Clinical Trial Note

A randomized Phase III trial of lobe-specific vs. systematic nodal dissection for clinical Stage I–II non-small cell lung cancer (JCOG1413)

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Abstract

In January 2017, the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group commenced a randomized Phase III trial to confirm the clinical benefit of lobe-specific nodal dissection for clinical Stage I–II non-small cell lung cancer. The primary endpoint is overall survival, and the main objective is to confirm the non-inferiority of lobe-specific in comparison to systematic nodal dissection with regard to lobectomy. The secondary endpoints are relapse-free survival, %local recurrence, %regional lymph node recurrence, operation time, blood loss, length of hospitalization, duration of chest tube placement and adverse events. A total of 1700 patients will be accrued from 44 Japanese institutions within 5 years. This study is the first and large prospective trial to evaluate whether the difference in the area of nodal dissection affects the overall survival of patients with relatively early-stage non-small cell lung cancer. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000025530.

Key words: non-small-cell lung cancer, lymph node dissection, lobe-specific, systematic, randomized Phase III study

Introduction

The standard treatment for resectable non-small cell lung cancer (NSCLC) is lobectomy. However, regardless of the advance in diagnostic imaging including positron emission tomography/computed tomography (PET/CT) scans, even tumors that have been preoperatively diagnosed as localized disease may have metastases in resected specimens of locoregional lymph nodes. The hilar and mediastinal lymph node metastasis, the N status, is known to be one of the most important outcome predictors after lung cancer surgery (1). Thus, systematic hilar and mediastinal lymphadenectomy that dissects a wide swath of the superior and inferior mediastinum, so-called ‘systematic nodal dissection (SND)’, has been generally advised along with lobectomy. Although previous randomized studies have all shown no survival benefit of SND over sampling (2–5), the current international guidelines still recommend SND for all resectable non-small cell lung cancer (NSCLC), irrespective of the tumor stage and/or location (6,7).
Since the 1990s, several retrospective studies in Japan have shown a lobe-specific pattern of nodal spread in NSCLC, and lobe-specific nodal dissection (LND) has been proposed (8–10). Although there were some previous variations of LND, the following type of LND is now generally used for upper- and lower-lobe tumors that meet certain preconditions (8,11–13). For upper-lobe tumors, subcarinal (inferior mediastinal) dissection is not necessary if the hilar and superior mediastinal nodes are tumor-free. For lower-lobe tumors, superior mediastinal and aortic node dissection can be omitted if the hilar and inferior mediastinal nodes are intact. Recent retrospective studies suggested that LND does not reduce the survival outcome in comparison with conventional SND (11,12,14), and LND is becoming popular in current clinical practice in Japan. Intrinsically, the clinical validity of LND should be confirmed in a prospective study. Therefore, a randomized Phase III trial was designed by the Japan Clinical Oncology Group-Lung Cancer Surgical Study Group (JCOG-LCSSG) to confirm the clinical benefit in terms of survival non-inferiority and less invasiveness of LND compared with SND in patients with clinical Stage I–II NSCLC.

Only the right lung includes a middle lobe, and lung cancer of the middle lobe is accounts for only 3.8–6.7% of all lung cancers (15). The survival outcome and the detailed nodal spread patterns of middle-lobe lung cancer are not well understood, and the concept of LND is currently not established. Therefore, in addition to a Phase III part (SND versus LND) for upper- and lower-lobe tumors, a non-randomized single-arm intervention study for middle-lobe tumors will be incorporated to elucidate the survival and mode of nodal metastasis of middle-lobe tumors.

The JCOG Protocol Review Committee approved the study protocol in October 2016, and patient enrollment began in January 2017. Approval was obtained from the Institutional Review Board at each institution prior to starting patient accrual. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000025530 (http://www.umin.ac.jp/ctr/index.htm).

Summary of the study protocol

Objectives

This study consists of two parts with the following objectives.

Part 1 (for upper- and lower-lobe tumors)
The aim of this part is to confirm the clinical benefit of LND for clinical (c-) Stage I–II NSCLC in comparison with SND by a randomized Phase III trial. The primary objective is to demonstrate the non-inferiority of lobectomy plus LND to lobectomy plus SND in terms of overall survival (OS).

Part 2 (for middle-lobe tumors)
The aim of this part is to elucidate the survival outcome and nodal spread pattern in patients who undergo right middle lobectomy for c-Stage I–II middle-lobe NSCLC.

Study setting

Part 1 (for upper- and lower-lobe tumors)
A multi-institutional, two-arm, open-label, randomized Phase III study.

