and SCLC is known to be challenging in some cases even with surgical specimens.

A previous study reported that the prognosis of patients with surgery alone for SCLC and LCNEC was poor; the 5-year survival was shown to be 35.7% for SCLC and 40.3% for LCNEC (4). However, several retrospective studies have described the favorable outcomes of clinical Stage I SCLC patients who underwent surgery followed by adjuvant chemotherapy (5). Based on these reports, surgery plus adjuvant chemotherapy is regarded as a standard therapy for clinical Stage I SCLC. Reports on LCNEC are very limited because it is still a new entity. However, post-operative chemotherapy has also been added as a standard therapy in practice for LCNEC because its prognosis after surgery alone is poor.

The Japan Clinical Oncology Group study, JCOG9101, which is a Phase II trial to evaluate the feasibility of etoposide and cisplatin (EP) for completely resected pathological Stage I–IIIA SCLC patients, demonstrated the sufficient feasibility of the EP regimen (6). The survival of each stage was better than that of pathological Stage I–III patients who were administered cyclophosphamide, doxorubicin and vincristine (CAV) in another prospective study (7). Thus, EP has been considered acceptable as a current standard post-operative adjuvant chemotherapy regimen for SCLC.

The only report of a prospective study on adjuvant chemotherapy in pathological Stage I–IV LCNEC revealed the favorable outcomes of EP (8). One retrospective review of adjuvant chemotherapy for LCNEC compared two major categories of regimens; one for a SCLC regimen, a combination of platinum and etoposide, and the other for NSCLC regimens, a combination of platinum and gemcitabine, taxanes or vinorelbine. The findings of this review showed that SCLC regimens significantly prolonged survival (median survival time 42 months versus 11 months, $P < 0.0001$) (9). Therefore, the EP regimen is regarded as a standard post-operative adjuvant therapy regimen for LCNEC in Japan.

JCOG9511, a Phase III trial comparing irinotecan plus cisplatin (IP) with EP in SCLC patients with extended disease (ED-SCLC), showed that survival was significantly longer in the IP arm than in the EP arm (12.8 months versus 9.4 months, $P = 0.002$ by the log-rank test) (10). However, all three randomized controlled trials conducted afterwards to confirm the superiority of IP failed to demonstrate a difference in survival between the two arms (11–13). On the other hand, a recent meta-analysis has suggested that overall survival may be superior with irinotecan plus platinum than with etoposide plus platinum (14). Therefore, IP is regarded as one of the standard treatment options for ED-SCLC patients and is also expected to be a promising regimen in adjuvant chemotherapy for completely resected HGNEC patients. Kenmotsu et al. (15) conducted a multicenter Phase II pilot study to evaluate the feasibility of IP in post-operative adjuvant chemotherapy for HGNEC patients, and showed that the proportion of completion of treatment and toxicities were acceptable.

Based on these backgrounds, we have commenced a multicenter randomized controlled trial to confirm the superiority of IP in terms of overall survival over EP as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary HGNEC patients.

The JCOG Protocol Review Committee approved this study protocol in February 2013 and patient enrollment began in March 2013. Approval was obtained from the Institutional Review Board prior to starting patient accrual at each institution.

PROTOCOL DIGEST OF THE JCOG1205/1206

Objectives

The purpose of this study is to confirm the superiority of IP in overall survival over EP as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary HGNEC patients.

Study Setting

A multi-institutional two-arm open label randomized Phase III study.

Endpoints

The primary endpoint is overall survival (OS) in all randomized patients. OS is defined as days from randomization to death from any cause, and it is censored at the last day when the patient is alive. The secondary endpoints are relapse-free survival (RFS), proportion of treatment completion, adverse events, serious adverse events and second malignancy. RFS is defined as days from randomization to relapse or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of relapse.

Eligibility Criteria

Inclusion Criteria

(1) Pathologically proven high-grade neuroendocrine carcinoma (small cell carcinoma including combined small cell carcinoma, or large cell neuroendocrine carcinoma including combined large cell neuroendocrine carcinoma)
(2) Pathological Stage I–IIIA based on the seventh UICC-TNM classification (16).
(3) Pathologically proven R0, R1 (is) or R1 (cy+) based on the seventh edition of the General Rule for Clinical and Pathological Record of Lung Cancer by the Japan Lung Cancer Society (17)
(4) Aged 20–74-years-old
(5) ECOG performance status of 0 or 1
(6) Lobectomy or more extended surgery was performed
(7) ND 2a-1 or more extended lymph node dissection was performed
(8) Within 28–56 days after surgery
(9) No distant metastasis including brain metastasis
(10) No prior chemotherapy or radiotherapy for any cancers

(11) Adequate organ functions
(12) No diarrhea or intestinal obstruction
(13) Written informed consent

Exclusion Criteria

(1) Synchronous or metachronous (within 5 years) malignancy, except for carcinoma *in situ* or mucosal tumors curatively treated with local therapy
(2) Active infection requiring systemic therapy
(3) Body temperature $\geq$38°C
(4) Pregnant or lactating women or women of childbearing potential
(5) Severe mental disease
(6) Serious post-operative complications
(7) Patients receiving systemic steroid medication
(8) Poorly controlled diabetes mellitus or receiving the routine administration of insulin
(9) Poorly controlled hypertension
(10) Unstable angina within 3 weeks, or with a history of myocardial infarction within 6 months
(11) Positive serum HBs antigen or HCV antibody
(12) Positive serum HIV antibody
(13) Interstitial pneumonia, pulmonary fibrosis or severe emphysema

Randomization

After confirming the eligibility criteria, registration is made by telephone, fax or a web-based system to the JCOG Data Center. Patients are randomized to either arm A (EP) or arm B (IP) by the minimization method balancing the arms with institution, sex (male versus female), pathological stage (Stage I versus Stage II–IIIA) and pathological type (SCLC versus LCNEC).

Treatment Methods

Patients in the EP arm receive four courses of post-operative EP (etoposide, 100 mg/m^2/day, Day 1–3; cisplatin 80 mg/m^2/day, Day 1) repeated every 3 weeks. Patients in the IP arm receive four courses of post-operative IP (irinotecan, 60 mg/m^2/day, Day 1, 8, 15; cisplatin, 60 mg/m^2/day, Day 1) repeated every 4 weeks. When the leukocyte count is decreased to $<$3000/mm^3 or the platelet count to $<$100 000/mm^3 on the planned first day of both arms, the start of chemotherapy is delayed until the counts recover to 3000/mm^3 or more and 100 000/mm^3 or more, respectively. The administration of irinotecan is skipped on Day 8 and/or 15 when at least one of the following occurs; a leukocyte count $<$2000/mm^3, platelet count $<$100 000/mm^3, diarrhea Grade 1 or higher or a fever of 37.5°C or higher. The dose of etoposide and irinotecan in the subsequent cycles is reduced by 20 mg/m^2 and 10 mg/m^2 from the planned dose, respectively, when the leukocyte count is $<$1000 mg/m^2, platelet count is $<$20 000/mm^3 and/or Grade 3 non-hematologic toxicities (excluding hyponatremia and weight loss) develop. The dose of cisplatin is reduced by 20 mg/m^2 in the EP arm and 10 mg/m^2 in the IP arm when patients have serum creatinine $>$1.5 mg/dl, but not exceeding 2.0 mg/dl, Grade 2–3 peripheral motor or sensory neuropathy, myalgia, arthralgia or other Grade 3 non-hematologic toxicities (excluding hyponatremia and weight loss). The protocol treatment is terminated when serum creatinine exceeds 2.0 mg/dl or patients develop Grade 4 non-hematologic toxicities (other than hyperglycemia, hypernatremia, hyponatremia, hyperkalemia and hypokalemia). After completion of the protocol treatment, patients are observed without anti-cancer treatment until recurrence is detected.

Follow-up

All randomized patients are followed-up for at least 5 years after patient accrual is completed while analysis of the primary endpoint is conducted 3 years after accrual completion.

Chest X-rays are performed every 6 months for the first 5 years and every year afterwards. Tumor markers (CEA, NSE and ProGRP), enhanced computed tomography of the thorax and enhanced computed tomography or ultrasound of the upper abdomen are evaluated every 6 months for the first 3 years and every year from the fourth to the fifth year.

Study Design and Statistical Analysis

This randomized trial is designed to confirm the superiority of IP in terms of overall survival over EP as post-operative adjuvant chemotherapy for pathological Stage I–IIIA completely resected pulmonary HGNEC patients.

We assumed the 3-year survival with post-operative EP to be 70% and expected a 10% increase in the 3-year survival with post-operative IP. According to Schoenfeld and Richter's method (18), the sample size was calculated as 104 patients per arm with a one-sided alpha level of 5%, a power of 70%, an expected accrual period of 6 years and a follow-up period of 3 years. Eighty-eight events in total are expected. The total sample size was set at 220 patients to account for patients lost to follow-up. All statistical analyses will be conducted at the JCOG Data Center.

Interim Analysis and Monitoring

We plan to conduct two interim analyses, taking multiplicity into account using the Lan–DeMets method with the O'Brien and Fleming type alpha spending function (19). The first interim analysis will be conducted after half of the planned number of patients is enrolled and the second interim analysis after the planned patient accrual and their protocol treatment is completed. The Data and Safety Monitoring Committee (DSMC) of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. If the superiority of the IP arm is demonstrated with a one-sided P value of the stratified log-rank test below an adjusted alpha level, the study will be terminated.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

UMIN Registration Number

This trial has been registered at the UMIN Clinical Trials Registry as UMIN000010298 [http://www.umin.ac.jp/ctr/index.htm].

