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Clinical Trial Note

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Sublobar resection versus lobectomy for patients with resectable stage I non-small cell lung cancer with idiopathic pulmonary fibrosis: a phase III study evaluating survival (JCOG1708, SURPRISE)

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Abstract

The standard treatment for the patients with surgically resectable early non-small cell lung cancer (NSCLC) is lung lobectomy. However, if patients have idiopathic pulmonary fibrosis combined with early stage lung cancer, there is no standard treatment for this population. Patients with idiopathic pulmonary fibrosis have chronic progressive decline in respiratory function; thus, the preservation of respiratory function is essential. The aim of this trial is to confirm the clinical effectiveness of sublobar resection such as wedge resection or segmentectomy for early NSCLC with idiopathic pulmonary fibrosis compared with lobectomy in a randomized phase III trial. The primary endpoint is overall survival. If the non-inferiority of overall survival and minimal invasiveness are proven, it can be a new standard treatment for early NSCLC with idiopathic pulmonary fibrosis. A planned total 430 patients will be enrolled from 50 institutions over 5 years. This trial has been registered in the UMIN Clinical Trials Registry with code UMIN000032696 [http://www.umin.ac.jp/ctr/index.htm].

Key words: non-small cell lung cancer, idiopathic pulmonary fibrosis, sublobar resection, lobectomy, randomized phase III trial

Introduction

The standard treatment for the patients with surgically resectable clinical stage I lung cancer is lung lobectomy with hilar and mediastinal lymph node dissection, according to several guidelines of lung cancer practice (1–4). However, if patients have early stage lung cancer combined with idiopathic pulmonary fibrosis (IPF), which is a chronic and progressive lung disease, there is a unique problem when compared with lung cancer without IPF.

If the patients have severe IPF and have risk factors of acute IPF exacerbation, there is no standard treatment for this population. If

the patients have mild IPF and do not have risk factors of acute IPF exacerbation, lobectomy is the first choice for this population. However, the 5-year overall survival (OS) after lung cancer resection for pathological stage I lung cancer with IPF is about 50–60% (5). It is poorer compared with about 80% for lung cancer without IPF (5). Because of the high biological malignancy of lung cancer itself in the background of IPF, about 50% of cause of deaths after surgical resection are lung cancer (5). The remaining ∼50% are deaths from other illnesses, most of which are deaths from respiratory failure, including acute IPF exacerbations within 30 days after surgery and deaths during the postoperative chronic phase (6). For this reason, it is unknown whether lobectomy is appropriate for early lung cancer with IPF.

Postoperative acute exacerbation of IPF is about 10% when the standard treatment (lobectomy) is performed, and about half of them are fatal (5,7). On the other hand, it has been suggested that a sublobar resection such as wedge resection reduces postoperative acute IPF exacerbation (5.0 vs. 10.5%) and reduces respiratory failure deaths in the postoperative chronic phase (odds ratio 0.35), compared with lobectomy (6,7). The other benefit of sublobar resection to standard treatment (lung lobectomy) from past data (2,7,8) is reduction in operation time (93 vs. 175 minutes), reduction in intraoperative bleeding volume (10.0 vs. 78.5 ml) and preservation of postoperative respiratory function (no reduction vs. loss of vital capacity 6%). Although the risk of sublobar resection is shown to increase in local recurrence (18 vs. 6%), a retrospective study for clinical stage I NSCLC with interstitial lung disease including IPF suggested that there is no remarkable difference in OS between sublobar resection, such as wedge resection or segmentectomy, and lobectomy (3-year OS: 81.9 vs. 67.1%) (9).

Based on the above, sublobar resection such as wedge resection or segmentectomy could reduce complications and deaths due to acute IPF exacerbation and respiratory failure death after resection of lung cancer with IPF. Patients with IPF have chronic progressive decline in respiratory function; thus, the preservation of respiratory function is essential. Hence, we commenced the world's first multicenter large-scale randomized phase III trial to confirm the clinical effectiveness of sublobar resection such as wedge resection or segmentectomy for early NSCLC with IPF compared with lobectomy.

We excluded the patients with severe IPF or with risk factors of acute IPF exacerbation. As the severity of IPF is defined by only arterial oxygen pressure in the guidance of Japan Intractable Disease Information Center, we excluded the patients with $PaO_2 < 65$ torr (room air). We also excluded the patients with history of acute IPF exacerbation or history of systemic steroid administration, because those histories have been shown as significant risk factors for postoperative acute IPF exacerbation (7). Moreover, we excluded the patients with less $\%FEV_{1.0}$ or $\%DL_{CO}$ as a pulmonary function who were considered unfit for lobectomy according to European and American guidelines (10,11). For patients with these risk factors, the surgery itself should be discussed in individual patients; thus, it was considered inappropriate for inclusion in this study.

