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Clinical Trial Note

A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer (JCOG0802/WJOG4607L)

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A Phase III study was started in Japan to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter $\leq$2 cm) peripheral non-small cell lung cancer, excluding radiologically determined non-invasive cancer. This study began in August 2009, and a total of 1100 patients will be accrued from 71 institutions within 3 years. The primary endpoint is overall survival. The secondary endpoints are post-operative respiratory function, relapse-free survival, proportion of local recurrence, adverse events, proportion of patients who complete segmentectomy, duration of hospitalization, duration of chest tube placement, operation time, blood loss and number of autosutures used. This study is one of the first intergroup studies in Japan between the Japan Clinical Oncology Group and the West Japan Oncology Group.

Key words: non-small cell lung carcinoma – thoracic surgery – pneumonectomy – clinical trial – Phase III

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide for both men and women (1). Among patients who underwent surgery for this condition, 36.5% were diagnosed as clinical stage IA (2). Lobectomy with lymph node dissection remains a standard initial therapy even in clinical stage IA non-small cell lung cancer (NSCLC) (3). The Lung Cancer Study Group (LCSG) performed a pivotal study comparing limited resection (segment or wedge) with lobectomy for clinical stage IA NSCLC and found inferior overall survival and three times the local recurrence rate in the limited resection arm (4). However, the LCSG study suffered from issues such as (i) eligibility of tumors with diameter $>$2 cm; (ii) wedge resection without lymph node dissection performed as limited resection; and (iii) additional eligibility of non-peripheral NSCLC, causing higher local recurrence rates in the limited resection arm. Therefore, we have conducted a Phase III trial to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter $\leq$2 cm) peripheral NSCLC. Patients with radiologically determined non-invasive lung cancer are excluded, because in these cases, there is a minimal likelihood of having lymph node metastasis and therefore lobectomy with nodal resection is considered to be overly invasive (5).

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) and the West Japan Oncology Group (WJOG) approved this protocol in January 2009 and

the present study was activated in August 2009. This trial was registered at the UMIN Clinical Trials Registry as UMIN000001272 [http://www.umin.ac.jp/ctr/index.htm].

PROTOCOL DIGEST OF THE JCOG 0802/ WJOG4607L

Objectives

The aim of this study is to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter $\leq$2 cm) peripheral NSCLC, excluding radiologically determined non-invasive cancer.

Study Setting

The study was a multi-institutional randomized Phase III study.

Resources

The study was supported in part by Grants-in-Aid for Cancer Research (20S-2, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is overall survival in all eligible patients. Overall survival is defined as days from randomization to death from any cause, and it was censored at the last day when the patient was alive. The secondary endpoints are post-operative respiratory function, relapse-free survival, proportion of local recurrence, adverse events, proportion of patients who successfully undergo segmentectomy, duration of hospitalization, duration of chest tube placement, operation time, blood loss and number of auto-sutures used.

Relapse-free survival is defined as days from randomization to relapse or death from any cause, and it was censored at the latest day when the patient was alive without any evidence of relapse. Local recurrence is defined as tumor recurrence in the ipsilateral thorax, which includes the resection margin of the lung or bronchus, hilar lymph nodes, mediastinal lymph nodes and malignant pleural effusion. As for post-operative respiratory function, the difference between baseline respiratory function and that assessed 6 and 12 months after surgery is evaluated.

Eligibility Criteria

Two-step registration is applied because the imaging eligibility criteria are complicated and histological type of the tumor is to be confirmed intra-operatively in most patients.

Inclusion Criteria for the Primary Registration

For inclusion in the primary registration, patients are required to fulfill all of the following pre-operative criteria.

(i) Contrast-enhanced thoracic computed tomography (CT) fulfills all of the following conditions: (a) single tumor, (b) NSCLC suspected, (c) center of tumor located in the outer third of the lung field, (d) tumor not located at middle lobe, and (e) no lymph node metastasis. (ii) Thin-section CT fulfills both of the following conditions: (a) maximum tumor diameter of $\leq$2 cm and (b) not 'radiologically determined non-invasive cancer' (i.e. the proportion of the maximum diameter of the tumor itself to consolidation is $>$25%). (iii) Patient age 20–79 years old. (iv) No prior ipsilateral thoracotomy (prior diagnostic thoracoscopy is allowed). (v) No prior chemotherapy or radiation therapy for any malignant diseases. (vi) Expected post-operative FEV1.0 $\geq$ 800 ml and $PaO_2 \geq 65$ torr. (vii) Performance status of 0 or 1. (viii) Sufficient organ function. (ix) Written informed consent.

Exclusion Criteria for the Primary Registration

Patients are excluded from the primary registration pre-operatively if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within the past 5 years) double cancers; (iii) women during pregnancy or breast-feeding; (iv) interstitial pneumonitis, pulmonary fibrosis, or severe pulmonary emphysema; (v) psychosis; (vi) systemic steroidal medication; (vii) uncontrollable diabetes mellitus; (viii) uncontrollable hypertension; (ix) history of severe heart disease, heart failure, myocardial infarction within the past 6 months or attack of angina pectoris within the past 6 months.

Inclusion Criteria for the Secondary Registration

After the confirmation of the inclusion and exclusion criteria for the primary registration, patients are required to fulfill all of the following criteria for inclusion in the secondary registration.

Pre-operative criteria: (i) sufficient organ function and (ii) pre-operative body temperature of $\leq 38^{\circ}C$.

