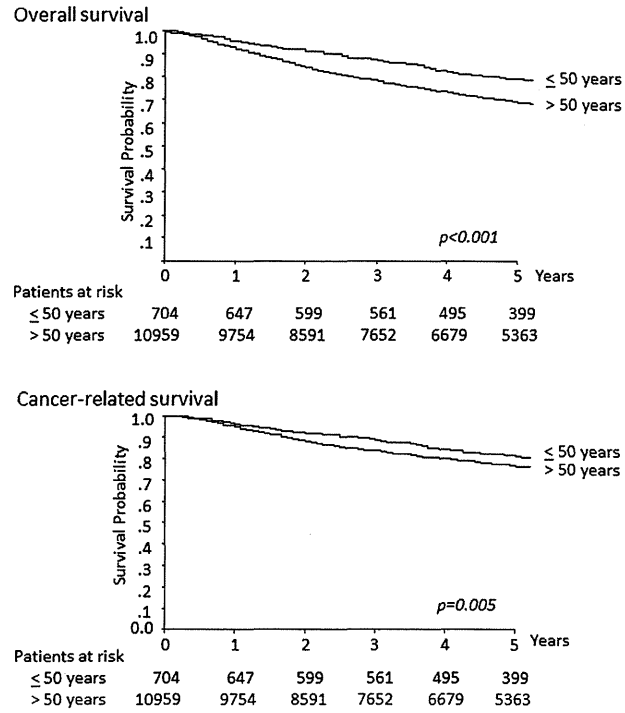

Fig. 1. The overall and lung-cancer related survival rates for patients aged up to and older than 50 years with surgical intervention. The postoperative survival rate was significantly better in the young group.

2.2. Statistical analyses

All data were extracted and analyzed by a JJCLCR member biostatistician (EM). Survival after pulmonary resection was estimated according to the Kaplan–Meier method, and survival differences were tested using the log-rank test. The prognostic effect of variables on survival was analyzed using the multivariate Cox regression model with variables of sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant chemotherapy. The χ^2-test was used to compare the rates between groups. A p value less than 0.05 was considered significant.

3. Results

Patients' characteristics, with a comparison of patients aged up to 50 years and older than 50 years, are shown in Table 1. The proportion of females was significantly higher in the young group than in the old group ($p < 0.001$). Performance status (ECOG) was significantly better in the young group ($p < 0.001$). Smoking history and preoperative comorbidity were significantly more frequent in the old group ($p < 0.001$). The operative procedure was significantly different ($p = 0.013$) and the rate of pneumonectomy was higher in the young group. The distribution of p-stage showed the significant difference, and the proportion of p-stage IB and IIA was lower and that of locally advanced disease with p-stage IIIA was higher in the young group as compared to the old group. The proportion of histopathology was significantly different ($p < 0.001$) and the rate of adenocarcinoma was higher in the young group. Young patients received both preoperative and postoperative adjuvant therapy more frequently than old patients.

The 5-year overall survival rate (5Y-OS) was 79.2% and 69.0% in the young and old groups, respectively ($p < 0.001$), as shown in Fig. 1. The 30-days mortality was 1/704 (0.1%) and 47/10959 (0.4%), and the hospital mortality was 2/704 (0.3%) and 134/10959 (1.2%) in the young and old groups, respectively. The morbidity was

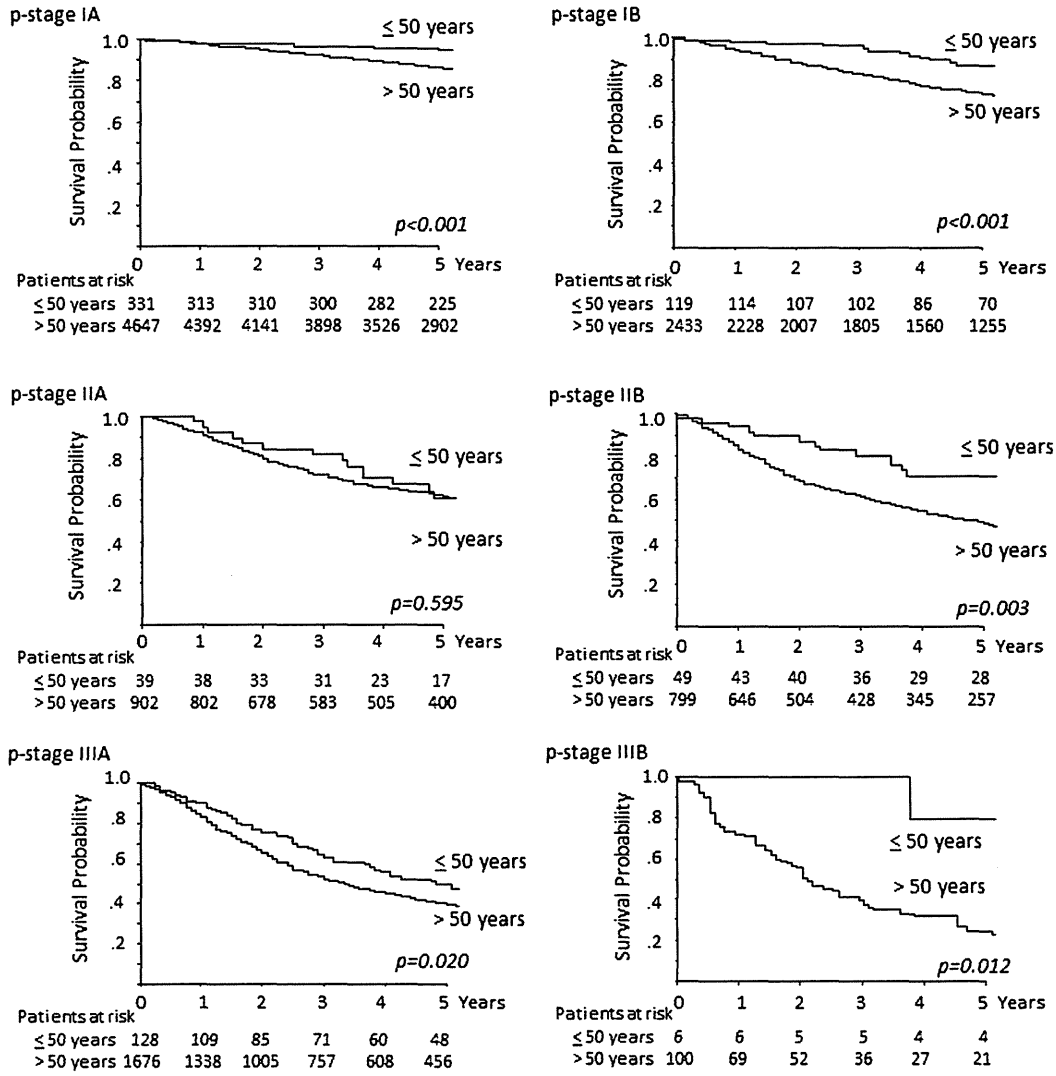

Fig. 2. The survival curves of patients aged up to and older than 50 years with surgery according to p-stage using UICC version 7. The postoperative survival was significantly better in the young group for each p-stage IA – IIIB except stage IIA.