Participating Institutions (from North to South)

Asahikawa Medical Center, National Hospital Organization Hokkaido Cancer Center, KKR Sapporo Medical Center, Miyagi Cancer Center, National Hospital Organization Sendai Medical Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital and Cancer Center, Tochigi Cancer Center, National Nishigunma Hospital, Gunma Prefectural Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba University Graduate School of Medicine, National Cancer Center Hospital, Kyorin University Faculty of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, National Center for Global Health and Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University Hospital, Yokohama City University Medical Center, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Niigata Cancer Center Hospital, Kanazawa University School of Medicine, Gifu Municipal Hospital, Shizuoka Cancer Center, Nagoya University School of Medicine, Aichi Cancer Center Hospital, National Hospital Organization Nagoya Medical Center, Aichi Cancer Center Aichi Hospital, Kyoto University Hospital, Osaka City University Hospital, Kinki University Faculty of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Disease, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka City General Hospital, Kobe City Medical Center General Hospital, Hyogo Cancer Center, Kurashiki Central Hospital, Okayama University Hospital, National Hospital Organization Kure Medical Center Chugoku Cancer Center, Hiroshima University Hospital, National Hospital Organization Yamaguchi-Ube Medical Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, School of Medicine Fukuoka University, Nagasaki University Hospital, Kumamoto University Medical School, Kumamoto Chuo Hospital, Kumamoto Regional Medical Center Hospital and National Hospital Organization Okinawa Hospital

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Conflict of interest statement

None declared.

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CURRENT TOPICS REVIEW ARTICLE

Current status of induction treatment for N2-Stage III non-small cell lung cancer

Masafumi Yamaguchi · Kenji Sugio

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Abstract Locally advanced non-small cell lung cancer (NSCLC), particularly clinical Stage IIIA NSCLC with mediastinal lymph node metastasis, is known to be quite heterogeneous, comprising approximately one-fourth of cases of NSCLC. In this subset, patients with a minor tumor load in the mediastinal lymph nodes, such as microscopically or pathologically proven N2 in the resected specimens, are treated with surgery followed by adjuvant chemotherapy. Meanwhile, the current standard of care for patients with bulky or infiltrative N2 disease is concurrent chemoradiotherapy. The potential role of surgery in multi-modality treatment for clinical N2-Stage IIIA remains controversial. Several prospective clinical trials of this subset have been conducted; however, the heterogeneity of the N2 status and differences in chemotherapy regimens and/or radiation modalities between clinical trials make the results difficult to compare. No optimal chemotherapy regimen has been established to control possible micrometastasis, and radiotherapy is often used to achieve maximum local disease control and minimize post-surgical complications. This review summarizes the findings of prospective clinical trials that assessed the role of surgery in treating clinical N2-Stage IIIA patients within the last two decades and discusses the present status of induction treatment followed by surgery for clinical N2-Stage IIIA NSCLC.

Keywords Non-small cell lung cancer · cN2-Stage IIIA · Induction treatment · Induction chemoradiotherapy · Surgery

M. Yamaguchi
Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1, Notame, Minami-ku, Fukuoka 811-1395, Japan

K. Sugio (✉)
Department of Thoracic and Breast Surgery, Faculty of Medicine, Oita University, 1-1, Idaigaoka, Hasama-machi, Yufu, Oita 879-5593, Japan
e-mail: ksugio@oita-u.ac.jp

Introduction

Approximately 8–20 % of non-small cell lung cancer (NSCLC) patients are diagnosed with clinical Stage IIIA disease with mediastinal lymph node metastasis (cN2-Stage IIIA) [1, 2], which has a 5-year survival rate of 19–42.8 % [2, 3]. The cN2-Stage IIIA NSCLC cases are known to be heterogeneous, and a clearly accepted characterization of its subgroups has not yet been defined, which might be responsible for the wide variation in the prognosis. The type of mediastinal lymph node metastasis (N2) varies: i.e., microscopic metastasis or macroscopic, bulky, extra-nodal, single station or multi-station metastasis, incidental or occult metastasis, and so on. The volume of cancer cells or extent of N2 status might have prognostic importance. Patients with microscopic or cStage IIIA NSCLC with pathologically proven N2 in resected specimens often have been reported to have a good prognosis even when treated with surgical resection alone, with a median overall survival (OS) of 28–57.5 month [4, 5], whereas surgical resection alone in patients with macroscopic N2-Stage IIIA NSCLC resulted in a median survival time of less than 23 months [5].

The recent definition proposed by the American College Of Chest Physicians (ACCP) thoroughly described the resectability of the tumor based on the N2 status, such as discrete or infiltrative type [6], and recommendations were

made according to this N2 status, with definitive chemoradiotherapy (CRT) recommended for infiltrative cN2 and definitive CRT or induction treatment, followed by surgery, recommended for other cases.

Several prospective clinical trials have established the survival benefit of concurrent chemoradiotherapy over radiotherapy alone [7] or chemotherapy followed by sequential radiotherapy therapy for cN2 NSCLC [8, 9], and concurrent definitive CRT is currently the standard of care for cN2-Stage IIIA NSCLC patients [10–13]. The role of surgery in the treatment of cN2-Stage IIIA NSCLC still remains controversial, mainly due to the heterogeneity of the N2 status [14]. Many retrospective analyses have reported the possible survival benefit of induction treatment followed by surgery in selected patients with cN2-Stage IIIA NSCLC [15–19]; however, many randomized phase III trials have failed to demonstrate the superiority of induction treatment followed by surgery, mainly because of the wide variation in the determination of cN2-Stage IIIA, i.e., radiologically determined N2 or pathologically proven N2 in the resected specimens, the presentation of the N2 status (bulky vs. occult N2) and whether there is single or multistation N2. We herein review the results of major studies that have assessed the role of induction treatment followed by surgery for cN2-Stage IIIA NSCLC.

Induction chemotherapy followed by surgery vs. upfront surgery

The results of selected phase III clinical trials that compared the survival benefit of primary surgery versus induction treatment followed by surgery are listed in Table 1 [20–24]. Two randomized studies reported strikingly positive results in favor of induction chemotherapy followed by surgery compared to upfront surgery, with statistical significance. MD Anderson Cancer Center [21] used cyclophosphamide, etoposide and cisplatin for induction chemotherapy, followed by surgery for pathologically proven cN2-IIIA NSCLC patients. The primary end point was the OS, and they planned to accrue a total of 130 patients (two-sided test, type I error 0.05, a power of 80 %). Patients treated with induction chemotherapy had an estimated MST of 64 months compared with 11 months for patients who had surgery alone ($p = 0.008$). This trial was prematurely terminated because the patient accrual was insufficient. Spanish groups [22] compared surgery with or without induction chemotherapy comprising mitomycin, ifosfamide and cisplatin. Most of the enrolled patients (73 %) were pathologically confirmed to have cN2, as detected by computed tomography (CT). The primary end point was also the OS, with an expected 9 % absolute benefit for the induction chemotherapy arm over

Table 1 Results of selected randomized phase III clinical trial of induction treatment followed by surgery vs. surgery alone for cStage IIIA NSCLC

Reference	Year	No. of pts.	Clinical stage (N2-IIIA %)	Treatment	RR (%)	Resection rate (%)	R0/1–2 (%)	Pn. (%)	Mortality[a] (%)	MST (m)	OS (m)	*p* valve	Status
Pass [20]	1992	27	IIIA	EP–Surgery–EP	50	–	–	–	0	28.7	–	0.095	No information
				Surgery–RTx	/	–	–	–	0	15.6	–		
Roth [21]	1994	60	IIIA	CEP–Surgery	35	61	31/69	21.4	3	64	56 (3y)	<0.008	Early closure
				Surgery	/	66	31/69	20.0	6	11	15 (3y)		
Rosell [22]	1994	60	IIIA (73)	MIP–Surgery	60	90	85/15	48	7.4	26	17 (5y)	<0.001	Early closure
				Surgery	/	100	90/10	53	6.7	8	9 (5y)		
Depierre [23] (FTOG)	2002	355	I–IIIA (34)	MIP–Surgery	64	89	92/8	48.6	10.3	37	43.9 (4y)	0.15	Completed
				Surgery	/	97	86/14	55.7	5.1	26	35.3 (4y)		
Nagai [24] (JCOG9209)	2003	62	IIIA	VP–Surgery	28	74.2	65/35	8.7	0	17	10 (5y)	0.527	Poor accrual
				Surgery	/	93.5	77/23	17.2	0	16	22 (5y)		

RTx radiation therapy, *RR* CR+PR, *Pn* pneumonectomy, *EP* etoposide, cisplatin, *CEP* cyclophosphamide, etoposide, cisplatin, *MIP* mitomycin, ifosfamide, cisplatin, *VP* vindesine, cisplatin, *Cb* carboplatin, *Pac* paclitaxel

[a] Mortality post-surgery

the upfront surgery arm. This trial was stopped because of the significant difference in survival at the interim analysis. The MST was 26 months in patients treated with induction chemotherapy, as compared with 8 months in patients treated with surgery alone ($p < 0.001$). Updated analyses of both studies continue to favor survival in the induction chemotherapy arms [25, 26]. However, these two studies have several problems for induction chemotherapy, such as small number of enrolled patients, use of older anticancer drugs, the application of the 1986 TNM staging system in which stage III is more heterogeneous and the use of adjuvant radiotherapy. In addition, the outcome of surgery-alone group was very poor in Rosell's study.