The study protocol has been approved by the Japan Clinical Oncology Group (JCOG) Protocol Review Committee in March 2018 and the institutional review board of each participating institution prior to initiating patient registration. Patient accrual was initiated in May 2018. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000032696 [http://www.umin.ac.jp/ctr/index.htm].

Protocol digest of JCOG1708

Objectives

The aim of this study is to confirm the non-inferiority of sublobar resection to lobectomy in terms of OS in clinical stage I NSCLC with IPF.

Study design

This study is a multi-institutional, two-arm, open-label, randomized phase III trial.

Endpoints

The primary endpoint is OS in all randomized patients. OS is defined as the period (days) from randomization to death from any cause, censored at the latest day of survival confirmation. The secondary endpoints are relapse-free survival (RFS), incidence proportion of local recurrence, operation time, blood loss, incidence proportion of acute IPF exacerbation, postoperative respiratory function at 6 months and 1 year after surgery [forced vital capacity, forced expiratory volume in 1 second ($FEV_{1.0}$) and %diffusing capacity of lung for carbon monoxide (DL_{CO})] and safety. RFS is defined as the period from randomization to relapse or death from any cause, censored at the latest day of survival confirmation for the patient without relapse. The diagnosis of acute IPF exacerbation within 30 days after surgery is defined as 'postoperative acute IPF exacerbation', as defined in Guidelines for the Diagnosis and Treatment of Idiopathic Interstitial Pneumonia (12).

Eligibility criteria

Inclusion criteria at the first registration (preoperative). For inclusion in the first (preoperative) registration, patients will be required to fulfill all of the following criteria.

(1) Imaging findings fulfill all of the following conditions:
   (i) T1a-2aN0M0 NSCLC suspected
   (ii) Center of tumor located in the outer third of the lung field
   (iii) Consolidation/tumor ratio is >0.5 if maximum diameter of the tumor is ≤3 cm
   (iv) Maximum diameter of the tumor ≤4 cm

(2) No additional tumor nodule other than primary tumor
(3) All of the following conditions for IPF are fulfilled:
   (i) Usual interstitial pneumonia (UIP) pattern or possible UIP pattern in the high-resolution computed tomography (CT) diagnosed by radiologists
   (ii) Interstitial lung disease of unknown etiology
   (iii) No history of acute exacerbation of IPF
   (iv) No history of systemic steroid for IPF

(4) No neuroendocrine tumors
(5) Aged 40 years or older
(6) Eastern Cooperative Oncology Group performance status of 0 or 1
(7) No previous treatment of chemotherapy within 2 years before registration
(8) No prior radiotherapy to lung, ipsilateral hilum or mediastinum
(9) Expected postoperative $\%FEV_{1.0} \geq 30\%$ and $\%DL_{CO} \geq 30\%$
(10) Sufficient organ functions: all of the following conditions are fulfilled:

(i) Neutrophil count $\geq 3000/mm^3$
(ii) Hemoglobin ≥ 8.0 g/dl
(iii) Platelet count $\geq 10 \times 10^4/mm^3$
(iv) Total bilirubin ≤ 2.0 mg/dl
(v) AST $\leq$ 100 U/l
(vi) ALT $\leq$ 100 U/l
(vii) Serum creatinine $\leq$ 1.5 mg/dl
(viii) $PaO_2 \geq 65$ torr (room air)

(11) No ischemic change on ECG
(12) Written informed consent

Inclusion criteria at the second registration (intraoperative). After satisfying the eligibility criteria for the first registration, patients will be required to fulfill all of the following criteria for inclusion during surgery:

(1) Within 14 days of the first registration
(2) Histologically confirmed NSCLC
(3) Technically possible to perform lobectomy or sublobar resection such as wedge resection or segmentectomy
(4) No malignant effusion, dissemination, regional lymph node metastases and direct invasion into surrounding organs except for adjacent lobe macroscopically

Exclusion criteria. Patients will be excluded from the first (preoperative) registration preoperatively if they meet any of the following criteria:

(1) Synchronous or metachronous (within 2 years) malignancy except cancer with 5-year relative survival rate of 95% or more such as carcinoma *in situ*, intramucosal tumor or early stage cancers
(2) Active infection requiring systemic therapy
(3) Fever of 38° or higher at registration
(4) Female during pregnancy, within 28 days of postparturition or during lactation and male expecting partner's pregnancy
(5) Severe psychological disorder
(6) Receiving continuous systemic corticosteroid or immunosuppressant treatment
(7) Uncontrollable diabetes mellitus
(8) Uncontrollable hypertension
(9) Unstable angina, myocardiac infarction within the past 6 months
(10) Uncontrollable valvular disease or uncontrollable dilated cardiomyopathy or uncontrollable hypertrophic cardiomyopathy

Randomization

Registration is conducted through a web-based system of the JCOG Data Center, Tokyo, Japan. Patients are randomized to receive either lobectomy (standard arm) or sublobar resection (test arm). The process is performed using the minimization method with random component to balance for the institution, solid component tumor size ($\leq$3 vs. 3 cm<), $\%DL_{CO}$ ($\leq$55 vs. 55%<), and radiologic pattern of IPF (UIP pattern vs. possible UIP pattern).