58/704 (8.2%) and 1921/10959 (17.5%) in the young and old groups, respectively ($p < 0.001$). When analyzing disease-specific outcome, the 5-year lung cancer-related survival rate was 81.3% and 76.6% in the young and old groups, respectively ($p = 0.005$), as shown in Fig. 1. According to p-stage, the 5Y-OS was 94.8% and 86.2% for IA ($p < 0.001$), 87.0% and 73.2% for IB ($p < 0.001$), 61.0% and 61.6% for IIA ($p = 0.595$), 71.0% and 48.4% for IIB ($p = 0.003$), 49.6% and 39.4% for IIIA ($p = 0.020$), and 80.0% and 24.8% for IIIB ($p = 0.012$), in the young and old groups, respectively, as shown in Fig. 2.

Among male patients, the 5Y-OS was 75.1% and 62.3% in the young and old groups, respectively ($p < 0.001$), although there was no significant difference among female patients and the 5Y-OS was 83.5% and 80.7%, respectively (Fig. 3). The cause of death, preoperative comorbidities, smoking history, and adjuvant therapy were examined by age and sex. Lung cancer-unrelated death was higher (25.3%) in the old group than that in the young group (6.8%) in males ($p < 0.001$), while no significant difference was observed in females. Preoperative comorbidities were frequent in the old group in both male and female patients. Smoking history was significantly more frequent in the old group in males, while it was less frequent in females. Male patients in the young group more frequently had both preoperative and postoperative adjuvant therapies as compared to the old group, while no significant difference was found in female patients.

According to operative procedure, the 5Y-OS was better in the young group than in the old group for all procedures: 59.1% and 42.0% for pneumonectomy ($p = 0.050$), 79.9% and 71.7% for lobectomy ($p < 0.001$), 87.3% and 73.1% for segmentectomy ($p = 0.034$), and 93.5% and 65.9% for wedge resection ($p < 0.001$), in the young and old groups, respectively (Fig. 4). According to histological type, the 5Y-OS for adenocarcinoma was 80.3% in the young group which was significantly better than 74.5% in the old group, though no significant survival difference was observed for squamous cell carcinoma. The 5Y-OS after recurrence was 17.9% and 13.4% in the young and old groups, respectively ($p = 0.016$). In the young group, the 5Y-OS was significantly better for female patients (83.5%) than for male patients (75.1%, $p = 0.002$). 5Y-OS was better for the histology of adenocarcinoma (80.3%) than for squamous cell carcinoma (68.5%, $p = 0.013$).

Since the comparison of survival difference between young and old patients might be affected by patients older than 70 years, who are expected to have poor long-term survival, another comparison of survival difference between patients aged up to 50 years ($n = 704$) and those 50–70 years ($n = 6152$), which was a young elderly cohort,

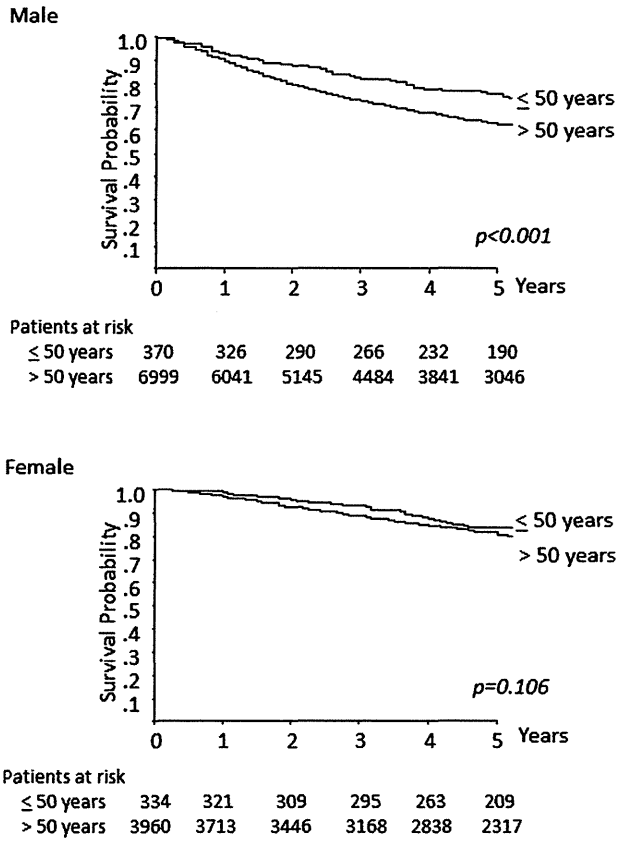

Fig. 3. The survival curves of patients aged up to and older than 50 years with surgery according to sex. Among male patients, the overall survival in patients aged up to 50 years was significantly better than that in patients older than 50 years. No significant difference was found in female patients.

were also performed. The 5Y-OS was 79.2% and 73.7% in the young and young elderly groups, respectively ($p = 0.002$). According to p-stage, the 5Y-OS was 94.8% and 90.6% for IA ($p = 0.022$), 87.0% and 79.0% for IB ($p = 0.027$), 61.0% and 66.9% for IIA, 71.0% and 54.7% for IIB ($p = 0.027$), 49.6% and 44.7% for IIIA, and 80.0% and 27.7% for IIIB ($p = 0.023$), in the young and young elderly groups, respectively. These differences showed a similar tendency to have a better survival rate in the young group as seen with the comparative results between those aged up to and those older than 50 years shown above. However, survival after postoperative recurrence did not show a significant difference between the young and young elderly groups.

The prognostic factors were tested by multivariate analyses using the variables of age, sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant therapy (Table 2). Age up to 50 years was identified to be an independent prognostic factor with a hazard ratio of 1.451. Female, good ECOG-PS, no smoking history, no comorbidity, early p-stage, and no preoperative adjuvant therapy were also identified as predictors of a better prognosis. When analyzing age as continuous variable in multivariate analysis, age was identified as an independent prognostic factor with the hazard ratio 1.026 (CI: 1.022–1.030).