Intra-operative criteria: (i) date of surgery within 28 days of initial registration; (ii) histologically confirmed adenocarcinoma, adenosquamous carcinoma, large cell carcinoma or NSCLC (detailed category unknown); (iii) neither malignant pleural effusion nor pleural dissemination; and (iv) technically possible to perform lobectomy, segmentectomy and nodal dissection.

Randomization

After the confirmation of the inclusion criteria for the secondary registration, registration is made by telephone or fax to the JCOG Data Center or WJOG Data Center. Patients are randomized in each group, JCOG or WJOG, by minimization method balancing the arms with institution, histologic type

(adenocarcinoma or others), gender, age (<70 or ≥ 70 years old) and thin-section CT findings (solid or non-solid).

Treatment Methods

In the standard treatment arm, lobectomy with hilar and mediastinal lymph node dissection is performed. Systemic or selective lymph node dissection is mandatory, and nodal sampling is not allowed. The distance from the dissection margin to the tumor edge must be evaluated intra-operatively. If the distance is either less than the maximum tumor diameter or <20 mm, the absence of cancer cells in the resection margin must be histologically or cytologically confirmed before finishing surgery.

In the experimental treatment arm, segmentectomy with hilar and mediastinal lymph node dissection is performed. As with lobectomy, systemic or selective lymph node dissection is mandatory, and nodal sampling is not allowed. The distance from the dissection margin to the tumor edge must be evaluated in the same manner as with lobectomy. When lymph node metastasis is present or resection margin is not cancer-free, the surgical procedure must be converted to a lobectomy.

To confirm that the randomized surgical procedures are performed properly, we review the procedures centrally by photograph in all patients.

In both arms, post-operative adjuvant chemotherapy is recommended if the pathological findings reveal a tumor diameter >2 cm or if lymph node metastasis is present.

Follow-up

All randomized patients are followed up for at least 5 years. Tumor markers and chest X-rays are evaluated at least every 6 months, and enhanced chest CT is evaluated at least every 6 months during the first 2 years and at least every 12 months for the duration of follow-up.

Study Design and Statistical Analysis

This trial is designed to demonstrate that segmentectomy is not inferior to lobectomy in terms of overall survival. If the non-inferiority of segmentectomy is verified and the expected reduced toxicity of segmentectomy is observed, segmentectomy will be the preferred treatment for small peripheral NSCLC.

The planned sample size is 1100 patients, with 550 cases per arm. We anticipate 5 years of follow-up after 3 years of accrual, ensuring at least 80% power with a one-sided α of 5% and a non-inferiority margin of 5% in terms of 5-year survival for the primary endpoint. This assumes an expected 5-year overall survival of 90% in each arm.

Interim Analysis and Monitoring

We plan on conducting two interim analyses, taking multiplicity into account using the Lan–DeMets method with O'Brien and Fleming type alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by each Data Center to evaluate and improve study progress and quality.

Procedure of Intergroup Study

The present study is one of the first Japanese collaborative studies between JCOG and WJOG. Patient registration, randomization, data collection, in-house monitoring and audits are performed in each data center. Each group uses a single study protocol, and protocol amendment or revision is done simultaneously. At the interim and final analyses, the data from WJOG Data Center are sent to JCOG Data Center and integrated. It is these integrated data, and not the separate data from each data center, that are used in the primary analysis.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Japan Clinical Oncology Group

Sendai Medical Center, Tohoku University Hospital, Iwaki Kyoritsu Hospital, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center, Gunma Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba University Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, Cancer Institute Hospital, Juntendo University Hospital, Kanagawa Cancer Center, Niigata Cancer Center, Kanazawa University Hospital, Saku Central Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Kyoto University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Prefectural medical Center for Respiratory and Allergic Diseases, Kinki-chuo Chest Medical Center, Osaka City General Hospital, Hyogo Cancer Center, Okayama University Hospital, Hiroshima University Hospital, Kure Medical Center, Shikoku Cancer Center, Kyushu Cancer Center, Fukuoka University Hospital, Nagasaki University Hospital, Kumamoto Chuo Hospital and Okinawa National Hospital.

West Japan Oncology Group

Kitasato University Hospital, Kanagawa Cardiovascular and Respiratory Center, Sagamihara Kyodo Hospital, Toyama University Hospital, Ishikawa Prefectural Central Hospital, Gifu City Hospital, Hamamatsu Medical University Hospital, Seirei Hamamatsu General Hospital, Aichi Cancer Center Aichi Hospital, Nagoya Medical Center, Nagoya University Hospital, Nagoya Ekisaikai Hospital, Shiga University of Medical Science Hospital, Osaka University Hospital, Osaka City University Hospital, Kinki University Hospital, National Toneyama Hospital, Rinku General Medical Center, Suita Municipal Hospital, Kobe University Hospital, Kobe City

Medical Center General Hospital, Hyogo Medical College University, Hyogo Prefectural Awaji Hospital, Himeji Red Cross Hospital, Kurashiki Central Hospital, Kawasaki Medical School Hospital, Hiroshima City Hospital, Hiroshima City Asa Hospital, Yamaguchi Ube Medical Center, University of Occupational and Environmental Health, Nippon Steel Yawata Memorial Hospital, Iizuka Hospital, Saga University Hospital, Kumamoto University Hospital, Kumamoto Regional Medical Center, Saiseikai Kumamoto Hospital and Oita Prefectural Hospital.

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Conflict of interest statement

None declared.

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