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Ⅳ．研究成果の刊行物・印刷

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Clinical Trial Note

OXFORD

Clinical Trial Note

Multicenter observational cohort study of post-operative treatment for completely resected non-small-cell lung cancer of pathological Stage I (T1 >2 cm and T2 in TNM classification version 6)

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Abstract

Post-operative adjuvant chemotherapy has been considered an effective strategy to reduce cancer recurrence and improve survival for resected non-small-cell lung cancer. The Japan Clinical Oncology Group has completed patient accrual for a randomized Phase III study (JCOG0707), which compares the survival benefit of UFT and S-1 for completely resected pathological Stage I (T1 >2 cm and T2 in TNM classification version 6) non-small-cell lung cancer. However, there is a growing concern that those who participated in clinical trials are highly selected patients and do not represent the 'real-world' population. This multicenter observational cohort study aims to analyze the backgrounds, pattern of care and outcomes of the patients who were excluded from the JCOG0707 study during the accrual period. The results of this cohort study will be useful for external validity of the results of clinical trial such as JCOG0707.

Key words: non-small-cell lung cancer, early stage, post-operative adjuvant chemotherapy, randomized Phase III study, observational cohort study

Introduction

Non-small-cell lung cancer (NSCLC) accounts for ~85% of primary lung cancer cases, which is the leading cause of cancer-related deaths globally. Surgery is considered the most effective therapeutic modality for the early stage of NSCLC, however, further improvement is needed for post-operative survival. The Japanese nationwide lung cancer registry report analyzed a total of 11 663 patients who underwent surgery in 2004. This study showed that the 5-year overall survival rate

was 85.9% for pathological (p-) Stage IA and 69.3% for p-Stage IB based on the TNM classification version 6 (1, 2). The survival for the entire p-Stage IA group seems to be excellent, but the 5-year overall survival rate for p-Stage IA group with a tumor size >2 cm (2.1–3.0 cm) was reported to be unsatisfactory at 69%, as well as for p-Stage IB disease (3).

Post-operative adjuvant chemotherapy has been considered an effective strategy to reduce the risk of cancer recurrence and improve survival. Many randomized controlled trials have evaluated the effect of adjuvant cisplatin-based chemotherapy in resected NSCLC. However, the pooled meta-analysis from the five largest trials (4584 patients) revealed no survival benefit for p-Stage I disease [hazard ratio (HR) for Stage IA: 1.40; 95% confidence interval (CI): 0.95–2.06; HR for Stage IB: 0.93, 95% CI: 0.78–1.10] (4).

In 2004, a large Japanese Phase III trial showed that post-operative oral tegafur-uracil (UFT, a pro-drug of 5-FU developed in Japan) monotherapy significantly improved overall survival compared with surgery alone for resected p-Stage I adenocarcinoma, especially for p-Stage IB (T2 disease in TNM version 6) adenocarcinoma (HR: 0.48, 95% CI: 0.29–0.81) (5). A meta-analysis of 2003 patients enrolled in six clinical trials in Japan indicated the efficacy of UFT, regardless of histological type (HR for adenocarcinoma: 0.69, 95% CI: 0.56–0.85; HR for squamous cell carcinoma: 0.82, 95% CI: 0.57–1.19) (6). Subsequent exploratory analysis indicated a survival benefit of UFT for p-Stage IA disease with T1 >2 cm (HR: 0.62, 95% CI: 0.42–0.90 (7). Based on these results, the current Japanese treatment guidelines recommend post-operative UFT therapy for patients with completely resected p-Stage I (T1 >2 cm and T2 in TNM version 6) NSCLC (recommendation Grade B) (http://www.haigan.gr.jp/modules/guideline/index.php?content_id=3).

S-1 (TS-1®, a combination preparation of tegafur, gimeracil and oteracil potassium) is a new and potent 5-FU derivative developed after UFT, which is believed to be a more promising agent in an adjuvant setting (8). The Japan Clinical Oncology Group (JCOG) conducted and completed patient accrual for a randomized Phase III study [JCOG0707, the UMIN Clinical Trials Registry as UMIN000001494 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000001799&type=summary&language=E)] to evaluate the efficacy of post-operative adjuvant S-1 compared with UFT for resected p-Stage I (T1 >2 cm and T2 in TNM version 6) NSCLC in Japan starting in October 2008.

A Phase III study of post-operative adjuvant chemotherapy usually requires more time than expected, and the JCOG0707 study actually needed >5 years to complete the planned patient accrual. One reason is the low implementation rate of post-operative chemotherapy, reported to be only 30–54% in clinical practice (9–11). Another reason is the inclusion/exclusion criteria of the study limited the study candidates. The population enrolled in a Phase III study may be highly selected from a 'real-world' population. Therefore, establishing an external validity is essential to reproduce the results of a Phase III study into clinical practice. Observational cohort studies of the 'excluded' patients (e.g. those who declined participation or were ineligible) have been reported to complement randomized trial data for better utilization of new evidence (12); however, they have not been included in studies of post-operative chemotherapy for NSCLC.

We hereby planned a multicenter observational cohort study for the patients who were candidates for but were not enrolled in the JCOG0707 study to explore the factors preventing enrollment in the trial and to analyze the outcome compared with that of the JCOG0707 study population.

Summary of the study protocol

Purpose

This study consists of two subsets (Study A and B), and the purpose is as follows.

Study A

Study A will be conducted to clarify background factors and post-operative treatment of patients who had completely resected p-Stage I (T1 >2 cm and T2 in TNM classification version 6) NSCLC but were not enrolled in the clinical trial of post-operative adjuvant chemotherapy (JCOG0707). The factors inhibiting enrollment of patients in the clinical trial will be explored to create a future strategy for efficient patient accrual of clinical trials.

Study B

Study B will be conducted to clarify the long-term survival of patients (with a follow-up period >5 years) enrolled in Study A. Additionally, comparative analysis of the survival data with that of the patients who have participated in the JCOG0707 study will be performed.