4. Discussion

The postoperative survival of young lung cancer patients remains unclear due to their low numbers, though several studies have been reported so far [3–10]. Radzikowska et al. and Minami et al. investigated patients younger than 50 years and showed significantly better survival as compared to old patients [4,6]. Among several studies with definition of the young group as up to 40 years, Tian et al. reported higher 5Y-OS in young patients, though no superior survival was shown in the study by Hanagiri et al. or by Maruyama et al. [5,7,8]. In the present epidemiological study, cancer patients aged up to 50 years who underwent surgery were extracted from the Japanese Lung Cancer Registry Study 2004 [2],

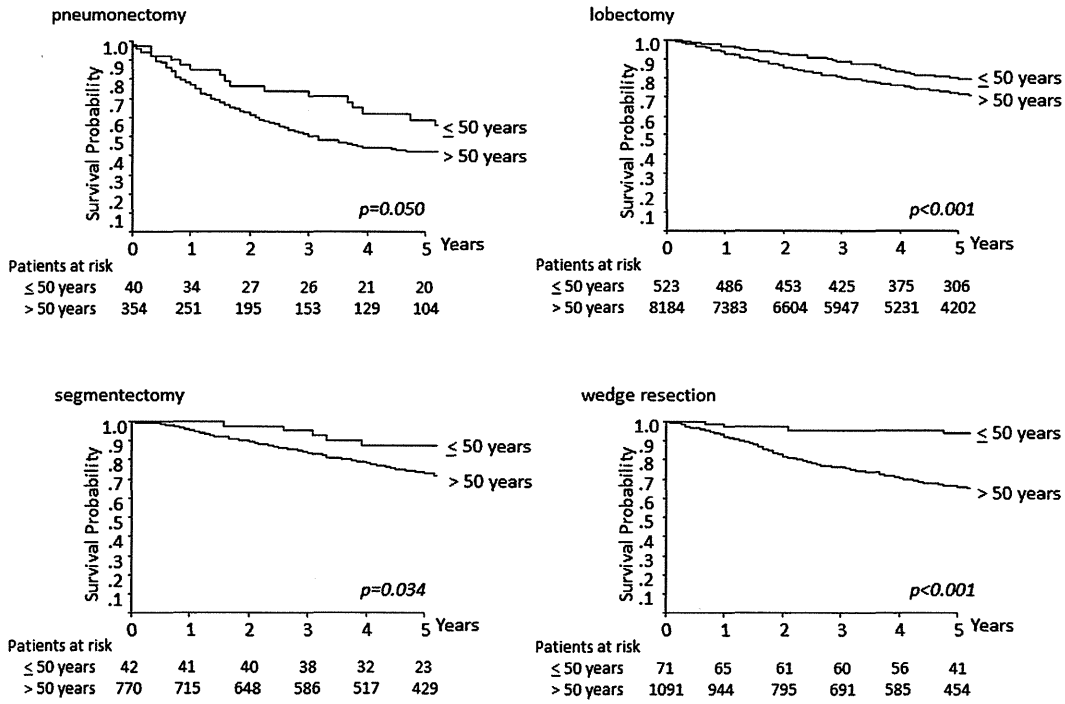

Fig. 4. The survival curves of patients aged up to and older than 50 years with surgery according to operative procedure. The postoperative survival was significantly better in the young group for each procedure.

Table 1
Patients' characteristics.

	Age ≤ 50 years	Age > 50years	p value
Sex			p < 0.001
Male	370 (52.6%)	6999 (63.2%)	
Female	334 (47.4%)	3960 (36.8%)	
PS			p < 0.001
0	665 (94.5%)	8943 (81.6%)	
1	27 (3.8%)	1661 (15.1%)	
Others	12 (1.7%)	355 (3.3%)	
Smoking history			p < 0.001
No	308 (43.8%)	3777 (34.5%)	
Yes	334 (47.4%)	6290 (57.4%)	
Unknown	62 (8.8%)	892 (8.1%)	
Comorbidity			p < 0.001
No	562 (79.8%)	7151 (65.3%)	
Yes	79 (11.2%)	3048 (27.8%)	
Unknown	63 (8.9%)	760 (6.9%)	
c-stage			p < 0.001
Stage IA	420 (59.7%)	5875 (53.6%)	
Stage IB	88 (12.5%)	2700 (24.6%)	
Stage IIA	36 (5.1%)	167 (1.5%)	
Stage IIB	45 (6.4%)	854 (7.8%)	
Stage IIIA	84 (11.9%)	856 (7.8%)	
Stage IIIB	13 (1.8%)	394 (3.6%)	
Stage IV	18 (2.6%)	113 (1.0%)	
Operative procedure			p < 0.001
Pneumonectomy	40 (5.7%)	354 (3.2%)	
Bilobectomy	18 (2.6%)	357 (3.3%)	
Lobectomy	523 (74.3%)	8184 (74.7%)	
Segmentectomy	42 (6.0%)	770 (7.0%)	
Wedge resection	71 (10.1%)	1091 (10.0%)	
Others	10 (1.3%)	203 (1.9%)	
p-stage			p < 0.001
Stage IA	331 (47.0%)	4647 (42.4%)	
Stage IB	119 (16.9%)	2433 (22.2%)	
Stage IIA	39 (5.5%)	902 (8.2%)	
Stage IIB	49 (7.0%)	799 (7.3%)	
Stage IIIA	128 (18.2%)	1676 (15.3%)	
Stage IIIB	6 (0.9%)	100 (0.9%)	
Stage IV	32 (4.5%)	402 (3.7%)	
Histology			p < 0.001
Adenocarcinoma	554 (78.7%)	7367 (67.2%)	
Squamous cell carcinoma	52 (7.4%)	2548 (23.3%)	
Large cell carcinoma	30 (4.3%)	357 (3.3%)	
Small cell carcinoma	11 (1.6%)	232 (2.1%)	
Others	57 (8.0%)	455 (4.1%)	
Preoperative adjuvant therapy			p < 0.001
Yes	73 (10.4%)	520 (4.7%)	
No	631 (89.6%)	10,439 (95.3%)	
Postoperative adjuvant therapy			p < 0.001
Yes	221 (31.4%)	2682 (24.5%)	
No	483 (68.6%)	8277 (75.5%)	
Total	704 (100%)	10,959 (100%)	

PS, Eastern Cooperative Oncology Group performance status; Smoking history, including both current and ex-smokers; Comorbidity, including current smoking history, obesity with BMI > 30 kg/m^2, cerebrovascular disease, chronic obstructive pulmonary disease, interstitial pneumonia, ischemic heart disease, renal dysfunction with creatinine> 2.0 g/dL, liver cirrhosis with Child-Turcotte classification > B, diabetes mellitus with HbA1c > 8%, anemia with Hb < 8 g/dL, and treatment for other malignancy within a year.