The French Thoracic Oncology Group study compared surgery with or without induction treatment using mitomycin, ifosfamide and cisplatin in 355 resectable clinical stage I–IIIA NSCLC patients, including 122 (34 %) with CT-confirmed cN2-Stage IIIA disease [23]. The primary end point was the OS. The MST was 37 months in the induction arm and 26 months in the surgery-alone arm ($p = 0.15$). Interestingly, survival benefit was shown in patients with N0–1 disease ($p = 0.027$), but not in patients with N2 disease ($p = 0.85$). In this study, approximately 50 % of the patients underwent pneumonectomy despite the fact that this trial included almost 50 % cStage IB–II patients.

The Japan Clinical Oncology Group (JCOG 9209) performed a randomized trial in patients with potentially resectable, histologically or cytologically confirmed cN2-Stage IIIA NSCLC [24]. This trial was also prematurely terminated because of the slow accrual of eligible patients. The hypothesis of this trial was that there would be a 15 % increase (25–40 %) in the 3-year survival in the induction chemotherapy arm compared with the surgery-alone arm. However, only 62 patients were enrolled in this study. The induction treatment regimen applied in this trial was vindesine and cisplatin. Pneumonectomy was performed in 17.2 % of the cases in the surgery-alone arm, whereas it was performed in only 8.7 % of those in the induction treatment arm. The 5-year survival rate was 10 % for the induction chemotherapy arm and 22 % for the surgery-alone arm, which was not significantly different ($p = 0.527$).

These trials revealed a marginally consistent trend toward an improved overall survival after induction treatment vs. upfront surgery; however, most of them included a small number of patients, and the differences between the arms were not statistically significant. Berghmans et al. [27] reported a meta-analysis of six prospective clinical trials concerned with induction treatment followed by surgery vs. surgery mainly for clinical Stage IIIA NSCLC, and showed a hazard ratio for the combined results of 0.66 (95 % CI, 0.48–0.93) in favor of induction chemotherapy. Burdett et al. [28] reported the results of a meta-analysis from seven RCTs, including 988 NSCLC patients, and showed that the combined results indicated a significant increase in survival associated with the use of preoperative chemotherapy ($p = 0.02$), with a hazard ratio of 0.82 (95 % CI, 0.69–0.97) in clinical Stage IA–IIIB cases and an absolute survival benefit of 6–7 % in clinical Stage IIIA NSCLC patients. Recently, a systematic review and meta-analysis of individual participant data from NSCLC Meta-analysis Collaborative Group have been reported [29]. The interpretation of this review was that preoperative chemotherapy significantly improved overall survival, time to distant recurrence and recurrence-free survival in resectable NSCLC, suggesting that this was a valid option for most of these patients.

Comprehensively, these data indicated that upfront surgery for cN2-Stage IIIA NSCLC was inferior to the induction treatment modality. However, most of these clinical trials involved small numbers of patients. Although the information about the cN2 status in these trials cannot be drawn from the reports, it is possible that most of the patients in these trials had a relatively small tumor load in the cN2 nodes, which made surgeons select upfront surgery for the patients.

Induction concurrent chemoradiotherapy followed by surgical resection

The 2013 ACCP guidelines [6] defined N2 nodes that have extranodal progression and an invasive nature as infiltrative nodes, while others are defined as discrete nodes. This definition made the treatment decision for cN2-Stage IIIA NSCLC easier. Compared to the patients included in trials with induction chemotherapy followed by surgery or upfront surgery, the patients enrolled in trials of definitive chemoradiotherapy had a higher tumor load in the N2 nodes, with so-called "bulky", "infiltrative" or "unresectable" tumors. The possible differences in the tumor load in the N2 nodes in the subgroups make a comparison of the results of the different trials difficult.

The clinical benefit of definitive concurrent chemoradiotherapy over radiotherapy alone for cStage III NSCLC was confirmed by Jeremic et al. [11, 30] in their randomized phase III trial. The West Japan Lung Cancer Group subsequently demonstrated the same findings in a phase III trial with 320 patients who were randomly assigned to receive thoracic radiotherapy (56 Gy) either sequentially after or concurrent with cisplatin, vindesine and mitomycin [10]. Patients receiving concurrent therapy had an MST of 16.5 months compared with 13.3 months for the sequentially treated patients ($p = 0.03998$), and the 5-year survival rate was also superior in the concurrently treated

patients compared with the patients who received sequential therapy (15.8 vs. 8.9 %). Thus, concurrent chemoradiotherapy has been the standard of care as a definitive therapy for locally advanced NSCLC.

In the West Japan Thoracic Oncology Group (WJTOG) 0105 trial, 456 eligible patients, including 52 % cStage IIIA patients, were randomly assigned to receive MVP, carboplatin plus irinotecan or carboplatin plus paclitaxel, all concurrent with 60 Gy of radiotherapy. The MST and 5-year survival rates in the MVP arm were 20.5 months and 17.5 %, while they were 19.8 months and 17.8 % in the carboplatin plus irinotecan arm and 22.0 months and 19.8 % in the carboplatin plus paclitaxel arm, respectively [31]. The survival outcome of definitive chemoradiotherapy has been improving during the last two decades; however, one unanswered question is whether the addition of surgery contributes to a cure or prolongs the survival of patients with locally advanced NSCLC.

The phase II clinical trials that assessed the impact of induction concurrent chemoradiotherapy on the survival for cStage IIIA NSCLC patients reported in the past two decades are listed in Table 2. The radiotherapy dose was generally lower than that used for definitive chemoradiotherapy to avoid the development of fatal postoperative complications. The rate of pneumonectomy was around 40 %, and was somewhat higher compared to the rates of reported trials of induction chemotherapy or upfront surgery listed in Table 1. The mortality rate varied from 3 to 11 % of the patients enrolled each trial.

The Southwest Oncology Group (SWOG) 8805 trial [32] included 126 cStage III NSCLC patients, 60 of whom had pathologically proven cN2-Stage IIIA. Two cycles of etoposide and cisplatin were used concurrent with 45 Gy of radiotherapy as an induction treatment. There was a 10 % treatment-related death rate, but good locoregional control was obtained with an encouraging median survival of 27 months in the cN2-Stage IIIA patients. Katakami et al. [33] performed a multi-center phase II trial to assess the feasibility of concurrent induction chemoradiotherapy that included cisplatin and etoposide on days 1–5, every 4 weeks, concurrent with 50 Gy of radiotherapy. Forty-two patients were enrolled, and 10 (24 %) of them had cStage IIIA disease, including seven cases with bulky N2 lesions, without pathological confirmation. The response rate to induction chemoradiotherapy was excellent; however, only 21 patients (50 %) underwent surgery. Among them, the MST of completely resected patients was 19.4 months.

Thomas et al. [34] adopted induction treatment using ifosfamide, etoposide and carboplatin, then concurrent chemoradiotherapy with carboplatin, vindesine and 45 Gy of radiotherapy, followed by surgery. Forty-six percent of the patients had pathologically proven cN2-Stage IIIA. The tumor response rate to the induction treatment was 69, and 74 % of the patients underwent surgery. The survival was modest, with an MST of 20 months, and the 3 -year survival rate was 30 % for the overall patient population. The Swiss Group for Clinical Cancer Research (SAKK) used third-generation drugs, docetaxel and cisplatin, concurrent with 44 Gy of radiotherapy [35]. A relatively good tumor response of 66 and a 100 % resection rate were obtained. The survival was also fair, with an MST of 35 months and a 3-year survival rate of 36 %.

A recent report by the Radiation Therapy Oncology Group (RTOG 02-29) evaluated the mediastinal nodal clearance (MNC) after definitive concurrent chemoradiotherapy with a radiation dose of 61.2 Gy used as an induction treatment [36]. The hypothesis of this trial was that there would be a 20 % absolute benefit of MNC over the reported MNC of 50 % in the SWOG 8805 trial [32]. This trial included 27 patients with MNC, and the primary end point was reached. The toxicity was acceptable, and a better MST of 26.6 months was reported with full dose radiotherapy.

Phase III trials of induction treatment followed by surgery

The reported results of phase III trials assessing the survival benefits of surgery compared to definitive radiotherapy and/or induction chemoradiotherapy followed by surgery for cStage III NSCLC are listed in Table 3. Despite the variety in the regimens and doses of radiation, the rate of delivery of induction treatment ranged from approximately 78 to 95 %, with acceptable grade 3/4 toxicities, primarily including hematologic adverse events, with a frequency of approximately 40 % to less than 75 %. The tumor response after induction treatment varied between the trials: 25–96 % and approximately 60–90 % patients underwent surgery, with the exception of a rate of 17 % in one trial [37]. The median mortality rate in these trials was 4 % (range: 0–9.2 %). Therefore, in general, all trials showed acceptable rates of toxicity and mortality.