Study setting

This study is a non-interventional observational cohort study for the patients who had completely resected p-Stage I (T1 >2 cm and T2 in TNM classification version 6) NSCLC but were not enrolled in the JCOG0707 study. This study is based on an investigation of the medical records of each patient.

Methods of analysis

The patients will be classified into the following five categories based on non-participation in the JCOG0707 study: (i) failure to satisfy the eligibility criteria for clinical studies, (ii) patient refusal to participate, (iii) the protocol was temporarily unavailable, (iv) the attending physician forgot to give information about the study, and (v) the attending physician decided that specific post-operative chemotherapy or observation only (no chemotherapy) should be used for the patient. The patients will also be classified into two groups according to the post-operative treatment status; (i) post-operative treatment group who received any post-operative therapy as a clinical practice and (ii) without post-operative treatment group.

In Study B, the survival data will be comparatively analyzed with that of patients enrolled in the JCOG0707 study. The patient backgrounds and overall survival will be analyzed among the three groups: (i) the patients who have participated in the JCOG0707 study and have received allocated post-operative chemotherapy, (ii) the patients who have not participated in the JCOG0707 study but have received post-operative chemotherapy as a clinical practice, and (iii) the patients who did not participate in the JCOG0707 study nor received any post-operative chemotherapy. The enrollment rates in the JCOG0707 study will also be analyzed according to each patient's background, institution and year.

Endpoints

Study A

Primary endpoint:

- Reasons why the patients were not enrolled in the clinical trial of post-operative chemotherapy (JCOG0707) and the percentages

Secondary endpoints:

(1) Patient backgrounds
(2) Implementation rate, contents and adherence to post-operative chemotherapy
(3) Overall survival
(4) Disease-specific survival
(5) Correlations among above endpoints

Study B
Primary endpoint:

Overall survival*

Secondary endpoints:

(1) Disease-specific survival*
(2) Patient backgrounds*
(3) Implementation rate and adherence to post-operative chemotherapy*
(4) Correlations among above endpoints

*Will be comparatively analyzed with the survival data of the patients enrolled in the JCOG0707 study.

Eligibility criteria

Approximately 5000 Japanese patients with completely resected NSCLC who satisfy all of the following eligibility criteria will be enrolled.

(1) Pathologically diagnosed NSCLC except for low-grade malignant tumors such as carcinoid, mucoepidermoid carcinoma and adenoid cystic carcinoma.
(2) Pathological Stage I disease with a tumor size >2 cm (T1 >2 cm and T2 in TNM classification version 6).
(3) Complete (R0) resection has been confirmed pathologically.
(4) Lobectomy or larger lung resection has been performed.
(5) Standard hilar/mediastinal lymph node dissection has been performed.
(6) No prior treatment before lung resection.
(7) Not enrolled in the clinical trial of post-operative chemotherapy (JCOG0707).

Enrollment and study period

Enrollment period:

From January 2015 to June 2015

Study period:

From January 2015 to March 2016 (Study A)
From April 2016 to March 2019 (Study B)

Statistical consideration

The planned sample size ($n = 5000$) was determined by estimated number of patients in all institutions who were candidate for the JCOG0707 study during the accrual period. The association between patient backgrounds and survival (overall and disease-specific survival) will be analyzed using pertinent statistical methods including the Kaplan–Meier method and the Cox proportional hazard model by statistical collaborator.

Funding

This study is sponsored by the Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. However, the funds for Study A are provided by Taiho Pharmaceutical Co., Ltd. according to a contract. The secretary for the CSPOR will perform the clerical work for the study but will not make decisions in association with planning, implementation, and publication of the study. Additionally, this study will be administered independent of the provider of the funds, and the provider of the funds will never be involved in the decision making for the planning, implementation, analysis and publication of the study. The decisions regarding the planning, implementation, and publication of the study will be made by the executive committee for the study.

Conflict of interest statement

None declared.

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Pathology International

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Letter to the Editor

A resected case of combined small cell lung carcinoma with carcinosarcoma

To the Editor:

A 73-year-old male with a previous abdominal aortic aneurysm was referred to our institution for a further examination of a pulmonary tumor found one month earlier on a routine health check-up. His history included smoking 20 cigarettes a day for 50 years (B.I = 1000).

The blood chemistry data were unremarkable, except for a carcinoembryonic antigen (CEA) level of 10.4 ng/ml (normal range, 0–5 ng/ml). Chest computed tomography (CT) demonstrated a well-defined tumor with inner heterogeneity measuring 3.2 cm in diameter in the left lower lobe (Fig. 1a). The border with the upper lobe was indistinct, and permeation to the upper lobe was suggested. No marked enlargement of the lymph nodes was observed. A bronchoscopic examination showed obstruction of B^6a. The histological diagnosis of the biopsied specimen was adenocarcinoma. Head magnetic resonance imaging (MRI), abdominal CT and bone scintigraphy detected no signs of distant metastases (cT2aN0M0-stage IB).

VATS left lower lobectomy, combined left upper lobe wedge resection and lymph node dissection (ND2a) were performed. A histopathologic examination revealed combined small cell carcinoma and carcinosarcoma (adenocarcinoma + squamous cell carcinoma + small cell carcinoma + chondrosarcoma). The histological staging was as follows: grade 4, pl3, pm0, Ly1, v1, R1, disseminated nodule in the pleural cavity (pM1a), surgical margin (-), pT2aN0M1a stage IV.