Table 2
Results of multivariate analysis in lung cancer patients with surgical resection.

Variables		Hazard ratio	95% Confidence Interval	p value
Age				
≤50 years		1.000		
>50 years		1.451	1.211–1.739	<0.001
Sex				
Male		1.000		
Female		0.664	0.593–0.744	<0.001
ECOG PS				
PS 0		1.000		
PS 1		1.582	1.441–1.736	<0.001
PS 2		2.041	1.600–2.604	<0.001
PS 3		2.706	1.717–4.266	<0.001
Smoking history				
No		1.000		
Yes		1.150	1.026–1.289	0.016
Comorbidity				
No		1.000		
Yes		1.232	1.135–1.338	<0.001
Operative procedure				
Pneumonectomy		1.000		
Bilobectomy		1.089	0.873–1.358	0.450
Lobectomy		0.782	0.665–0.920	0.003
Segmentectomy		0.978	0.786–1.218	0.844
p-stage				
IA		1.000		
IB		1.958	1.741–2.203	<0.001
IIA		2.878	2.488–3.329	<0.001
IIB		4.031	3.505–4.637	<0.001
IIIA		6.940	5.288–9.108	<0.001
Histology				
Pre-invasive lesion		1.000		
Squamous cell carcinoma		1.280	0.318–5.151	0.728
Small cell carcinoma		1.961	0.481–7.994	0.348
Adenocarcinoma		1.166	0.291–4.682	0.828
Large cell carcinoma		1.721	0.425–6.978	0.447
Adjuvant therapy				
Preoperative	No	1.000		
	Yes	1.169	1.018–1.342	0.027
Postoperative	No	1.000		
	Yes	0.923	0.850–1.002	0.055

ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; Adjuvant therapy includes systemic chemotherapy and radiation therapy.

and better postoperative survival was observed in these young lung cancer patients, although the proportion of advance disease was higher as compared to the old group. It was also found that, among young patients, women and those with adenocarcinoma had a better survival, which was similar to the results of all-generation analyses [2].

The higher proportion of young patients who underwent pneumonectomy could imply that they were better able to tolerate surgery, as a previous report showed similar results [5]. Pneumonectomy was, however, reported to increase the perioperative morbidity in elderly patients in a case-control study [11], and sleeve lobectomy, if possible, is recommended as an alternative procedure to pneumonectomy, with lower mortality and better survivals [12]. The results of the present study might indicate the importance given to curative intention over the preservation of pulmonary function in young patients. The superior 5Y-OS in young group treated with a pneumonectomy in the present study could suggest that pneumonectomy is still a considerable option for resectable locally advanced disease in the young patients.

Higher rates of both preoperative and postoperative adjuvant therapy in the young group could reflect the higher proportion of stage IIIA advanced disease, which is a prime indication for induction therapy [13], in addition to the ability of young patients to tolerate such treatment. Radzikowska et al. also reported similar results with more aggressive treatment in young patients [4]. The rate of preoperative adjuvant therapy in the young group was more than 2-fold that in those old group (Table 1). These results indicate a planned active multimodal strategy in young patients with good performance status, while the clinical effect to the survival is unclear. Since postoperative adjuvant chemotherapy was adopted as an evidence-based treatment in a practice guideline for lung cancer treatment in 2005 in Japan, quoting several meta-analyses and randomized studies [14–17], only a proportion of patients with stage IB-IIIA analyzed in the present study had received adjuvant therapy. Thus, it might be expected that postoperative survival in patients with locally advanced disease has potentially become better with postoperative chemotherapy, though further investigation is necessary to identify the issue.

The overall survival rates for patients with stages IA, IB, IIB, IIIA, and IIIB were better for patients aged up to 50 years than for

patients older than 50 years. We added another comparison of survival between patients aged up to 50 years and those 50–70 years, because it is expected that patients older than 70 years could have more frequent lung cancer-unrelated death. The similar results to the comparison between patients aged up to and older than 50 years might suggest other factors in addition to the natural aging bias. Though we could not analyze the treatment after recurrence in the present study, young patients with good performance status might have more chance to receive second and third lines of chemotherapy. Further investigation is required to clarify the clinical impact on survival of the aggressive multimodality therapy in young patients with postoperative recurrence using recent cases.

The worse postoperative survival in males older than 50 years was probably due to the greater number of lung cancer-unrelated deaths in that group. This cohort with more comorbidities and smoking history could have cardiopulmonary diseases or second primary malignancies related to tobacco exposure. The poor general status of the old patients might also be related to the less frequent use of adjuvant therapies. As a result, the young male patients without comorbidity or smoking history might improve the survival of the entire patient group. The death rate of male is reported to be twice higher than that of female in 30–84 year-old population by Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare, Japan. Thus, such natural biological bias might also influence to the results.

The tendency for favorable survival in female patients and in patients with adenocarcinoma histology was the same as that seen with all-generation analyses [2]. Bronchioloalveolar carcinoma (BAC) showing ground glass opacity on CT scanning, which is currently classified as adenocarcinoma in situ or minimally invasive adenocarcinoma [18], is generally recognized to be a slow growing, low-grade adenocarcinoma and a unique subtype related to a never-smoking history, female sex, and Asian race [19]. Though CT findings were not analyzed in the present study cohort, higher proportions of adenocarcinoma and females in the Japanese young patients' group might change the patients' characteristics, with a higher rate of BAC and low-grade malignant behavior. Further investigations including CT findings are necessary to resolve these issues.

The present epidemiological study has several limitation and speculation for the results. The retrospective study cannot clarify the prognostic effect of multimodal therapy in young patients due to the lack of data for chemotherapy regimens or molecular target therapy. Younger age is well-known better prognostic predictor in other malignancies and the influence of other factors except the variables analyzed in this study cannot be completely denied. Further prospective analyses using high volume surgically and non-surgically treated lung cancer patients are required to clarify the cause for the better prognosis of young patients treated surgically.