The Radiation Therapy Oncology Group (RTOG89-01) and Eastern Cooperative Oncology Group (ECOG) conducted phase III trials during the early 1990s to assess the differences in survival and local control between patients treated with chemotherapy using cisplatin, vinblastine and mitomycin C sequentially followed by radiotherapy (50 Gy), and the same chemotherapy followed by surgery to compare the role of surgery [38]. All eligible patients were pathologically confirmed to have cN2-Stage IIIA disease. The stratification was made based on whether there was bulky N2 (defined as visible on chest radiography) or other N2 disease. The primary end point was survival. The studies were designed to show a 40 % difference in the

Table 2 Results of selected phase II trials of induction chemoradiotherapy followed by surgery for cStage IIIA NSCLC

Reference	Year	No. of pts.	cN2-IIIA (%)	Chemotherapy	RTx (Gy)	RR (%)	Resection rate (%)	Pn. (%)	Mortality[a] (%)	MST (IIIA) (m)	OS (IIIA) (%)
Albain [32] (SWOG8805)	1995	126	60	PE+RTx	45	59	85 (N2-IIIA)	36	10	13	27 (3y)
Katakami [33]	1998	42	24	PE+RTx	50	81	45	45	11	24.9	20 (5y)
Thomas [34]	1999	54	46	Ifo+E+Cb, Cb+V+RTx	45	69	74	–	9	20	30 (3y)
Betticher [35]	2006	75	100	Pl+DOC+RTx	44	66	100	53	3	35	36 (3y)
Suntharalingam [36] (RTOG02-29)	2012	57	98.2	Cb+Pac+RTx	61.2	–	65	8	2.7	26.6	54 (2y)

RTx radiotherapy, *RR* CR+PR, *Pn* pneumonectomy, *PE* cisplatin, etoposide, *Ifo* ifosfamide, *Pl* platinum, *Doc* docetaxel, *Cb* carboplatin, *Pac* paclitaxel

[a] Mortality post-surgery

MST between the regimen containing surgical resection and the regimen containing radiotherapy. To show the statistical significance of the differences between the treatments, it was estimated that 224 patients would be required (alpha, 0.05 and beta, 80 %); however, this trial was terminated after the enrollment of only 73 eligible patients because of the slow patient accrual, and this made this trial inconclusive. No difference in MST was found, with values of 19.4 vs. 17.4 months between the surgery and radiotherapy arms.

The Medical Research Council Lung Cancer Working Party also tried to define the benefit of surgery over radiotherapy after chemotherapy using four cycles of mitomycin, vindesine and cisplatin or mitomycin, ifosfamide and cisplatin, which were administered every 3 weeks [37]. The eligible patients had cT3N1-Stage IIIA or cN2-Stage IIIA disease and were unresectable, but had the potential to become resectable after induction chemotherapy. However, this phase III trial was also prematurely terminated because of the slow patient accrual. Only four of the 23 patients (17.4 %) who were allocated to the surgery arm actually underwent surgical resection. The MST was similar in both arms, at 11.2 months in the surgery arm and 13.8 months in the radiotherapy arm, respectively, with no statistically significant difference noted between the arms.

The European Organisation for Research and Treatment of Cancer-Lung Cancer Group (EORTC 08941) conducted a large phase III trial that compared surgery to radiotherapy as a post-induction treatment [39]. Pathologically or cytologically proven, unresectable cN2-Stage IIIA patients were eligible for the trial. The primary end point was the OS. Assuming 10 % superiority with surgery over a 15 % 5-year survival rate with radiotherapy, a two-sided alpha error of 5 % and a power of 80 %, 358 patients were estimated to be necessary for the study. A total of 640 patients were planned to be accrued, with an expected randomized rate of 56 %. After three cycles of platinum-based therapy, 332 (57 %) patients were randomized. The response rate was 95 % in all participating patients. The resection rate of 92 % was high compared to that of other phase III trials. The MST was 16.4 months in the surgery arm and 17.5 months in the radiotherapy arm, which was not a statistically significant difference.

Three phase III trials assessed the benefit of concurrent chemoradiotherapy as an induction treatment followed by surgery to definitive radiotherapy. The German Lung Cancer Cooperative Group (GLCCG) accrued 558 cStage III patients and randomized 524 patients, including 125 (23.9 %) pathologically confirmed N2-cStage IIIA patients to surgery after induction chemotherapy (cisplatin and etoposide, 3 cycles) and sequentially concurrent chemoradiotherapy (carboplatin and vindesine once a week concurrent with 45 Gy of radiotherapy) and induction chemotherapy (cisplatin and etoposide, 3 cycles) followed by surgery as a control arm [40]. The primary end point was the median progression-free survival. Despite intensive induction treatment for the intervention arm, the response rate was 47 % and was not significantly different from that in the control arm of 46 %. The resection rate of this trial was relatively low (54 % in the intervention arm and 59 % in the control arm), which might have been because the majority of the patients in this study had cStage IIIB disease. The postoperative mortality rate was 9.2 % in the intervention arm vs. 4.5 % in the control arm. The survival was better compared to other trials listed in Table 2; however, no statistically significant improvement was obtained in the intervention arm.

The INT0139 trial is one of the most widely known phase III trials performed regarding the issue of induction chemoradiotherapy followed by surgery. The trial applied cisplatin and etoposide concurrent with radiation therapy:

Table 3 Results of selected phase III trials of induction treatment followed by surgery vs. definitive chemoradiotherapy for cStage IIIA NSCLC

Reference	Year	No. of pts.	Clinical stage (N2-IIIA %)	Chemotherapy	RTx (Gy)	RR (%)	Resection rate (%)	Pn (%)	Mortality[a] (%)	DFS (m)	MST (m)	5y OS (%)	*p* value	Status
Johnstone [38] (RTOG89-01)	2002	73	IIIA	MVP-S	/	–	79.3	–	6.9	–	19.4	22 (4y)	NS	Poor accrual
				MVP-RTx	50	–	/	–	3.1	–	17.4	22 (4y)		
Stephens [37]	2005	48	IIIA (85)	MIC or MVP-S	/	–	17	–	–	–	11.2	–	NS	Poor accrual
				MIC or MVP-RTx	50	–	/	–	–	–	13.8	–		
van Meerbeeck [39] (EORTC08941)	2007	332[b]	IIIA	PI base-S	/	96	92	47	4.0	9	16.4	15.7	NS	Completed
				PI base-RTx	60–62.5	94	/	/	0.6	11.3	17.5	14.0		
Thomas [40] (GLCCG)	2008	524	IIIA/B (24)	PE-Cb+V+RTx-S	45	47	54	35.2	9.2	19.6	32.4	39	NS	Completed
				PE-S	/	46	59	35.1	4.5	21.3	33.0	31		
Albain [41] (INT0139)	2009	429	IIIA	PE+RTx-S	45	–	76.7	34.8	8	12.8	23.6	–	NS	Early closure
				PE+RTx	61	–	/	/	4	10.5	22.2	–		
Katakami [42] (WJTOG9903)	2012	60	IIIA	Cb+Doc+RTx-S	40	25	89.7	3.6	0	12.4	39.6	51.7 (3y)	NS	Poor accrual
				Cb+Doc-S	/	25	86.2	0	0	9.7	29.9	39.3 (3y)		

RTx radiation therapy, *RR* CR+PR, *Pn* pneumonectomy, *S* surgery, *NS* not significant, *MVP* mitomycin, vindesine, cisplatin, *MIC* mitomycin, ifosfamide, cisplatin, *PI* platinum, *Cb* carboplatin, *V* vindesine, *PE* cisplatin, etoposide, *Doc* docetaxel

[a] Mortality post-surgery

[b] Number of patient randomized

45 Gy for the surgery arm and 61 Gy for the definitive radiotherapy arm [41]. The primary end point was the OS, assuming a 10 % absolute improvement in the surgery arm over the 25 % 2-year OS associated with definitive chemoradiotherapy. With a one-sided log-rank test with a type I error rate of 0·05 and 93 % statistical power, the target sample size was 612 (556 eligible) patients initially, but the size was recalculated later because of slower accrual than planned. The revised sample size was 510 (484 eligible) patients and terminated with 429 randomly assigned patients. Induction therapy was well tolerated in both arms (95 % in the surgery arm and 92 % in the definitive radiotherapy arm), and the resection rate in the surgery arm was 76.7 %. The postoperative mortality rate in the surgery arm was relatively high (8 %). Among the patients in the surgery arm, 34.8 % underwent pneumonectomy and 14 of these 51 patients (27.5 %) died post-surgery. The survival analysis in this trial was on an intention-to-treat basis. Although the progression-free survival was significantly longer in the surgery arm than in the definitive radiotherapy arm (median 12.8 vs. 10.5 months, HR 0.77 (95 % CI 0.62–0.96), $p = 0.017$), no statistically significant difference was observed between the arms; the MST was 23.6 months in the surgery arm and 22.2 months in the definitive radiotherapy arm, respectively ($p = 0.24$). In an exploratory analysis, OS was improved for patients who underwent lobectomy, but not pneumonectomy, versus chemotherapy plus radiotherapy. In their interpretation, chemoradiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA(N2) NSCLC.