The patient received adjuvant chemotherapy consisting of CDDP+VNR. A CT scan performed two months after surgery revealed anterior mediastinal lymphoid swelling. Anterior mediastinal lymph node dissection (#3a, #4 L), thymectomy and left upper lobe wedge resection via median sternotomy were performed three months after the first surgery. A histopathologic examination showed that the #3a LN was positive for metastasis, although #4 L was negative, and the cancer had invaded the thymus with a positive surgical margin. No invasion was observed in the left upper lobe. There was a residual tumor in the dorsal left upper lobe. The patient received three courses of CBDCA+VP-16. Because an evaluation after chemotherapy revealed progressive disease (PD) in a CT scan, he received heavy particle radiotherapy (72 G/16 Fr) for the residual tumor. This achieved a partial response (PR) with a cytoreductive effect consistent with Response Evaluation Criteria in Solid Tumors (RESIST) on a CT scan. Routine follow-up chest CT performed 14 months after the first surgery showed pleural dissemination.

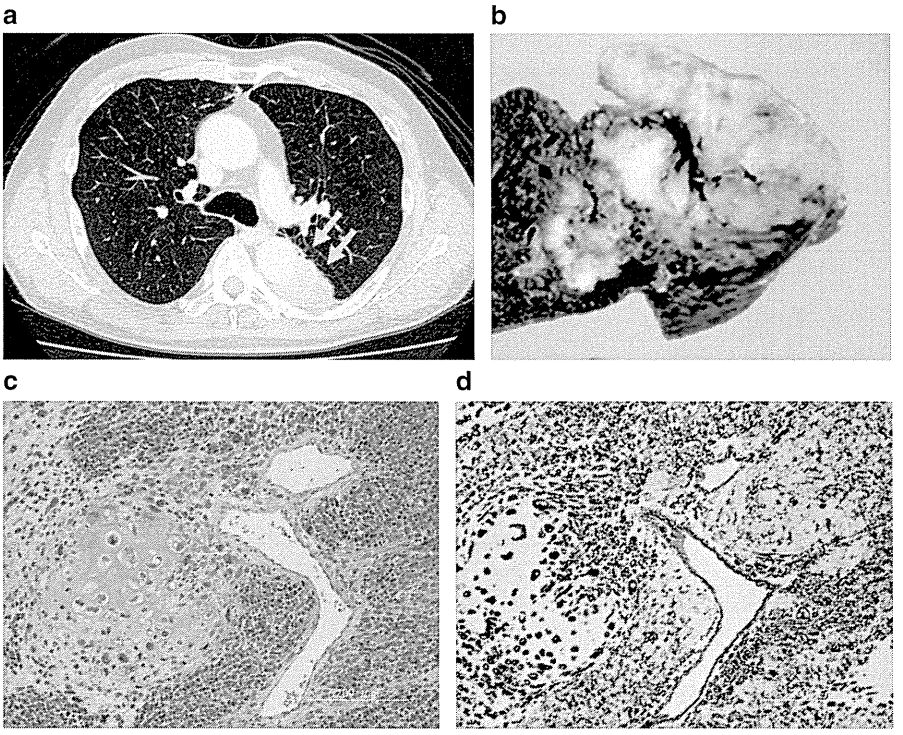

Figure 1 (**a**) Chest CT demonstrated a well-defined tumor with inner heterogeneity measuring 3.2 cm in diameter in the left lower lobe. (**b**) The gross pathological examination showed that the tumor was a 4.0 × 3.0 × 3.0-cm well-circumscribed grayish-white mass with necrosis, hemorrhage and invasion of the visceral pleura in left segment 6. Especially, it has a gelatinous grayish-white mass reflecting chondroid matrix on area A. (**c**) Sheets-like growth of small oval cells was detected on a microscopic routine examination. A component of chondrosarcoma, producing chondroid matrix, was also seen in focal area. (**d**) The examination revealed a mixture of vimentin(+)/keratin(-) area.

Following the administration of best supportive care, the patient died 17 months after the first surgery.

The gross pathological examination showed that the tumor was a 4.0 × 3.0 × 3.0-cm well-circumscribed grayish-white mass with necrosis, hemorrhage and invasion of the visceral pleura in left segment 6. Especially, it has a gelatinous grayish-white mass reflecting chondroid matrix on area A (Fig. 1b).

Sheets-like growth of small oval cells was detected on a microscopic routine examination. A component of chondrosarcoma, producing chondroid matrix, was also seen in focal area (Fig. 1c). Immunohistochemical stainings were performed to evaluate the histological classification of tumor. The examination revealed a mixture of vimentin(+)/keratin(-) area (Fig. 1d), suggesting immature and/or undifferentiated mesenchymal neoplasia, and vimentin(-)/keratin(+) area. This component is composed of small oval cells those are densely packed with scanty cytoplasm, granular chromatin, indistinct nucleoli and frequent mitotic figures (Fig. 2a). Immune positive reaction for CD56 are observed on cell membranes (Fig. 2b) and for synaptophysin in cellular cytoplasm (Fig. 2c). This area is diagnosed as small cell carcinoma.

A detailed histological examination revealed further two neoplastic epithelial components. One was glandular differentiation with acinar/tubular structures represent adenocarcinoma (Fig. S1a), which part is positive for TTF-1 (Fig. S1b). The other was squamous cell carcinoma exhibiting islands of large polygonal cells showing keratinizing matrix and intercellular bridges (Fig. S1c).

We stained the p53 to check the clonal growth of each part of the tumor. However every part of tumor is not stained in this case.

These findings led to a histological diagnosis (WHO) of combined small cell carcinoma and carcinosarcoma (adenocarcinoma + squamous cell carcinoma + small cell carcinoma + chondrosarcoma). Tumor invaded to the upper lower lobe parenchyma (pl3). The histological findings were follows: grade 4, pl3, pm0, Ly1, v1, R1, disseminated nodule in the pleural cavity (pM1a), surgical margin (-), (pT2aN0M1a stage IV), according to the 'General rules for clinical and pathological recording of lung cancer, 7th edition (Japan Lung Cancer Society).'