5. Conclusion

In conclusion, surgically treated young lung cancer patients showed the highest rate of locally advanced disease and received active multimodality therapies. Their postoperative survival was better than that of patients older than 50 years, and age was identified as an independent better prognostic factor. Even when comparing cancer-related survival, the outcome was significantly better in young lung cancer patients.

Conflict of interest statement

All authors contributing to this work have no other conflict of interest to declare.

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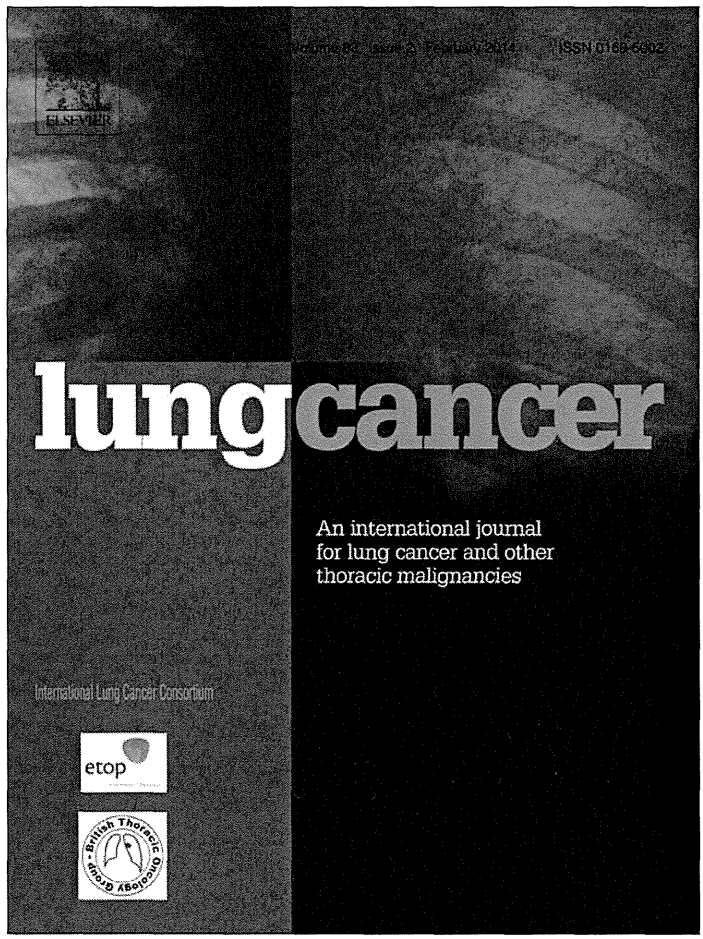

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Case report

Bilateral ovarian metastasis of non-small cell lung cancer with *ALK* rearrangement

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ABSTRACT

The discovery of a distinct subtype of non-small cell lung cancer (NSCLC) positive for rearrangement of the anaplastic lymphoma kinase gene (*ALK*) has had a substantial impact on personalized therapy for this disease. The clinical features associated with metastasis in individuals with *ALK* rearrangement-positive NSCLC remain to be fully characterized, however. We now describe a case of ovarian metastasis from NSCLC with *ALK* rearrangement. A 39-year-old woman underwent a right middle lobectomy for acinar-type adenocarcinoma of the lung (pT2aN2M0, stage IIIA). Fluorescence in situ hybridization (FISH) analysis of the resected tumor tissue revealed the presence of an *ALK* rearrangement. Twenty months later, a large intrapelvic mass was detected in the patient at follow-up. She underwent both left salpingo-oophorectomy and right ovarian cystectomy. Histological examination of the ovarian tumors showed acinar adenocarcinoma, and FISH analysis revealed the presence of *ALK* rearrangement, confirming a diagnosis of *ALK* rearrangement-positive NSCLC with ovarian metastasis. Although the ovary is an uncommon site for metastasis from lung cancer, physicians should be aware of the possibility for such metastasis during follow-up for female patients with *ALK* rearrangement-positive NSCLC. Further investigation is warranted to clarify the incidence of ovarian metastasis in NSCLC patients with *ALK* rearrangement.

1. Case presentation

A 39-year-old woman who smoked one pack per day underwent a right middle lobectomy for adenocarcinoma of the lung (pT2aN2M0, stage IIIA) in August 2009. Mutation analysis of the resected tissue revealed that the tumor was wild type for the epidermal growth factor receptor gene (*EGFR*). Fluorescence in situ hybridization (FISH) analysis of the tumor tissue with break-apart probes for the anaplastic lymphoma kinase gene (*ALK*) revealed the presence of an *ALK* rearrangement, however, and subsequent reverse transcription and polymerase chain reaction analysis confirmed the presence of transcripts for the fusion gene. The patient received four cycles of combination therapy with cisplatin and vinorelbine as postoperative adjuvant chemotherapy. One year later, multiple asymptomatic brain metastases were detected, and the patient underwent whole-brain radiotherapy followed by gamma knife radiosurgery. At 20 months after lung resection, a large intrapelvic mass was detected on follow-up examination by positron emission tomography-computed tomography (PET-CT) (Fig. 1A). The maximum standardized uptake value (SUV_{max}) was relatively high at 12.2. Magnetic resonance imaging (MRI) revealed a multilobulated ovarian tumor (15 by 10 cm), which was suspected to be a tumor of the left ovary because of a negative beak sign for the adjacent uterus to the right (Fig. 1B). The patient underwent both left salpingo-oophorectomy (Fig. 1C) and right ovarian cystectomy. Half of the excised left ovarian tumor was cystic, filled with old blood, whereas the remaining half comprised heterogeneous, slightly yellow and white solid tissue with small cysts that showed displacing growth. Microscopic examination of both ovaries revealed acinar adenocarcinoma with a morphology similar to that of the lung cancer diagnosed 20 months earlier (Fig. 2A and B). FISH analysis also showed the presence of *ALK* rearrangement in the ovarian tumor tissue (Fig. 2C). The pathological and molecular findings thus supported a diagnosis of *ALK*