The West Japan Oncology Group (WJTOG 9903) conducted a randomized clinical trial that compared the benefits of chemoradiotherapy over chemotherapy as an induction treatment [42]. The primary end point was the 5-year survival rate. The target sample size was 180 patients to detect a 20 % absolute improvement in the concurrent chemoradiotherapy arm, assuming a 20 % 5-year OS in the chemotherapy arm. This trial was also prematurely terminated because of the slow patient accrual, which made this trial inconclusive. The survival analysis was also done based on an intention-to-treat method. Both induction treatment arms were well tolerated. However, the OS was not improved in the CRS (chemoradiation followed by surgery) arm versus the CS (chemotherapy followed by surgery) arm, which had MST of 39.6 vs. 29.9 months (HR 0.77 (95 % CI, 0.42–1.41), $p = 0.397$), respectively.

Although the subset analyses of the prospective clinical trials themselves showed only implications with no statistical meaning, favorable prognostic factors drawn from the prospective trials listed in this review are provided in Table 4. Frequently identified factors include pathological

Table 4 Factors predicting a favorable outcome based on the findings of selected prospective trials of induction treatment followed by surgery for cStage IIIA NSCLC

Reference	Year	Phase	No. of pts.	Favorable factor(s)	Median OS (m)	OS (%)	*p* value
Albain [32]	1995	II	126	pN (−) vs. pN (+)	30 vs. 10	44 vs. 18 (3y)	0.0005
Katakami [33]	1998	II	42	R0 vs. R1–2	19.4 vs. 11.1	–	0.0014
				pCR vs. others	30.1 vs. 11.1	–	0.045
Thomas [34]	1999	II	54	Tumor regression >90 vs. <90 %	36 vs. 14	48 vs. 9 (3y)	0.02
Betticher [35]	2006	II	75	R0 vs. R1–2	62.5 vs. 17.3	–	<0.0001
				CR+PR vs. NC	62.5 vs. 17.1	–	0.003
				pN0 vs. N1 vs. N2	NR vs. 35.1 vs. 16.4	–	0.0001
van Meerbeeck [39] (EORTC08941)	2007	III	332	Lobectomy vs. Pneumonectomy	27 vs. 12	–	0.009
				pN0–1 vs. pN2	29 vs. 7	–	<0.001
				R0 vs. R1–2	27 vs. 7	–	<0.001
Thomas [40] (GLCCG)	2008	III	524	R0 vs. R1–2	50.6 vs. 20.4	–	<0.0001
				pN0 vs. pN1–2	57.5 vs. 25.1	–	0.003
Albain [41] (INT0139)	2009	III	429	Major weight loss	–	–	<0.003
				Single pN2 station vs. more	–	–	0.024
				pN0 vs. pN1–3 vs.no surgery	34.4 vs. 26.4 vs. 7.9	–	<0.0001
Suntharalingam [36]	2012	II	57	Node clearance vs. node residual vs. no surgery	–	75 vs. 52 vs. 23 (2y)	0.0002
				Lobectomy vs. Pneumonectomy	33.6 vs. 21.7	–	0.0027
Katakami [42]	2012	III	60	Downstaging (+) vs. (−)	63.3 vs. 29.5	–	0.021

sterilization and/or downstaging of the mediastinal lymph nodes [32, 35, 36, 40, 41] and the use of complete surgical resection [33, 35, 39, 40]. The surgical procedure, i.e., lobectomy or pneumonectomy, is also a prognostic factor in favor of lobectomy [36, 39]. The survival of patients with these favorable prognostic factors was found to be excellent, with an approximate MST of 19–62 months among patients with completely resected cN2-Stage IIIA NSCLC compared to 11–17 months among patients who received incomplete resection, with statistical significance. The presence of pathological mediastinal lymph nodes had no effect: an MST of approximately 30–58 months compared to 8–25 months in the pN-positive patients. However, the prognosis of patients without the above favorable factors was found to be poorer than expected following definitive chemoradiotherapy. The most important issue is that all of the favorable factors, except for body weight loss, post-induction treatment downstaging and the tumor response, are postoperatively proven factors.

Future directions

Many randomized phase III trials have failed to demonstrate the superiority of induction treatment followed by surgery. In addition, the principal clinical practice guidelines [43], except for the 2013 ACCP guidelines [6], state that the application of surgery is not primarily recommended based on the results of the phase III trials listed in this review. However, only two of five phase III trials assessed the survival benefits of induction chemotherapy, and two of six phase III trials conducted to certify the role of surgery versus radiotherapy in multimodality treatment for cN2-Stage IIIA NSCLC were fully completed, primarily due to the rate of patient accrual. Furthermore, there are no established pretreatment factors that enable clinicians to select appropriate candidates for curative treatment for cN2-Stage IIIA NSCLC. In addition, there is no universal agreement regarding the definition of unresectable locally advanced NSCLC. For example, it is thought that pneumonectomy should be avoided due to its poor rate of survival compared to that obtained with lobectomy in the subset analyses of prospective trials; however, a recent retrospective analysis demonstrated a non-inferior rate of survival and acceptable frequency of complications in cN2-Stage IIIA patients treated with pneumonectomy [44, 45]. Approximately, 20–70 % of cN2-Stage IIIA NSCLC patients suffer from distant metastasis after undergoing multimodality treatment. Recent improvements in radiological diagnostic modalities, such as the widespread use of fluorine-18 (F-18) deoxyglucose positron emission tomography (FDG-PET), may be applied to eliminate

minor asymptomatic distant metastases, thus identifying more suitable candidates for intensive local and systemic treatment, including surgery. The development of an accurate method for selecting patients for multimodality treatment is required. Furthermore, to obtain more effective systemic control, more appropriate chemotherapy regimens, including those involving recently developed molecular targeted agents, and/or treatment algorithms, i.e., the use of induction and/or consolidation therapy, should be examined in phase III clinical trials.

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ORIGINAL ARTICLE

A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients

Toshihiko Sato · Haruhiko Kondo · Atsushi Watanabe · Jun Nakajima · Hiroshi Niwa · Hirotoshi Horio · Jiro Okami · Norihito Okumura · Kenji Sugio · Satoshi Teramukai · Kazuma Kishi · Masahito Ebina · Yukihiko Sugiyama · Takashi Kondo · Hiroshi Date

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Abstract

Objective Lung cancer patients with interstitial lung diseases (ILDs) who have undergone pulmonary resection often develop acute exacerbation of interstitial pneumonia (AE) in the post-operative period. To predict who is at high risk of AE, we propose a scoring system that evaluates the risk of AE in lung cancer patients with ILDs.

Methods We derived a score for 30-day risk of AE onset after pulmonary resection in lung cancer patients with ILDs ($n = 1{,}022$; outcome: risk of AE) based on seven risk factors for AE that were identified in a previous retrospective multi-institutional cohort study. A logistic regression model was employed to develop a risk prediction model for AE.

Results A risk score (RS) was derived: 5 × (history of AE) + 4 × (surgical procedures) + 4 × (UIP appearance in CT scan) + 3 × (male sex) + 3 × (preoperative steroid use) + 2 × (elevated serum sialylated carbohydrate antigen, KL-6 level) + 1 × (low vital capacity). The RS was shown to be moderately discriminatory with a c-index of 0.709 and accurate with the Hosmer–Lemeshow goodness-of-fit test ($p = 0.907$). The patients were classified into three groups: low risk (RS: 0–10; predicted probability <0.1; $n = 439$), intermediate risk (RS: 11–14; predicted probability 0.1–0.25; $n = 559$), and high risk (RS: 15–22; predicted probability >0.25; $n = 24$).

Conclusion Although further validation and refinement are needed, the risk score can be used in routine clinical practice to identify high risk individuals and to select proper treatment strategies.

For the Japanese Association for Chest Surgery.

T. Sato · H. Date (✉)
Department of Thoracic Surgery, Kyoto University, 54 Kawaharacho, Shogoin, Sakyoku, Kyoto, Japan
e-mail: hdate@kuhp.kyoto-u.ac.jp

T. Sato
e-mail: tsato@kuhp.kyoto-u.ac.jp

H. Kondo
Department of Thoracic Surgery, Kyorin University School of Medicine, Tokyo, Japan

A. Watanabe
Department of Thoracic and Cardiovascular Surgery, Sapporo Medical University School of Medicine and Hospital, Sapporo, Japan

J. Nakajima
Department of Thoracic Surgery, University of Tokyo Graduate School of Medicine, Tokyo, Japan

H. Niwa
Division of Thoracic Surgery, Respiratory Disease Center, Seirei Mikatahara General Hospital, Hamamatsu, Japan

H. Horio
Department of Thoracic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

J. Okami
Department of General Thoracic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

N. Okumura
Department of Thoracic Surgery, Kurashiki Central Hospital, Kurashiki, Japan

K. Sugio
Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan

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Introduction

Pulmonary resection of lung cancer patients who have interstitial lung diseases (ILDs) may initiate a rapid and progressive deterioration of the lung diseases and this process is known as acute exacerbation (AE) [1–3]. AE shows a very distinctive clinical course, which differs from pneumonia as a post-operative morbidity. It often requires intensive care, including mechanical ventilation, and is associated with high mortality. We previously conducted a multi-institutional large cohort study with 1,763 lung cancer patients with interstitial lung diseases who underwent pulmonary resection, and elucidated that 9.3 % of the patients developed AE with a mortality rate estimated to be 43.9 % [4]. The incidence of AE in the entire patient population was estimated as 0.5 % in our cohort study (222/41,742), comparable to the figure (53/11,663) in the annual report by the Japanese Association for Thoracic Surgery [5]. Although this figure appears minor in terms of total morbidity after pulmonary resection, once patients develop AE, half of them will die. Such deaths are considered the major cause of death after pulmonary resection in Japan.