Reports of neoplasms containing carcinosarcoma and small cell carcinoma are extremely rare. According to the WHO classification (2004), our patient was diagnosed with 'combined small cell carcinoma with carcinosarcoma.' A review of carcinosarcoma written by A. Hereman *et al.*[1] in 1989 showed that there were no reports of small cell carcinoma with a carcinomatous component. In 2010, Hamai *et al.*[2] circumstantially reviewed 77 pulmonary carcinosarcoma cases that had been reported over the past 20 years and found only six cases containing carcinosarcoma and small cell carcinoma, including their own case.

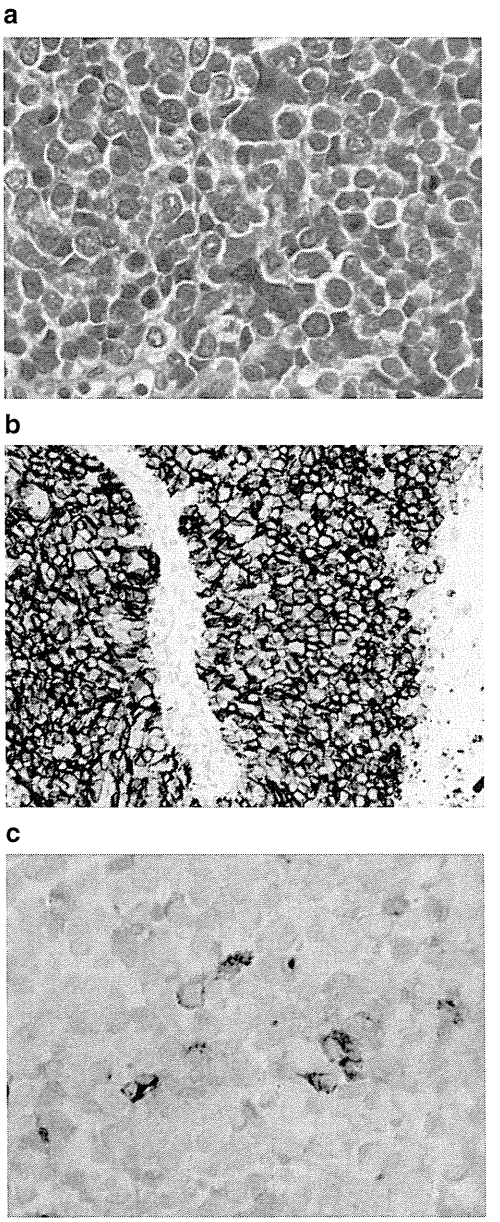

Figure 2 (**a**) Small oval cells are densely packed with scanty cytoplasm, granular chromatin, indistinct nucleoli and frequent mitotic figures in vimentin(-)/keratin(+) area. (**b**) Immune positive reaction for CD56 are observed on cell membranes. (**c**) Immune positive reaction for synaptophysin in cellular cytoplasm.

Pulmonary carcinosarcoma is a malignant tumor containing both epithelial and mesenchymal components that reportedly accounts for 0.1–0.3%[3,4] of all lung cancers. Generally, these reports include 'so-called carcinosarcoma' that resembles carcinosarcomas, such as pleomorphic carcinoma or pulmonary blastoma, that cannot be detected in muscle, bone or cartilage, histologically. Therefore, the frequency of 'true carcinosarcoma' is actually low. The carcinosarcoma components observed in our case is 'true carcinosarcoma' involving components of cartilage basement.

Koss *et al.*[4] reported that the male/female ratio of this disease is 7.25:1 and the median age at diagnosis is 68 years (range: 38–81 years). A strong association with a history of smoking has been noted.[3]

There are various theories as to the underlying mechanisms of the development of carcinosarcoma. The predominant theory is the 'monoclonal hypothesis,' which postulates that carcinosarcomas are derived from a single pluripotent stem cell that sequentially differentiates in epithelial and mesenchymal directions.[5] Another theory suggests that carcinoma cells undergo metaplastic changes to sarcomatoid cells.[6]

Moore[7] classified lung carcinosarcomas according to the site of origin as endobronchial and peripheral types arising from the central and peripheral bronchi, respectively. It has been reported that the endobronchial type is comparatively benign, while the peripheral type has a poorer prognosis. In our case, the tumor was present in a comparatively peripheral location, thought to be of the poor prognosis type.

Takayama *et al.*[8] reviewed 87 cases of 'true pulmonary carcinosarcoma' occurring over the past 20 years in Japan. The frequency of epithelial components consisting of squamous cell carcinoma is 56% (49/87), adenocarcinoma is 52% (45/87) and small cell carcinoma is 6% (5/87), while the frequency of sarcoma presenting as chondrosarcoma is 56% (49/87), rhabdomyosarcoma is 30% (26/87) and osteosarcoma is 24% (21/87). Therefore, the combination of carcinosarcoma and small cell carcinoma is extremely rare, as indicated above.

In our case, heavy particle radiotherapy was performed to treat the residual tumor, which showed a certain effect of cytoreduction, although the survival advantage was uncertain.

Reports of combined small cell carcinoma are extremely small in number, and there is no confirmed treatment. There are many considerations, such as the indications for surgery if other procedures can provide a diagnosis of combined small cell carcinoma before surgery and whether treating this neoplasm as small cell carcinoma with a therapeutic strategy is correct. Further accumulation of cases is required.

DISCLOSURE

The authors declare no conflicts of interest and all authors have approved the final article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 (a–b) A detailed histological examination revealed further two neoplastic epithelial components. One was glandular differentiation with acinar/tubular structures represent adenocarcinoma (Fig. S1a), which part is positive for TTF-1 (Fig. S1b). (c) Squamous cell carcinoma has islands of large polygonal cells showing keratinizing matrix and intercellular bridges.

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Thoracoscopic lung biopsy in 285 patients with diffuse pulmonary disease

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Abstract

Background: Surgical lung biopsy is generally considered the most appropriate method for diagnosing diffuse lung disease. However, there are few reports focusing on only one thoracoscopic technique. This study was designed to determine the morbidity and mortality related to video-assisted thoracoscopic lung biopsy in a single center, thereby providing data on the severity of morbidity and clarifying the risk factors.