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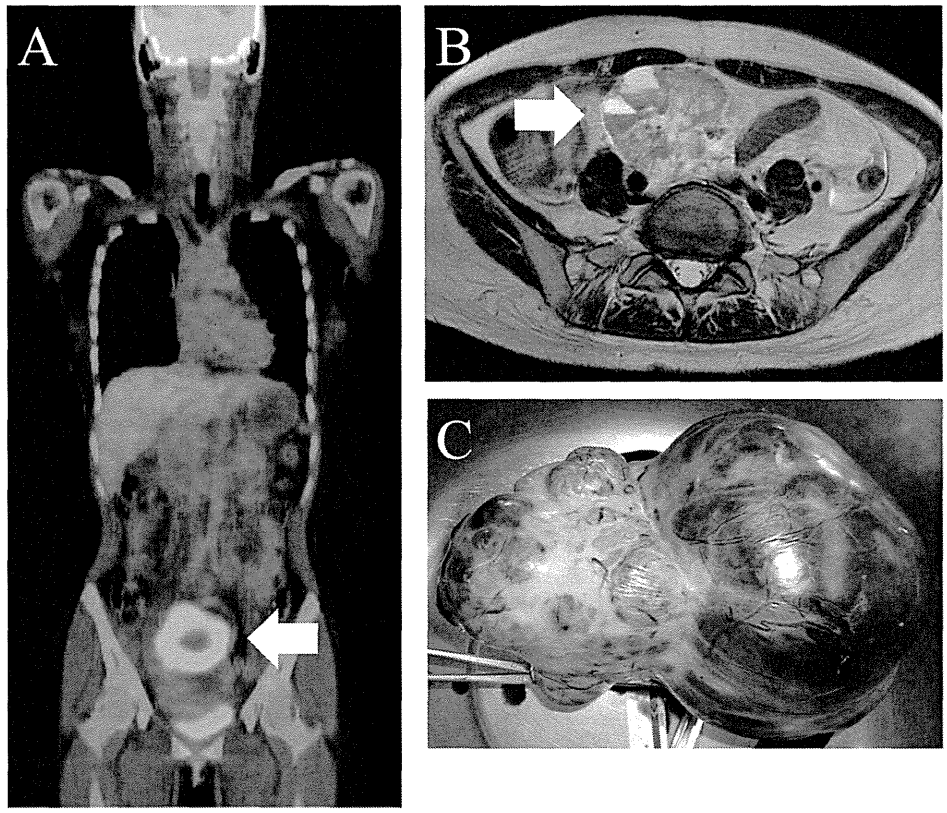

Fig. 1. Ovarian metastasis of lung cancer. (A) PET-CT showing the large intrapelvic mass (arrow) of the patient. (B) Pelvic MRI revealing an ovarian tumor (arrow) with solid and cystic portions that displaced the uterus to the right with a negative beak sign. (C) The excised left ovarian tumor.

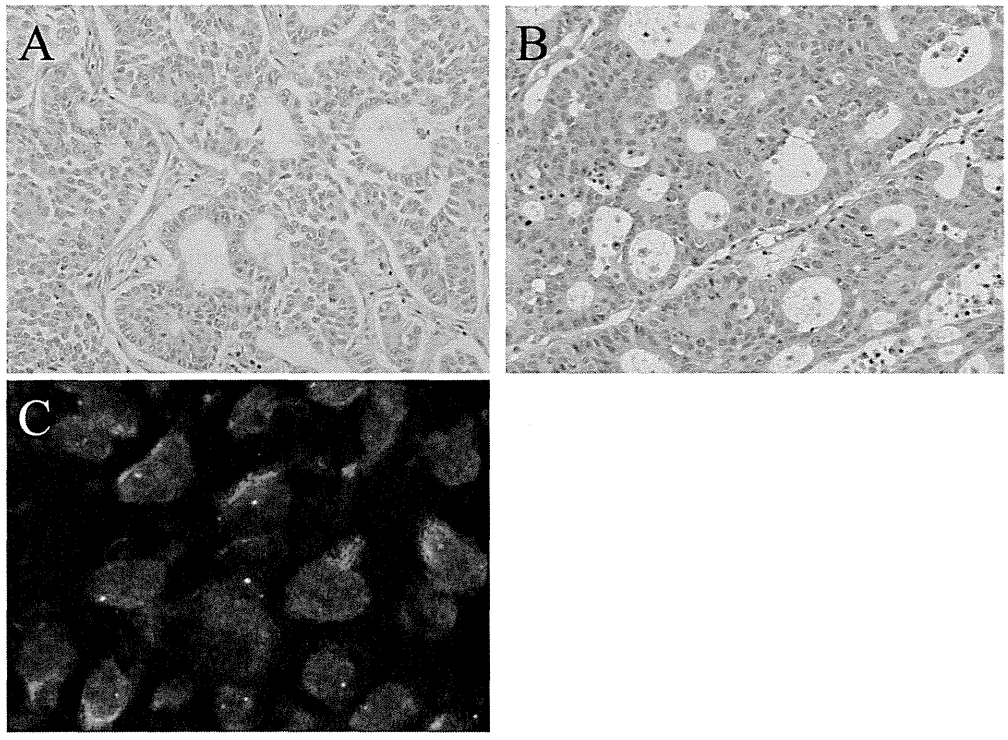

Fig. 2. Tumor histology and FISH analysis. (A) Hematoxylin–eosin staining of the lung adenocarcinoma showing a predominant acinar pattern. Original magnification, 100×. (B) Hematoxylin–eosin staining of the excised left ovarian tumor, revealing adenocarcinoma with a predominant acinar pattern similar to that of the lung cancer. Original magnification, 100×. (C) FISH analysis of the ovarian adenocarcinoma with break-apart probes (red and green fluorescence) for *ALK*. A pattern typical for *ALK* translocation is apparent. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

rearrangement-positive lung cancer with ovarian metastasis. Four months after resection of the ovarian metastases, right bony pelvic and cervical spine metastases were detected on follow-up PET-CT. Radiotherapy was performed for the bone metastasis and was followed by oral administration of crizotinib at a dose of 250 mg twice daily. The patient has shown no evidence of progression on regular follow-up for 4 years after the initial surgery for her primary lung cancer.