Treatments

In the standard arm, lobectomy with hilar and mediastinal lymph node dissection (ND2a-1 or ND2a-2) is performed.

In the test arm, wedge resection is performed in principle. However, if intraoperative findings (tumor size, localization, lung stiffness, etc.) indicate that technically sufficient resection margins are considered to be difficult, segmentectomy is allowed. Lymph node dissection is not required, but sampling and dissection of the hilar and mediastinal lymph nodes that are technically possible are allowed. When lymph node metastasis is present or resection margin is not cancer-free during the operation, the surgical procedure must be converted to a lobectomy.

To confirm that the randomized surgical procedures are performed properly, the procedures will be centrally reviewed by expert surgeons in intraoperative photographs, including pulmonary hilar lesions and the dissected surface of pulmonary parenchyma of all randomized patients who fulfill the second registration criteria.

In both arms, postoperative adjuvant chemotherapy is not recommended, because chemotherapy is a risk factor for acute exacerbation in lung cancer with IPF. Antifibrotic drug administration is not routinely recommended as a protocol treatment in this study.

Follow-up

All randomized patients who fulfill the second registration criteria will be followed up for 5 years. A physical examination including performance status is done at least for every 3 months in the first year postoperatively and every 6 months thereafter. A chest roentgenogram is done every 3 months in the first year. A chest CT is evaluated every 6 months for the duration of follow-up. A pulmonary function test is an important endpoint. Therefore, this must be measured at 6 months and every year thereafter, postoperatively.

Statistical analysis

This randomized phase III trial is designed to confirm the non-inferiority of sublobar resection to lobectomy in terms of OS for clinical stage I NSCLC with IPF. If the non-inferiority in terms of OS is confirmed and the minimal invasiveness of sublobar resection is not significantly different from previous assumptions (low incidence of adverse events, low incidence of postoperative acute IPF exacerbation, good postoperative respiratory function, short operation time and low bleeding volume), sublobar resection will be the standard treatment for patients with clinical stage I NSCLC with IPF. Conversely, if non-inferiority of OS is not demonstrated, lobectomy still remains the standard treatment. In addition, if non-inferiority of OS is proved but the minimal invasiveness of sublobar resection is not comprehensively recognized, the optimal surgical method should be selected for each patient.

We assumed a 5-year OS of 35% in each arm and a non-inferiority margin of 10% for sublobar resection compared with lobectomy. Based on Schoenfeld and Richter's method (13), the required sample size is 410 patients in total (required total number of events of 319), to give a power of 80% with a one-sided alpha level of 5%, an accrual period of 5 years and a follow-up period of 5 years. The planned total sample size of the second registration was set at 430 patients to account for patients lost to follow-up. We estimated that 5% of the patients would be ineligible at the second registration. Thus, the target sample size at the first registration was set at 500 patients. Stratified Cox proportional hazard model with solid component tumor size, $\%DL_{CO}$ and radiologic pattern of IPF as stratification factors will be performed to test the non-inferiority of sublobar resection to lobectomy in terms of OS. All statistical analyses will be performed at the JCOG Data Center.

Interim analysis and monitoring

We plan to conduct two interim analyses. The first will be performed after half of the planned number of patients are enrolled in the

second registration to determine whether we should continue patient accrual. The second interim analysis will be performed ~1 year after the completion of patient accrual and their protocol treatment has been completed. The Lan–DeMets method with an O'Brien and Fleming-type alpha spending function will be used to adjust the multiplicity of the two interim analyses and the primary analysis (14). The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and recommend early termination of the trial if necessary. In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate the study progress and improve the quality of data.

Participating institutions (from North to South)

National Hospital Organization Sendai Medical Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital & Cancer Center, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Chiba University Graduate School of Medicine, National Cancer Center Hospital, Kyorin University Faculty of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Keio University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo University Hospital, Juntendo University Hospital, Nippon Medical School Hospital, St. Marianna University School of Medicine, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kitazato University Hospital, Yokohama City University Medical Center, Niigata Cancer Center Hospital, National Hospital Organization Nishiniigata Chuo Hospital, Niigata University Medical and Dental Hospital, Kanazawa University School of Medicine, Gifu University Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, Osaka University Graduate School of Medicine, Osaka City General Hospital, Osaka International Cancer Institute, Osaka Habikino Medical Center, Osaka City General Hospital, Kobe University 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 Shikoku Cancer Center, National Hospital Organization Kyusyu Cancer Center, Hospital of the University of Occupational and Environmental Health Japan, Kyusyu University Hospital, Nagasaki University Hospital, Kumamoto University Medical School, Kumamoto Chuo Hospital and Oita University Faculty of Medicine.

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Conflict of interest statement

All authors state that they have no conflicts of interest associated with this manuscript.

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