Methods: We analyzed 285 patients with undiagnosed diffuse lung disease who underwent video-assisted thoracoscopic lung biopsy at Kanagawa Cardiovascular and Respiratory Center from February 2007 to April 2012. We recorded the severity of postoperative complications using the Clavien-Dindo classification.

Results: The surgical morbidity was 7.0% (20/285), including delayed pulmonary fistulas in 11 patients, acute exacerbation in 3, prolonged air leakage (>7 days) in 2, hypoxemia in 2, atrial fibrillation in 1, and premature ventricular contraction in 1. Based on the Clavien-Dindo classification, grade I, II, IIIa, IIIb, and IVa complications accounted for 20%, 10%, 50%, 5%, and 15%, respectively. The 30-day mortality was 0%. The diagnostic yield was 100%. Although acute exacerbation occurred in 2 patients with idiopathic pulmonary fibrosis and 1 with fibrotic nonspecific interstitial pneumonia, there were no distinctive features that allowed preoperative prediction of acute exacerbation.

Conclusions: Our findings indicate that video-assisted thoracoscopic lung biopsy is a feasible procedure. We hope to clarify risk factors in future research.

Keywords

Acute disease, biopsy, lung diseases, interstitial, postoperative complications, pulmonary fibrosis, thoracic surgery, video-assisted

Introduction

Surgical lung biopsy (SLB) is generally considered to be the most appropriate method for diagnosing diffuse lung disease.[1,2] SLB is recommended for patients with clinically undiagnosed conditions suggestive of interstitial lung diseases other than idiopathic pulmonary fibrosis (IPF).[3] SLB alters treatment in many patients who have undergone this examination, resulting in improvement of their clinical symptoms.[2,4] Most previous studies on SLB included cases of open lung biopsy as well as video-assisted thoracoscopic lung biopsy (VTLB), and there are few reports focusing only on one thoracoscopic technique.[2,4–7] Even reports dedicated to video-assisted thoracoscopic surgery alone did not provide details of the surgery.[8] Although the incidence of complications in SLB is reported to be 6%–25%, the evaluated severity and outcomes of these complications have not yet been reported in detail.[2,4,6,9] The Clavien-Dindo classification is widely

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used these days as an objective method of classifying complication severity.[10,11] We used this classification in the present study. Although acute exacerbation (AE) is currently recognized as a complication that is not rare and is associated with a high mortality rate, no definite risk factors have been demonstrated.[12,13] This study was designed to determine the morbidity and mortality related to VTLB in a single center, thereby providing data on the evaluated severity of morbidity and clarifying the risk factors.

Patients and methods

This was a retrospective study, and because individual patients were not identified, our institutional review board waived the requirement for obtaining patient consent and approved this study. From February 2007 to April 2012, 313 patients with undiagnosed diffuse lung disease underwent SLB at Kanagawa Cardiovascular and Respiratory Center for the purpose of tissue diagnosis. The inclusion criteria were male or female aged 18–85 years, no pathological diagnosis by biopsies such as transbronchial lung biopsy, clinical course or radiographic findings not typical of IPF, performance status $\leqslant 2$, no remarkable decrease in respiratory function, and no serious or uncontrolled comorbidities. Under these criteria, we considered the surgical indications at a joint conference of pulmonologists, radiologists, and thoracic surgeons. We excluded from the analysis 28 patients who underwent simultaneous lymph node biopsy and bullectomy; the final analysis included 285 patients. The medical records of all patients were retrospectively reviewed. Data gathered included age at the time of biopsy, sex, smoking status, comorbidities, preoperative corticosteroid use, preoperative O_2 dependence, laboratory findings, preoperative pulmonary function, arterial blood gases, demographic information, indications for biopsy, definitive diagnosis, perioperative morbidity and mortality. The clinical characteristics of the 285 patients are summarized in Table 1. At the time of SLB, 19 (6.7%) patients received corticosteroid therapy and 14 (4.9%) required supplemental oxygen therapy. Before SLB, 201 patients (70.5%) had undergone fiberoptic bronchoscopy and bronchoalveolar lavage, but no definitive diagnosis could be obtained. No patients had human immunodeficiency virus infection or active cancer. The median level of Krebs von den Lungen 6 was 947 U mL^{-1} (range 170–7696 U mL^{-1}).

High-resolution computed tomography (HRCT) data were available in all patients. We selected the biopsy site in consultation with a pulmonologist on the basis of chest HRCT findings, and indicated this site with a marker on the HRCT films. Intraoperatively, we considered the properties of the resected lung and then made a final determination. We left the electrocardiographic monitor in place until the 1st postoperative day. SLB was performed under general anesthesia with one lung ventilated using a double-lumen endotracheal tube, and with the patient in a full lateral position. The surgical procedure remained consistent throughout the study period. A 5-mm videothoracoscope was used with 3 access ports (5, 5 and 10 mm in diameter). An endostapler was employed to perform the wedge resection. The mean number of samples was 2.0, with one generally taken from the transition zone between normal and diseased lung, and the other from a site of active disease. Operative details are included in Table 1. Adhesion between the lung and chest wall was seen in 58 (20.4%) patients; partial in 49 and severe in 9. One case with dense pleural adhesions required conversion to a minithoracotomy. In 13 patients, we added a 5-mm port. All patients were extubated at the end of the surgical procedure.

Table 1. Clinical characteristics of 285 patients with diffuse pulmonary disease.