It is a matter of vital importance that pulmonologists and surgeons assess the risk of AE and classify patients properly; however, there is little consensus about which criteria are most appropriate to evaluate this group of patients. We, therefore, aimed to derive a simple risk scoring system to predict AE after pulmonary resection with two potential uses: to allow pulmonologists and surgeons to assess the risk of pulmonary resection when considering anticancer therapy for lung cancer patients with ILDs and secondly, to provide patients proper risk information before the surgery. In this study, we propose a simple scoring system using seven risk factors identified in the previous lung cancer study on patients with ILDs to predict AE. The seven risk factors include surgical procedures, history of AE, radiologic findings in CT, preoperative steroid use, gender, KL-6 level (Krebs-von-Lungen-6, serum sialylated carbohydrate antigen), and percent predicted vital capacity (%VC) [4].

Methods

The study was designed by T. Sato, S. Teramukai, and H. Date with assistance from both the advisory board of the Japanese Association for Chest Surgery and the Project Team for Diffuse Lung Diseases, organized by the Japanese Ministry of Health, Labour and Welfare. The study protocol was approved by the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine (Approval Number: E-982). The original data for analysis were derived from the former study and the details of the study are described elsewhere [4]. Briefly, the ILD diagnosis was made based on the radiographic appearance following the criteria proposed by both the Japanese Respiratory Society, which are consistent with the guideline of the American Thoracic Society in 2011 as follows: The usual interstitial pneumonia (UIP) pattern is characterized by the presence of basal-dominant reticular opacities and a predominantly basal and subpleural distribution of honeycomb lesions with multiple equal-sized cystic lesions of 2–10 mm diameter with a thick wall, and the non-UIP pattern is characterized by the presence of ground glass opacities and infiltrative shadows inconsistent with UIP patterns [6, 7]. Cases which were pathologically proven UIP but had shown no interstitial changes in the CT scan were not included to the study.

Medical records of the patients contained up to 82 categories, including blood analyses, respiratory function tests, oncological parameters, surgical procedures, operation time, and bleeding amount.

Definition of AE

AE caused by pulmonary resection was defined based on the criteria proposed by Yoshimura et al. and ATS Guidelines [1, 6]. These criteria were: (1) onset within 30 days after pulmonary resection, (2) intensified dyspnea, (3) increase in the interstitial shadow on a chest radiograph and on a chest CT scan, (4) decrease in arterial oxygen tension of more than 10 mmHg under similar conditions, (5) no evidence of pulmonary infection, and (6) exclusion

Present Address:
K. Sugio
Department of Thoracic and Breast Surgery, Oita University, Oita, Japan

S. Teramukai
Innovative Clinical Research Center, Kanazawa University, Kanazawa, Japan

K. Kishi
Department of Respiratory Medicine, Respiratory Center, Toranomon Hospital, Tokyo, Japan

M. Ebina
Respiratory Center, Tohoku Pharmaceutical University Hospital, Sendai, Japan

Y. Sugiyama
Department of Pulmonary Medicine, Jichi Medical University, Tochigi, Japan

T. Kondo
Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

of alternative causes, such as cardiac failure, pulmonary embolism, or other identifiable causes of lung injury.

Patients

The study patients had non-small cell lung cancer, had undergone pulmonary resection, and presented with a clinical diagnosis of ILDs between 2000 and 2009 at 64 institutions in Japan. Among the 1,763 eligible cases, information regarding important risk factors was not available for 741 patients (720 lacked information on KL-6 levels, 22 lacked %VC, nine lacked knowledge of preoperative steroid use, eight lacked information on type of surgical procedure, and two lacked information on past history of AE). Thus, data from 1,022 cases were included in the present study and evaluated for clinical features predictive of AE. The patient characteristics used for the risk prediction model for AE were those which were identified as significant risk factors in the previous multivariate analysis of all patients (1,763 cases) and included gender (male vs. female), history of AE (yes vs. no), preoperative steroid use (yes vs. no), KL-6 levels (over 1,000 U vs. less), %VC (80 % vs. less), CT findings (UIP pattern vs. non-UIP pattern), and surgical procedures (wedge resection vs. other procedure: segmentectomy, lobectomy, bilobectomy, pneumonectomy). In the analysis of the surgical procedures, the lobectomy/segmentectomy and bilobectomy/pneumonectomy groups from our previous study with 1,763 patients were both more likely to develop AE than the wedge resection group with odds ratios of 3.83 (95 % CI 1.941–7.567, $p < 0.001$) and 5.70 (95 % CI 2.381–13.66, $p < 0.001$), respectively [6]. In this study with 1,022 cases, first we trichotomized these categorical values as

Table 1 Patient characteristics

Categories	Cases for risk score[a] (n = 1,022)		All cases[b] (n = 1,763)		p value[c]
	Number of patients (%)	Median (range)	Number of patients (%)	Median (range)	
Age	1,022	71 (36–87)	1,763	71 (36–88)	0.914
Sex (male/female)	927/95		1,593/170		0.764
Smoking history					0.419
Never smoker	51 (5.0)		109 (6.2)		
Ex/current smoker	593/371		1,006/632		
Brinkman index	1,014	1,000 (0–3,960)	1,742	1,000 (0–5,760)	0.859
History of AE[d]					0.241
−	1,005 (98.3)		1,741 (98.9)		
+	17 (1.7)		20 (1.1)		
N/A	0		2		
Preoperative medication					0.192
None	937 (92.0)		1,638 (93.8)		
Steroids	77 (7.6)		103 (5.9)		
Others	5 (0.5)		6 (0.3)		
N/A	3		16		
Radiological diagnosis					0.937
UIP pattern	755 (73.9)		1,300 (73.7)		
Non-UIP pattern	267 (26.1)		463 (26.3)		
p stage					0.856
1/2/3/4	629/165/198/17		728/311/358/34		
N/A	13		32		
Surgical procedure					0.076
Wedge resection	189 (18.5)		275 (15.7)		
Segmentectomy	83 (8.1)		150 (8.6)		
Lobectomy	715 (70.0)		1,236 (70.4)		
Bilobectomy	22 (2.2)		61 (3.4)		
Pneumonectomy	13 (1.3)		33 (1.9)		

Brinkman Index: numbers of cigarettes smoked per day times smoking years

AE acute exacerbation, *UIP* usual interstitial pneumonia

[a] Cases addressed in this study. From the original data (n = 1,763) 741 cases were excluded due to lack of risk category data, mainly because of lack of KL-6 values (720 cases)

[b] Cases of the previous study

[c] Chi square test for categorical variables or Wilcoxon test for continuous variables

[d] History of treated AE prior to the pulmonary resection

[e] Preoperative therapy for interstitial pneumonia including steroid, immunosuppressant

we did in the previous study. However, the odds ratio of the bilobectomy/pneumonectomy group to the wedge resection group was reduced to 2.38 (95 % CI 0.63–9.02; $p = 0.24$) and was not statistically significant, while the odds ratio of the segmentectomy/lobectomy to the wedge resection group was 3.99 (95 % CI 1.82–8.72; $p < 0.001$) and was statistically significant. Since this reversal problem is attributable to the small number in the bilobectomy/pneumonectomy group (35 cases total, only four developed AE), we decided to dichotomize the cases into wedge resection and other procedures (segmentectomy, lobectomy, bilobectomy, pneumonectomy) instead of trichotomizing them. Preoperative steroid use indicates that patients were administered a steroid routinely for the treatment of ILDs or for another condition.

Statistical analysis

To develop a risk prediction model for AE and to estimate the predicted probabilities by risk score, we used a logistic regression model. To develop a practical risk score, we assigned the risk factors identified by multivariate analysis weighted points proportional to the β regression coefficient values (rounded to the nearest integer). A risk score was then calculated for each patient, and the population was divided into three categories: patients at low risk, patients at intermediate risk, and patients at high risk for AE development.

To validate the stability of variable selection in the complete cases ($n = 1{,}022$), we applied backward selection ($p < 0.25$) in 500 bootstrap samples drawn from the original sample. The model performance was assessed with respect to discrimination and calibration. Discrimination was evaluated with a concordance index (c-index), which is identical to the area under a ROC (receiver operating characteristic) curve. Calibration was examined with the Hosmer–Lemeshow goodness-of-fit test [8]. To verify the frequency of AE in resampled patients in each risk group (low, intermediate, and high), we used the 1,000 bootstrap resamples. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

In the Table 1, the characteristics and background of this study ($n = 1{,}022$) and of the previous study (1,763) are listed: 741 cases were excluded due to lack of certain risk factor information. A total of 1,022 patients with complete values for the 7 risk factors were included in this study. Out of 1,022 patients who had undergone pulmonary resection, 100 patients (9.8 %) developed AE. There were no significant differences in age, gender, smoking history, oncologic features, and variables of risk factors, including radiologic findings, KL-6 levels, and %VC between the patients of this study ($n = 1{,}022$) and the original patient population ($n = 1{,}763$).