2. Discussion

ALK translocation was recently identified as a targetable oncogenic driver. Crizotinib, the first clinically available ALK tyrosine kinase inhibitor, has shown marked and durable efficacy for the treatment of patients with non-small cell lung cancer (NSCLC) positive for *ALK* rearrangement [1]. The incidence of *ALK* rearrangement is only 3–5% in unselected NSCLC patients [2], and the clinical features of metastasis in such patients remain to be fully characterized. We now present the first reported instance of ovarian metastasis in a patient with NSCLC positive for *ALK* rearrangement. About 5–10% of malignant ovarian tumors are metastases from other sites, with primary lung cancer accounting for only 0.4% of metastatic ovarian tumors [3]. The ovary is thus an uncommon location for metastasis from lung cancer. A review of 32 cases of lung cancer that metastasized to the ovary revealed that 14 of these cancers were small cell carcinoma, 11 were adenocarcinoma, and 5 were large cell carcinoma [3]; the most common histological subtype of adenocarcinoma was acinar, with a cribriform architecture also being apparent in some tumors. Such features have been described as a prominent histological type for NSCLC positive for *ALK* rearrangement [4,5]. Women with metastatic ovarian adenocarcinoma from the lung were found to have a mean age of 46 years [3], with disease onset at a young age also being a prominent characteristic of *ALK* rearrangement-positive NSCLC [4]. Further investigation is thus warranted to clarify whether *ALK* rearrangement is associated with a distinct metastatic behavior of NSCLC—in particular, metastasis to the ovary. Physicians should be aware of the possibility for such metastasis when performing follow-up examinations for female patients with NSCLC positive for *ALK* rearrangement.

Conflicts of interest

All authors have no conflict of interest to disclose.

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Radiotherapy for Postoperative Thoracic Lymph Node Recurrence of Non–Small-Cell Lung Cancer Provides Better Outcomes If the Disease Is Asymptomatic and a Single-Station Involvement

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Objective: Thoracic lymph node recurrence after complete resection is common in non–small-cell lung cancer but it mostly occurs along with distant metastases. The recurrent disease might be localized and curative intent radiation therapy is the treatment of choice if no evidence of hematogenous metastasis is observed. We sought to describe the outcomes of thoracic radiotherapy for thoracic lymph node recurrences.

Methods: Fifty patients who had developed thoracic lymph node recurrence after complete resection received curative intent radiotherapy between 1997 and 2009. The clinical endpoints included the tumor response, overall survival, progression-free survival, locoregional recurrence within the irradiated field, and any other recurrence.

Results: The planned total radiotherapy was completed in 49 patients with minor toxicity. The median follow-up time after radiotherapy was 41 (19–98) months among the survivors. The response to treatment was complete response in 65%, partial response in 24%, and progressive disease in 10% of the evaluated patients. The median overall survival after radiotherapy was 37.3 months. The 5-year overall survival, progression-free survival, and local control rate were 36.1%, 22.2%, and 61.1%, respectively. A multivariate analysis revealed that the absence of symptoms and the involvement of a single lymph node station were significant factors associated with a better overall survival.

Conclusions: Radiation therapy for thoracic lymph node recurrence after complete resection is safe and provides acceptable disease control. This treatment provides a better outcome if the disease is asymptomatic and has a single-station involvement. Early detection of the recurrence may thus improve the effectiveness of this treatment.

Key Words: Radiotherapy, Lymph node recurrence, Non–small-cell lung cancer.

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Recurrence after surgery is common in patients with non–small-cell lung cancer (NSCLC). Once the disease has relapsed after surgery, it is seldom curable and the median survival time after recurrence is estimated to be 8.1 to 18.7 months.[1–3] Most recurrences occur in multiple sites including distant organs, thus chemotherapy is commonly used for this systemic state of the disease.[4]

Thoracic lymph node recurrence is one of the exceptions when there is no evidence of hematogenous spreading of the disease. The recurrent disease might be still localized in these patients and curative intent radiation therapy is the treatment of choice.[5] However, the efficacy and feasibility of radiotherapy for thoracic lymph node recurrence after a complete resection have not yet been clearly described. We retrospectively reviewed our experience to determine (1) progression-free survival, patterns of failure, and local control, (2) overall survival and associated factors, and (3) treatment compliance and toxicity.

PATIENTS AND METHODS

Patients

This study conducted a retrospective review of 1553 patients who underwent complete resection for NSCLC at the Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan, from January 1997 to December 2009. The ethics committee gave its approval for the publication of this retrospective study. The institutional prospective database of the general thoracic department included clinicopathological variables at surgery and the postoperative clinical course. The inclusion criteria for this study were patients with lymph node recurrence as the initial recurrence, which included intrathoracic lymph nodes and supraclavicular lymph nodes and that received radiation therapy for the recurrence. Patients with any other recurrence except the thoracic lymph nodes were excluded. The method how the patients were selected from the database was shown in a CONSORT chart (Fig. 1). Finally, we identified 50 patients who received radiotherapy for thoracic lymph node recurrence. The characteristics of these patients are summarized in Table 1. There were 17 patients with thoracic lymph node recurrence who did not receive radiotherapy.

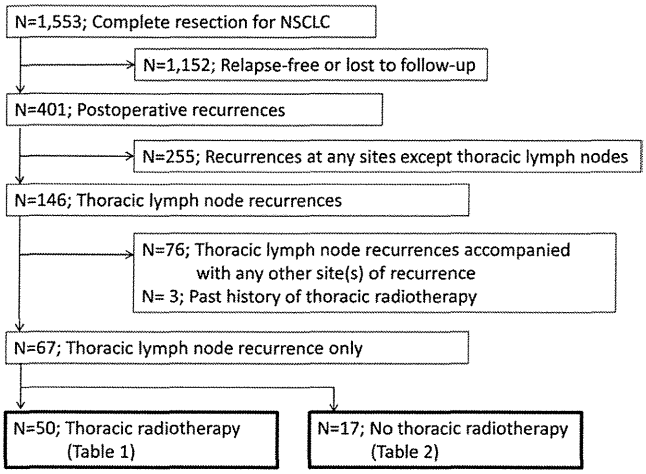

FIGURE 1. A flow chart of the patient selection. NSCLC, non–small-cell lung cancer.

The follow-up protocol for postoperative patients at this institution included a physical examination, chest radiograph, and blood testing including the value of carcinoembryonic antigen (CEA) every 3 to 6 months, and chest computed tomography (CT) every 6 to 12 months for at least 5 years. If patients were suspected of having developed recurrent disease, they were instructed to undergo systemic examinations including upper abdominal CT or abdominal echography, brain magnetic resonance imaging, and bone scintigraphy or ^{18}F-fluorodeoxy glucose-positron emission tomography (FDG-PET) before determining the treatment strategy. After undergoing thoracic radiotherapy, the patients were recommended to have more follow-up visits (every 1–3 months during the first 3 years) by surgeons and/or radiation oncologists. Six patients received concurrent systemic intravenous chemotherapy with radiotherapy.