Variable*	No. of patients
Age (years)	65 [18–85]
Sex (M/F)	161/124
Smoking status (current/ex-/non-)	36/133/116
Smoking index	230 [0–3000]
Comorbidities	203 (71.2%)
Preoperative corticosteroid	19 (6.7%)
Preoperative O_2 dependence	14 (4.9%)
Bronchoalveolar lavage	201 (70.5%)
Krebs von den Lungen 6 (U mL^{-1})	947 [170–7696]
PaO_2 (mm Hg) [range]	81.4% [52.1%–128.9%]
% of predicted vital capacity	84.9% [42.0%–178.8%]
% of predicted FEV_1	81.1% [39.8%–147.0%]
% of predicted forced vital capacity	83.7% [40.9%–154.0%]
% of predicted DLCO	79.0% [30.6%–198.0%]
Operating time (min)	63 [34–252]
Anesthesia time (min)	119 [79–315]
Blood loss (mL)	5 [0–100]
Adhesion (partial/severe)	49/9
Converted to minithoracotomy	1 (0.4%)
Biopsy sites (1/2/3)	16/244/25
Chest drainage (days)	1 [1–13]
Morbidity	20 (7.0%)
30-day mortality	0%
Diagnostic yield	100%

*Values given as median [range]. PaO_2: arterial oxygen tension; FEV_1: forced expiratory volume in 1 s; DLCO: carbon monoxide diffusing capacity of the lung.

Postoperatively, we did not administer prophylaxis for AE, such as steroids, immunosuppressants, or neutrophil elastase inhibitors. All biopsy specimens were swabbed for cultures and gently inflated with formalin, using a syringe and needle. The specimens were dehydrated and embedded in paraffin. Sections were routinely stained with hematoxylin and eosin. Biopsy slides were reviewed independently by at least two pathologists, and classified according to the American Thoracic Society/European Respiratory Society consensus classification of interstitial pneumonias.[14]

We classified the severity of postoperative complications based on the Clavien-Dindo classification (Table 2).[11] Postoperative AE was defined according to previous reports and the revised criteria for AE of IPF in Japan (see appendices in online supplementary material):[15,16] occurring within 14 days postoperatively, subjective worsening of dyspnea, new ground-glass opacities or consolidation on chest radiography or HRCT, decrease in arterial oxygen tension of more than 10 mm Hg under similar conditions, and absence of apparent infection or heart failure.

Data are expressed as the median value and range for continuous variables, and as number and percentage for categorical variables. All analyses were performed using statistical software (IBM SPSS Statistics 20; IBM Corp., Armonk, NY, USA).

Table 2. Severity of postoperative complications according to the Clavien-Dindo classification.

Grade	Definition
I	Any deviation from normal postoperative course and no need for pharmacological, surgical, endoscopic, or radiological intervention
II	Requiring pharmacological treatment
III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention without general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication requiring intensive care unit stay
IVa	Single-organ dysfunction
IVb	Multiorgan dysfunction
V	Death of the patient

Results

Twenty (7.0%) patients experienced postoperative morbidities (Table 3). Based on the Clavien-Dindo classification, the 11 patients with delayed pulmonary fistulas consisted of 3 in grade I (improvement with follow-up alone) and 8 in grade IIIa (requiring chest drainage). None of these patients required pleurodesis or reoperation. All 3 patients with AE were classified as grade IVa; 2 received medical treatment in our intensive care unit, including high-dose systemic corticosteroid therapy (methylprednisolone 500 mg day^{-1} for 3 days) followed by tapering of the dose and immunosuppressants. The other patient also received medical treatment in an intensive care unit, although the details are unknown because the treatment was given in another hospital. Prolonged air leakage (>7 days) in 2 patients resolved with continuing drainage (grade IIIa), although the hospital stay was extended. Hypoxemia in 2 patients required home oxygen therapy (grade II). Atrial fibrillation classified as grade IIIb occurred in the operating room just after SLB, but sinus rhythm was restored by defibrillation. Premature ventricular contraction did not require medication (grade I). The 30-day mortality was 0%. The diagnostic yield was 100%. The pathologic diagnoses after SLB are given in Table 4, and Figure 1 shows the typical histopathological findings of IPF. Among the 169 patients with idiopathic interstitial pneumonia, 60 had a diagnosis of IPF and 60 had nonspecific interstitial pneumonia (NSIP), consisting of 52 with fibrotic NSIP and 7 with cellular NSIP. The lung tissues obtained by SLB were also cultured, but yielded no specific findings. AE

Table 3. Evaluation of the severity of postoperative complications based on the Clavien-Dindo classification.

Complication	No. of patients	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IVa	Grade IVb	GradeV
Pulmonary fistula	11 (100%)	3 (27%)	0	8 (73%)	0	0	0	0
Acute exacerbation	3 (100%)	0	0	0	0	3 (100%)	0	0
Prolonged air leakage (>7 days)	2 (100%)	0	0	2 (100%)	0	0	0	0
Hypoxemia	2 (100%)	0	2 (100%)	0	0	0	0	0
Atrial fibrillation	1 (100%)	0	0	0	1 (100%)	0	0	0
Premature ventricular contraction	1 (100%)	1 (100%)	0	0	0	0	0	0
Total	20 (100%)	4 (20%)	2 (10%)	10 (50%)	1 (5%)	3 (15%)	0	0

Table 4. Definitive diagnosis in 285 patients.

Diagnosis	No. of patients
Idiopathic interstitial pneumonias	169
Idiopathic pulmonary fibrosis	60
Nonspecific interstitial pneumonia	60
Fibrotic nonspecific interstitial pneumonia	52
Cellular nonspecific interstitial pneumonia	7
Cryptogenic organizing pneumonia	4
Acute interstitial pneumonia	1
Respiratory bronchiolitis-associated interstitial lung disease	1
Unclassified	43
Interstitial pneumonia associated with collagen vascular disease	47
Chronic hypersensitivity pneumonitis	29
Lymphoproliferative disorders	14
Summer-type hypersensitivity pneumonitis	4
Pneumoconiosis	4
Acute lung injury	3
Drug-induced pneumonia	2
Bronchitis	2
Eosinophilic pneumonia	1
Idiopathic pulmonary upper lobe fibrosis	1
Langerhans cell histiocytosis	1
Pulmonary alveolar proteinosis	1
Alveolar hemorrhage	1
Pulmonary ossification	1
Sarcoidosis	1
Asbestosis	1
Other granulomatous disease	1
Others	2