Table 2 Results of logistic regression analysis ($n = 1{,}022$)

Risk factors	*N*	AE (%)	Odds ratio	95 % CI	*p* value
CT findings					
Non-UIP pattern	267	11 (4.1)	1.00	–	–
UIP pattern	755	89 (11.8)	3.37	1.74–6.54	0.0003
Surgical procedures					
Wedge resection	189	8 (4.2)	1.00	–	–
Others	833	92 (11.0)	3.84	1.77–8.35	0.0007
KL-6 (U/mL)					
≤1,000	816	67 (8.2)	1.00	–	–
>1,000	206	33 (16.0)	2.05	1.28–3.29	0.003
Preoperative steroid use					
No	945	83 (8.8)	1.00	–	–
Yes	77	17 (22.1)	2.49	1.27–4.89	0.008
History of AE[a]					
No	1,005	94 (9.4)	1.00	–	–
Yes	17	6 (35.3)	4.57	1.38–15.21	0.013
Sex					
Female	95	5 (5.3)	1.00	–	–
Male	927	95 (10.3)	2.37	0.91–6.19	0.078
%VC					
>80	857	78 (9.1)	1.00	–	–
≤80	165	22 (13.3)	1.40	0.82–2.41	0.221

UIP usual interstitial pneumonia, *CI* confidence interval

[a] History of treated AE prior to the pulmonary resection

The estimated odds ratios and their confidence intervals according to the risk factors are shown in Table 2. All risk factors were selected in >50 % of bootstrap samples (a minimum of 52 % for %VC; a maximum of 100 % for surgical procedure and CT findings). A linear function based on the estimated regression coefficients was as follows: 1.52 (history of AE: yes) + 1.35 (surgical procedure: others) + 1.22 (CT findings: UIP) + 0.91 (preoperative steroid use: yes) + 0.86 (gender: male) + 0.72 (KL-6: >1,000 U/mL) + 0.34 (%VC: ≤80 %). From the weight of variables in the function, we derived a simplified risk score (RS) as follows:

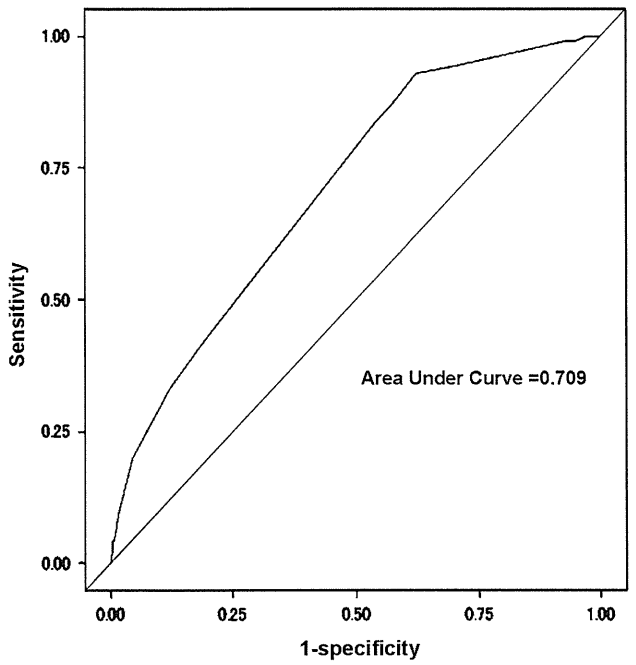

Fig. 1 The receiver operator characteristics (ROC) curve for predictive value of the risk score

RS = 5 (History of AE:yes) + 4 (Surgical procedure: others)
+ 4 (CT findings: UIP pattern)
+ 3 (Preoperative steroid use: yes)
+ 3 (Gender: male) + 2 (KL-6: > 1,000 U/mL)
+ 1 (%VC: ≤ 80).

The receiver operating characteristic (ROC) curve is shown in Fig. 1. The RS was moderately discriminatory with a c-index of 0.709 and accurate with the Hosmer–Lemeshow goodness-of-fit test ($p = 0.907$).

The RS of patients ranged between 0 and 22 and the relationship between RS and predicted probability is shown in Table 3 and in Fig. 2. On the basis of the predicted probabilities for AE, patients were classified into three risk groups, i.e., low risk group (RS: 0–10; predicted probability: <0.1; $n = 439$), intermediate risk group (RS: 11–14; predicted probability: >0.1 and <0.25; $n = 559$), and high risk group (RS: 15–22; predicted probability: >0.25; $n = 24$). The median observed proportions of AE estimated from the resamples were 0.036 (range 0.012–0.071), 0.134 (range 0.089–0.183), and 0.375 (range 0.059–0.739) for low risk, intermediate risk, and high risk group, respectively.

Table 3 Distribution of the patients and their predicted risk for AE

Score	Number of patients	Predicted incidence (%)	95 % CI (%)	Observed incidence (%)	Patient's risk
0	2	0.4	0.1–1.0	0	Low risk (<10 %, $n = 439$)
1	0	0.5	0.2–1.3	0	
2	0	0.7	0.3–1.6	0	
3	24	0.9	0.4–2.0	0	
4	21	1.3	0.6–2.5	1 (4.7)	
5	11	1.8	1.0–3.2	0	
6	8	2.4	1.4–4.0	0	
7	226	3.3	2.1–5.0	5 (2.2)	
8	64	4.4	3.1–6.3	1 (1.6)	
9	50	6.0	4.5–7.9	6 (12)	
10	33	8.0	6.4–10.0	3 (9.1)	
11	375	10.7	8.8–12.9	43 (11.5)	Intermediate risk (10–25 %, $n = 559$)
12	64	14.1	11.6–17.0	8 (12.5)	
13	83	18.4	14.8–22.5	13 (15.7)	
14	37	23.6	18.4–29.7	11 (29.7)	
15	5	29.8	22.5–38.4	2 (40)	High risk (>25 %, $n = 24$)
16	8	36.8	26.9–48.0	3 (37.5)	
17	5	44.5	31.9–57.8	0	
18	2	52.4	37.2–67.1	2 (100)	
19	3	60.2	42.8–75.3	1 (33.3)	
20	0	67.5	48.5–82.0	0	
21	0	74	54.3–87.0	0	
22	1	79.6	60.0–91.1	1 (100)	

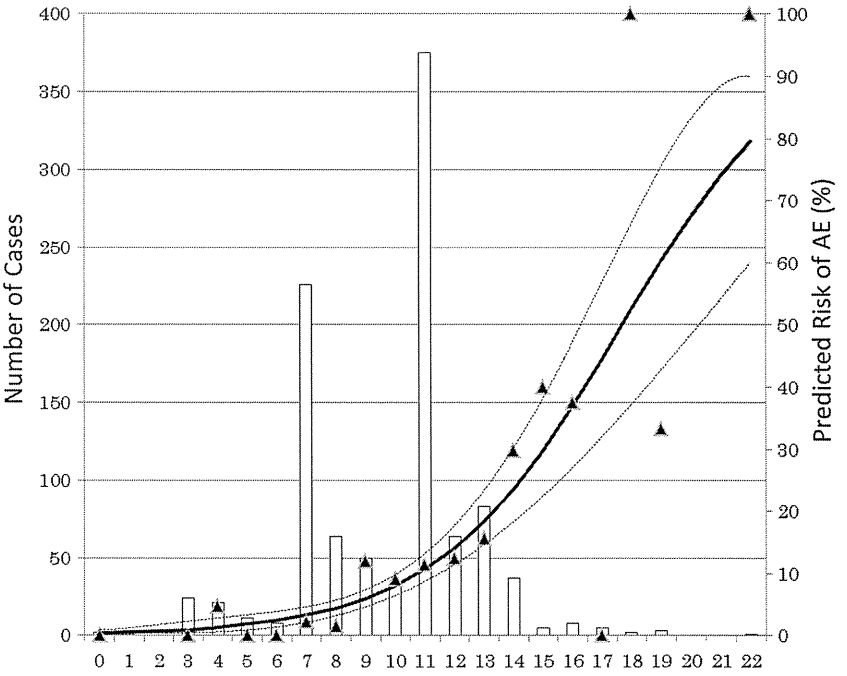

Fig. 2 *Bars* represent the number of the patients. *Triangles* observed AE (%), *curve* predicted AE (%), *dotted curves* 95 % CI, *horizontal axis* risk scores

Discussion

Previous studies showed that interstitial lung diseases were associated with higher incidence of lung cancer than the general population with relative risk of 7.3–14.1, and the prevalence of lung cancer among the ILDs patients ranged from 5 to 15 % [9]. For patients with interstitial lung diseases, surgical insult even if it is small, such as an open lung biopsy, may trigger the acute deterioration of interstitial lung diseases, termed acute exacerbation (AE) [2, 10]. The clinical course and manifestations of AE are similar to those which occur in patients who are under follow-up or are being treated for IPF, and its annual incidence rate is known to be approximately 5–10 % [11, 12]. AE is characterized by worsening of dyspnea, impaired gas exchange, and newly developed ground glass opacity presenting in a diffuse distribution in a CT scan. Once the patients develop AE, they have a rapid deterioration, sometimes requiring aggressive treatments, including mechanical ventilation, and the survival rate is very low. In our previous study, the incidence of acute exacerbation after pulmonary resection was 9.3 % in the lung cancer patients with ILDs. The mortality of this group was calculated to be 43.9 %, identical to the figure reported in AE cases among IPF patients. Generally for the IPF patients who developed AE, treatment consisted of administration of high-dose corticosteroid, but no completely effective treatment has been identified [3]. One study with a limited number of patients conducted by Azuma and colleagues showed that pirfenidone decreased the risk of AE [13]. Regarding post-operative AE, there have been some reports on the prophylactic effects of the steroid, sivelestat-sodium hydrate, fluid limitation, and low-dose oxygen administration during anesthesia, but no preventive measures have been confirmed in previous studies, including ours [4]. Therefore, a risk score system has been long desired which would stratify the ILDs patients and elucidate the individual's risk for AE.