Diagnosis of Lymph Node Recurrence

The diagnosis and status of lymph node recurrence of the patients who received radiotherapy are summarized in Table 1 (n = 50). The diagnosis of lymph node recurrence was based on the radiological findings of chest CT, FDG-PET, physiological examination, the value of CEA, and/or bronchoscopic sampling for cytology. Among 50 eligible patients, the cytological evidence was obtained in 10 patients (20%). Swollen lymph nodes exhibited significantly increased standard uptake values on PET scans in 31 patients (62%), and growing lymph nodes detected on at least two consecutive CT scans were observed in nine patients (18%). In these patients, radiotherapy was commenced without conducting further interventional examinations to obtain cytological evidence because lymph node recurrence was apparent on the radiological findings. The status and the treatment of recurrent diseases of the patients who did not receive radiotherapy are summarized in Table 2 (n = 17). There were more symptomatic diseases, more N3 level recurrences, and more multistation involvements in this group.

Protocol of Radiotherapy

The patients were treated using three-dimensional conformal techniques using a CT-based planning system (Eclipse; Varian Medical Systems, Palo Alto, CA). The gross tumor volume (GTV) was defined based on the assessment of the involved nodal region in the CT images. In addition, lymph nodes that were positive for FDG accumulation by PET/CT were included in the GTV, even if their sizes were within the normal limits on CT. The clinical target volume was defined as the GTV plus a 5-mm margin. Two different radiotherapeutic approaches, regional nodal irradiation and involved-field irradiation, were used in this study. Regional nodal irradiation covered two or more areas of five thoracic lymph node areas (right- and left-hilar areas, superior mediastinum area, supraclavicular area, and subcarinal area) in the GTV whether or not involved lymph nodes were present in the stations, whereas the involved-field irradiation covered only metastatic lymph nodes regardless of the anatomical compartment of thoracic lymph node areas. Radiotherapy was not systematically performed according to the predetermined protocol for all cases. Basically, a regional nodal irradiation approach was considered the first choice for all patients, but if the coverage of all involved stations elevated normal tissue toxicity or the patients had impaired medical conditions, the involved-field irradiation technique was applied. The treatment approach was determined on an individual basis by the experienced radiation oncologist (Table 1). Planning treatment volume denoted the clinical target volume and 5 to 15 mm margins for geometric uncertainties and respiratory motion. The prescribed dose was calculated with a heterogeneous dose calculation algorithm (pencil beam convolution or anisotropic analytical algorithm). Conventional fractionation was used (2–3 Gy per fraction) and the preplanned radiation dose ranged from 60 to 66 Gy in 43 patients. In four patients, the dose was reduced to 50 Gy because of the radiation field and/or patient's medical condition. In three patients, the dose was increased up to 70 to 84 Gy. Treatment was delivered using 6- or 10-MV photons of the linear accelerator (Clinac 2100C/23EX; Varian Medical systems). Dose prescription was defined according to International Commission on Radiation Units and Measurements recommendations.

Clinical Endpoints

Clinical endpoints after radiotherapy included the overall survival, progression-free survival, tumor response, and locoregional recurrence within the irradiated field and any other recurrence. All responses were evaluated 3 to 6 months after the completion of radiotherapy based on follow-up CT and/or PET scan. Complete response (CR) was defined as the shrinking of metastatic nodes to normal size (the longest diameter was <10 mm) on chest CT without significant accumulation of FDG on PET. The value of CEA was also required to be within the normal limit if it was elevated before the radiotherapy. Partial response required more than 30% reduction of the longest diameter. Progressive disease was defined as increase of more than 20% of the longest diameter and/or progression of any other recurrent disease. Local tumor recurrence was defined as progressive abnormal CT images within the irradiated field during the follow-up period. The time of recurrence

TABLE 1. Patient Characteristics, the Diagnosis, and Status of Lymph Node Recurrence, and Treatment Protocol of Thoracic Radiotherapy

Variables	N = 50	Univariate Analysis for Overall Survival, *p*
Age at LN recurrence, years old		0.6915 (≤67 vs. >68)
Median (range)	68 (48–84)	
Sex (male/female)	42/8	0.4085
Smoking status (nonsmoker/smoker)	11/39	0.9443
Primary site		
Right/left	32/18	0.5459
Upper or middle/lower	31/19	0.7960
Surgery		
Limited resection (wedge/segmentectomy)	6 (3/3)	0.5875
Standard surgery (lobectomy/bilobectomy/pneumonectomy)	44 (39/4/1)	
Histology (adenoca/squamous/others)	21/27/2	0.5706
Stage[a] at surgery		0.5723 (I or II vs. III)
IA/IB/IIA/IIB/IIIA	11/3/10/0/26	
Disease-free interval after surgery, days		0.2965 (≤365 vs. >365)
Median	324	
Range	86–3088	
Diagnostic procedure		
Patho- or cytological examination	10	
PET/CT	31	
CT (+symptom or elevated CEA)	9	
Number of stations (single/multiple)	30/20	0.0457
Site of LN recurrence		0.2331 (N1 vs. N2/N3)
N1 level		
Ip–hilar only	10	
N2 level		
Upper med. (+ip–hilar)	19	
Lower med. (+ip–hilar)	5	
Upper and lower med. (+ip–hilar)	4	
N3 level		
SC (+upper or lower med.)	10	
Cl–hilar and upper med.	2	
Symptoms at recurrence ([b]present/absent)	13/37	0.0017
Maximum diameter of involved LN (mm)		0.4784
20 or smaller/21 or larger	26/24	
Radiation approach		0.3853
Regional nodal/involved-field	23/27	
Radiation dose (Gy)		0.4325 (≤60 Gy vs. >60 Gy
50~59/60~69/70~	4/43/3	
Concurrent chemotherapy		0.6185
Yes/no	6/54	

[a]The stages were described according to the 7th edition.
[b]Details are cough in seven patients, sputum production in five patients, bloody sputum in two patients, breathlessness in two patients, and hoarseness in two patients.
LN, lymph node; PET, positron emission tomography; CT, computed tomography; Ip–hilar, ipsilateral hilar; med., mediastinal; SC, subclavicular; cl–hilar, contralateral hilar.

was recorded using the interval-censored techniques. The duration of survival and time to failure were determined from the initiation of the radiation therapy until the date of death and the time of recurrence, respectively. The patients lost to the follow-up were censored at the date of last contact with the institution. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria scale version 2.0.

Statistics

Survival was calculated by the Kaplan–Meier method, and differences in survival were assessed by a log-rank analysis. The factors whose p values were less than 0.10 (borderline significant) in the univariate analysis in Table 1 were further examined using a multivariate analysis. A multivariate analysis for prognostic factors was performed using the Cox