occurred in two 67-year-old men and one 76-year-old woman on postoperative day 6, 12, and 14. Table 5 lists the clinical features of patients with and without AE. The non-AE group consisted of 169 patients with idiopathic interstitial pneumonia, 47 with interstitial pneumonia associated with collagen vascular disease, and 29 with chronic hypersensitivity pneumonitis. Patients with other diseases were excluded from the non-AE group because there are no reports of AE in such cases. AE occurred in 2 of 60 (3.3%) IPF patients and in 1 of 52 (1.9%) fibrotic NSIP patients. Two of these patients were ex-smokers and one had never smoked. No patient received corticosteroid therapy or required supplemental oxygen therapy. None of the patients had clinical evidence of apparent infection or heart failure, and none had shown an accelerated decline before SLB. No SLB, bronchoalveolar lavage, or spirometry had been performed at the time of AE,

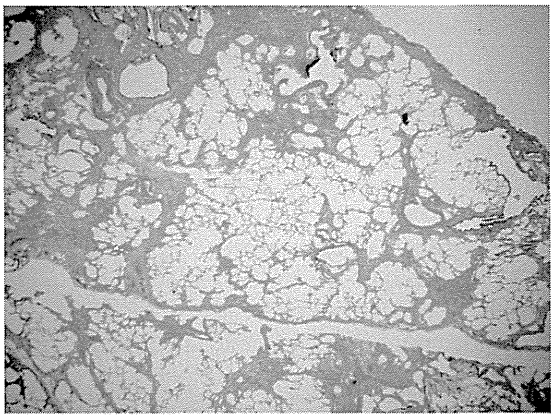

Figure 1. Histopathological findings in a 74-year-old man undergoing video-assisted thoracoscopic lung biopsy. The typical background of idiopathic pulmonary fibrosis includes patchwork fibrosis, honeycombing, and traction bronchiolectasis. Hematoxylin and eosin stain, original magnification ×4.

because iatrogenic procedures can induce, aggravate, or accelerate worsening of respiratory conditions. Although all 3 patients survived to discharge from the hospital, 2 later died from disease progression at 3 and 4 months after discharge; the other patient has survived for 41 months so far.

Discussion

In this study, we retrospectively reviewed patients with diffuse lung disease who underwent VTLB in our institution. VTLB reportedly reduces the mortality rate and the length of hospital stay: VTLB was found to be safe for diagnosing UIP, with no short-term mortality, although open-lung biopsy had a mortality rate of 5.3% within 1 month after the procedure, with morbidity rates of 2.9% (1/34) after VTLB and 14.3% (6/42) after open-lung biopsy.[7] On the other hand, the only randomized controlled trial of SLB for interstitial lung disease, reported by Miller and colleagues[17] in 2000, revealed no statistically significant differences in outcomes such as length of hospital stay, complications, and total morphine dose in 20 patients who underwent thoracoscopy and 22 who underwent a limited thoracotomy. Four major complications occurred in each group, and definitive pathologic diagnoses were made in both groups. However, this study dealt with a limited number of patients, and the thoracoscopic method was left to the discretion of the surgeon. Most previous reports on SLB included a mixture of cases with open lung biopsy and VTLB because of the long study periods.[2,4–7] In contrast, we focused only on cases of VTLB performed using the same technique in a single center. In addition, to exclude the influences of other procedures such as lymph node biopsy, the subjects of this study were restricted to those who underwent lung

Table 5. Clinical features of patients with and without acute exacerbation.

Variable*	Acute exacerbation ($n=3$)	No exacerbation ($n=245$)
Age (years)	67 [67–76]	65 [64–67]
Operating time (min)	72 [69–81]	62 [60–65]
Anesthesia time (min)	135 [105–150]	118 [115–123]
Lactate dehydrogenase (U mL^{-1})	237 [200–262]	245 [238–250]
C-reactive protein (mg dL^{-1})	0.20 [0.10–0.37]	0.15 [0.13–0.18]
Krebs von den Lungen 6 (U mL^{-1})	1451 [1058–1470]	1015.5 [919–1130]
Surfactant protein D (ng mL^{-1})	325 [184–591]	186 [175–207]
PaO_2 (mm Hg)	80.3 [75.9–92.2]	81.4 [80.1–83.0]
% of predicted VC	62.7% [59.7%–78.9%]	84.8% [81.9%–87.1%]
% of predicted FEV_1	82.9% [70.9%–83.7%]	80.8% [79.9%–81.9%]
% of predicted FVC	64.1% [54.4%–76.2%]	83.1% [78.6%–86.7%]
% of predicted DLCO	93.2% [52.4%–101.6%]	78.4% [75.0%–81.8%]

*Values given as median [95% confidence interval]. DLCO: carbon monoxide diffusing capacity of the lung; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PaO_2: arterial oxygen tension; VC: vital capacity.

biopsy alone. The morbidity rate (7.0%) in this study was not inferior to that in previous reports. In our institution, we apply SLB criteria to select appropriate candidates for SLB, and make efforts to avoid the implementation of unnecessary SLB by holding joint conferences. Our institution has a respiratory disease specialist who is an expert on interstitial lung disease. Because of this, many patients are referred to our institution from neighboring hospitals, and therefore, the number of our SLB cases is high, being the largest such patient population in Japan.

In this study, we used the Clavien-Dindo classification for evaluation of the severity of complications. The Clavien-Dindo classification was proposed in 1992 and revised in 2004, and has to date served as an objective method of classifying the severity of complications related to surgery.[10,11] Its reproducibility and validity were demonstrated in a large-scale cohort study. This classification is currently used worldwide in all areas of surgery, with its usefulness being demonstrated in the field of thoracic surgery as well. The present report is the first to focus on complications of SLB determined on the basis of the Clavien-Dindo classification. The percentage of major complications at grade III/IV was 70%, whereas that for minor complications of grade I/II was 30%. Thus the incidence of complications after SLB requiring intervention was high. Delayed pulmonary fistula often required chest drainage, highlighting the necessity of careful postoperative follow-up by chest radiography.