We included seven predictors in our scoring system; each of them can be reliably and routinely ascertained in typical clinical settings. These predictors, including history of AE, surgical procedures, CT findings, preoperative steroid use, gender, serum KL-6 level, and percent predicted vital capacity, were identified as independent risk factors for post-operative AE in our previous study [4]. Our previous study had focused on the association of the onset of acute exacerbation and risk factors and the current study is focusing on evaluation of the predictability of the risk. In this study, we derived a risk score system by giving weight to each factor. This composite risk score improved the prediction of AE by considering each factors' weight, and the clinician can stratify the patients comprehensively into low, medium, and high risk group. We believe this simple stratification is also beneficial for the patients when they need to assess the risk ahead of them.

In this proposed scoring system, the history of AE prior to the operation proved to be the most weighted factor. Those who have a history of treated AE in their course of disease are very likely to develop AE after the pulmonary resection, as a strong association with the AE onset (9/17,

OR 4.57; 95 % CI 1.38–15.21, $p = 0.013$) was shown in multivariate analysis. These patients are minor in the whole cohort (17 out of 1,022); however, we believe that distinction of this minor group and warning the clinicians and patients are very imperative. In general, the IPF patients who previously developed AE tended to have repeat AE [14]. Those with a history of respiratory hospitalization showed poor prognosis in the literature, although the details were not clearly described [15]. The surgical indication should be carefully determined for this group of patients considering that the prognosis of those who have a history of AE is very poor.

In our previous study, the type of surgical procedures had shown the strongest association with the incidence of AE and the odd ratios of each procedure were observed as gradually augmented from wedge resection, segmentectomy, lobectomy, bilobectomy to pneumonectomy conferring to the resected lung volume, from 3.68 (95 % CI 1.586–8.519, $p < 0.002$) to 6.95 (95 % CI 2.260–21.39, $p < 0.001$), respectively [4]. Although in this composite risk score system, the difference between the procedures became not as clear as previously described, it should be noted that the AE risk of bilobectomy/pneumonectomy patients had been shown almost twice as high as that of segmentectomy/lobectomy patients. Due to the small number of pneumonectomy cases, the difference between bilobectomy/pneumonectomy and the segmentectomy/lobectomy was not clear in this model; we dichotomized the patients into two groups, namely, wedge resection and others. In conjunction with surgical procedures, whether minimally invasive procedures give any impact of the AE risk should be a matter of interest for the surgeon. We could not detect any implication for the impact of the minimally invasive approach would reduce the risk of the AE in the previous study.

The UIP pattern on the CT scan had a significant impact on AE onset, similar in importance as the surgical procedures. There have been no comparative studies between patients with the UIP pattern and those with the non-UIP except ours. Suzuki and colleagues [16] reported that the prevalence of a honeycomb lesion on the preoperative high-resolution CT showed association with the incidence of post-operative AE.

Patients who were previously treated with steroids proved to have greater risk for AE (OR 2.457, 95 % CI 1.356–4.454, $p = 0.003$) [4]. Patients taking other immunosuppressive agents might have an equal risk, but the number of such patients was very small, thus we did not include them in the risk scoring system.

Gender differences in post-operative AE have not been identified in the literature. ILDs are more common in men and we were the first to describe the contribution of the male gender to AE in our large multi-institutional study [4]. Males proved to have an intermediate influence on AE onset in the risk score. Very little has been discussed on gender as a predictor for the AE onset so far. Only Kutlu and colleagues [17] had documented that male patients developed acute lung injury/acute respiratory distress syndrome (ALI/ARDS) after pulmonary resection at nearly 4 times the rate of females. Thus, the male lung may be more susceptible to the insult of surgical intervention.

The elevated level of KL-6, serum sialylated carbohydrate antigen had a weighting factor calculated as 2 in the scoring system. The KL-6, sialylated carbohydrate antigen, has been shown as a biomarker/predictor for IPF patient survival [18]. KL-6 has been widely acknowledged as a basic biomarker reflecting the progression of pulmonary fibrosis since Kohno et al. [19] first reported in 1989 in Japan. This is a circulating glycoprotein expressed on both type 2 alveolar pneumocytes and bronchiolar epithelial cells, whose high value reflects incessant repair of the pneumocytes, and is accepted as an indicator of damage to alveolar cells.

Low percent vital capacity (%VC) had been identified as independent risk factor for AE in multiple studies including ours, but it had less impact on AE onset in the scoring system [3, 4, 20]. Percent vital capacity has been considered to be an important predictor for both AE and mortality of IPF patients, together with low percent predicted Dlco [21]. The ability to easily measure %VC and prevalence of its measurement in daily clinical settings are great advantages. Values of %VC were recorded in 99 % of the patients, while the values of Dlco were recorded in only 64 % of the patients in our cohort. Together with the fact that Dlco did not prove to be an independent factor in our previous analysis, only %VC was included as a factor in the risk score.

Unfortunately, no prophylactic treatment with clear efficacy for AE has been identified so far [4, 6, 14]. Stratifying the patients and identifying those at high risk are very relevant to preventing or to decreasing the mortality of post-operative AE. Early detection of AE may lead to more effective treatment, including high-dose corticosteroid administration, although its use is not well evaluated. Those identified as being in the intermediate or high risk group in our proposed risk scoring system are recommended to have intensive surveillance, such as a routine chest CT scan on post-operative day four or five, the most likely time of AE onset [4]. Another future application for this scoring system is the identification of patients who should be treated prophylactically. Now a prospective study on the prophylactic effect of pirfenidone is being carried out in Japan. The administration of prophylactics, such as pirfenidone, which is frequently associated with gastrointestinal side effects, including dyspepsia, nausea, and gastro-esophageal reflux diseases (GERD), can be

limited to the high risk patients identified by the risk scoring system. In the same way, nintedanib (BIBF1120), a tyrosine kinase inhibitor which reportedly reduces the progression of fibrosis and AE for IPF patients [22], may be selectively administered for those at high risk of AE.

Only the type of surgical procedure among the seven risk factors can be modified based on the patient's potential risk and curability. For the patients stratified in the high risk group of whom the predicted AE incidence is over 25 %, the surgeon should deliberately down grade the procedure from lobectomy to wedge resection, or should consider the surgical indication ab initio. For the patients stratified in the high risk group, by changing surgical procedure from lobectomy to wedge resection a reduction of four points shall be realized in the risk score, resulting in a 20–30 % reduction of predicted AE risk. For example, the risk score of a male patient with history of AE and a UIP pattern who is going to undergo lobectomy has a risk score of 16 points. For this patient, the risk of AE is calculated as 36.8 %. However, if he undergoes a wedge resection instead of lobectomy, the risk will be reduced to 14.1 %. We should take into account that the conversion to the limited wedge resection possibly brings cancer recurrence which results in less favorable long-term prognosis.

For those identified as high risk patients in our risk scoring system, it is a matter of argument if there is an alternative therapeutic modality other than the type surgical procedure. Chemotherapy and radiation have been shown to provoke acute deterioration of ILDs with high mortality [23]. Based on the recent studies that identified a specific agent likely to provoke AE for IDs patients [24], chemotherapy with safer drugs/approaches may be the better choice for those at high risk. In terms of radiotherapy, several reports suggested that the outcomes of the hypofractionated stereotactic body radiotherapy (SBRT) for primary lung cancer were comparable to those of surgical resection. Although there has been no study specifically addressing ILDs patients, considering the report on the outcomes for surgical poor risk patients, SBRT could be an alternative for the high risk patients defined in our scoring system [25]. Large cohort studies on the outcomes of anticancer therapy for this entity are long-waited, which will allow multidisciplinary teams to decide the most suitable treatment for the ILDs patients.

We should note our study limitations. The primary cohort study was composed of retrospective patients' data, which do not reflect the whole population of the patients. As noted in the previous study, the inclusion criteria were mainly based on the CT images. Since we were unable to carry out central controlled image diagnosis, the patients' inclusion criteria may vary between each institute. The original cohort consisted of 1,763 cases, but the defect of variables, especially that of KL-6, resulted in reduction of number to 1,022. As shown in Table 1, there were no significant differences in their background between two groups and together with the result of the bootstrap resampling, this reduction less likely to impair validity of the results. However, this reduction might have hindered the more detailed stratification of the surgical procedures. A prospectively well-designed validation study in another population of patients is required.

In conclusion, we derived a simple scoring system comprising seven parameters that can be used in routine clinical practice to identify high risk individuals for AE who require careful and intensive observation after pulmonary resection and that can facilitate clinical decision-making. Additional research using data from other large populations of lung cancer patients with ILDs is needed to validate the applicability and accuracy of our scoring system.

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