We used a 3-port complete thoracoscopic approach. All of our patients were able to tolerate one-lung ventilation. Although adhesions were found in 20% of patients, conversion to a minithoracotomy occurred in only one. Biopsy specimens were obtained from at least 2 sites in 269/285 (94%) patients. Because sufficient quantities of tissue were obtained, the diagnosis was established in all 285 SLB cases, and there were no deaths related to the procedure. Our VTLB can be considered as a safe and useful procedure, in agreement with previous reports. The incidence of AE was low. Although postoperative AE occurred in 3 (1.1%) patients, all recovered to discharge. It is said that the annual incidence of AE is 5%–10% during the natural course of IPF,[12] and AE reportedly occurred in 2.4% of patients with IPF who underwent bronchoalveolar lavage.[18] Kondoh and colleagues[6] reported that postoperative AE occurred in 5 of 236 (2.5%) patients with diffuse lung disease who underwent SLB. The low incidence of AE in our study is presumably attributable to the small total number of patients or the scarcity of cases of severe progressive interstitial lung disease. Although any type of chronic fibrosing interstitial lung disease can cause AE, clinical data are limited as to AE in interstitial lung diseases other than IPF, such as NSIP.[19,20] Park and colleagues[19] found that the annual incidence of AE was 4.2% among patients with idiopathic NSIP not accompanied by collagen disease, but they reported favorable prognoses. Yano and colleagues[20] studied patients with lung cancer accompanied by interstitial pneumonia who underwent surgical resection, and reported that AE occurred in 1 of 7 patients with IPF and 4 of 25 with fibrotic NSIP. Although further accumulation of data is important, caution regarding AE may be necessary in patients with fibrotic NSIP, as it is in those with IPF.

Although there are many reports on postoperative AE, no risk factors have been established.[12,13] In this

study, patients with AE tended to have the following features: advanced age, prolonged operation and anesthesia, high values of Krebs von den Lungen 6 and surfactant protein D, and low vital capacity and forced vital capacity. However, there were no distinctive features that allowed preoperative prediction of AE (Table 5). Careful follow-up with the possibility of postoperative AE in mind is warranted in all patients with chronic interstitial lung disease that shows fibrosis on computed tomography. Our institution does not adopt an aggressive application of perioperative prophylactic medication for AE because sufficient evidence of its efficacy is lacking.

The limitations of this study include the rarity of AE events, which precluded appropriate statistical processing, and selection bias. Although AE has become widely recognized, its occurrence in relation to minimally invasive VTLB is low. In addition, we set a strict criterion for AE occurrence within 14 postoperative days because our goal was to identify direct influences of VTLB. Although the number of VTLB cases was greater in this study than in any previous investigation of its kind, the number of AE events was very low. Some potential subjects with advanced disease might have been excluded as candidates for SLB by the pulmonologist who examined them at presentation, representing a selection bias. It is hoped that a future multicenter randomized controlled trial will clarify the risk factors for AE.

In conclusion, the morbidity rate was 7% and the mortality rate was 0% among patients with diffuse lung disease who underwent the same VTLB technique, indicating that VTLB is a feasible procedure. Our procedure is recommended for operable patients with clinically undiagnosed conditions, but with a clinical course or radiographic findings not typical of IPF. Based on the Clavien-Dindo classification for evaluating the severity of complications, grade III/IV complications requiring some form of intervention occurred in 70% of cases, but improvement was achieved in all of these. Although AE occurred in 2 patients with IPF and 1 with fibrotic NSIP, there were no distinctive features allowing the prediction of AE preoperatively. We hope to clarify the risk factors in future research.

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Conflict of interest statement

None declared.

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Clinical Trial Notes

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A Phase III Trial Comparing Irinotecan and Cisplatin with Etoposide and Cisplatin in Adjuvant Chemotherapy for Completely Resected Pulmonary High-grade Neuroendocrine Carcinoma (JCOG1205/1206)

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A randomized Phase III trial commenced in Japan in March 2013. Post-operative adjuvant chemotherapy with etoposide plus cisplatin is the current standard treatment for resected pulmonary high-grade neuroendocrine carcinoma including small cell lung cancer and large cell neuroendocrine carcinoma. The purpose of this study is to confirm the superiority of irinotecan plus cisplatin in terms of overall survival over etoposide plus cisplatin as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary high-grade neuroendocrine carcinoma patients. A total of 220 patients will be accrued from 54 Japanese institutions within 6 years. The primary endpoint is overall survival and the secondary endpoints are relapse-free survival, proportion of treatment completion, adverse events, serious adverse events and second malignancy. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000010298 [http://www.umin.ac.jp/ctr/index.htm].

Key words: lung neoplasms – high-grade neuroendocrine carcinoma – adjuvant chemotherapy – Phase III

INTRODUCTION

Lung cancer has been the leading cause of cancer-related deaths in Japan since 1988. High-grade neuroendocrine carcinoma (HGNEC) including small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) accounts for ~15% of all lung cancers (1,2).

LCNEC was first proposed by Travis et al. (3), who added LCNEC as the fourth category of pulmonary neuroendocrine tumors, which had originally been classified into three categories, typical carcinoid, atypical carcinoid and SCLC. Although it has been classified into a non-small cell lung cancer (NSCLC) by the WHO classification, LCNEC has neuroendocrine features and an aggressive clinical course that are common with SCLC and both are recognized as HGNEC. LCNEC is typically diagnosed post-operatively using surgical specimens and rarely diagnosed pre-operatively with biopsy specimens because of the difficulties associated with its diagnosis from a small amount of specimens. Furthermore, a differential diagnosis between LCNEC