Part 2 (for middle-lobe tumors)
A multi-institutional, single-arm, exploratory intervention study.

Endpoints

Both parts use the same endpoints.

Primary endpoint: OS

Secondary endpoints: Relapse-free survival (RFS), proportion of local recurrence, proportion of local lymph node recurrence, operation time, blood loss, length of hospitalization, duration of chest tube placement, adverse events and serious adverse events.

OS is defined as days from the second (intra-operative) registration to death from any cause, and is censored at the last day when the patient is alive. RFS is defined as days from the second registration to relapse or death from any cause, and is censored at the last day when the patient is alive without any evidence of relapse. Local recurrence is defined as tumor recurrence in the resection margin of the lung or bronchus, ipsilateral/contralateral hilar or mediastinal lymph nodes, ipsilateral malignant pleural effusion/dissemination or ipsilateral lung. Local lymph node recurrence is defined as tumor recurrence in the ipsilateral hilar or mediastinal lymph nodes. Serious adverse events include Grade 4 non-hematologic adverse events, early death (within 30 days) and treatment-related death.

Eligibility criteria

In each part, a two-step registration is applied because, for many patients, histological type and nodal status are determined intraoperatively.

Inclusion criteria for the first (pre-operative) registration

For inclusion in the first (pre-operative) registration, patients will be required to fulfill all of the following criteria:

1. Tumor suspected to be NSCLC on thoracic computed tomography (CT).
2. No other tumor nodule in a different lobe from the primary tumor.
3. Clinical Stage I–II disease diagnosed by CT and positron emission tomography/computed tomography (PET/CT) scans except for the following conditions (UICC-TNM ver. 8):
   (i) Maximum diameter of the tumor including ground glass attenuation (GGA) is ≤2 cm and cN0.
   (ii) GGA-dominant (Consolidation/Tumor ratio ≤0.5), maximum diameter of the tumor is >2–3 cm and cN0.
   (iii) cT3N0 with direct invasion to the chest wall, phrenic nerve or pericardium.
   (iv) cN1 with extranodal invasion (defect image in bronchial or vascular walls).
4. No neuroendocrine tumors.
5. Aged 20–79 years.
6. ECOG performance status of 0 or 1.
7. None of the following surgical history:
   (i) Ipsilateral thoracotomy.
   (ii) Ipsilateral thoracoscopic resection of the lung, esophagus, or mediastinum (except for the thoracoscopic resection of bullae).
   (iii) Contralateral thoracotomy or thoracoscopic surgery except for wedge resection of the lung.
8. No prior chemotherapy (prior postoperative adjuvant chemotherapy and hormone therapy for other cancers are allowed).
9. No prior radiotherapy fulfilling the following conditions:
   (i) Radiotherapy for the ipsilateral hilum or mediastinum.
   (ii) Ipsilateral radiation pneumonitis (≥Grade 2).
10. Expected postoperative FEV1.0 ≥ 800 ml and SpO2 ≥93% (room air).
11. Technically possible to perform all resections (lobectomy, lobectomy plus one segmentectomy or lobectomy plus ≤2 wedge resections) at a time.
12. Sufficient organ functions.
13. Written informed consent.

Exclusion criteria for the first (pre-operative) registration
Patients will be excluded from the first (pre-operative) registration preoperatively if they meet any of the following criteria:

1. Synchronous double/multiple cancer or metachronous double/multiple cancer with a disease-free period of 5 years or shorter, except for cancers with a good prognosis.
2. Active infection that requires systemic therapy.
3. Fever of 38°C or higher at registration.
4. Female during pregnancy, within 28 days of postparturition, or during lactation.
5. Severe psychological disorder.
6. Receiving continuous systemic corticosteroid or immunosuppressant treatment.
7. Insulin-dependent or uncontrollable diabetes mellitus.
8. Uncontrollable hypertension.
9. History of severe heart disease, heart failure, myocardial infarction within the past 6 months or attack of angina pectoris within the past 6 months.
10. Interstitial pneumonitis, pulmonary fibrosis or severe pulmonary emphysema.

Inclusion criteria for the secondary (intra-operative) registration
After satisfying the inclusion and exclusion 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 feasible to perform lobectomy and lymph node dissection (SND or LND).
4. No malignant effusion, dissemination, macroscopic hilar (stations 10 and 11)/mediastinal node metastasis, or macroscopic direct invasion into surrounding organs except for an adjacent lobe.
5. Negative hilar (stations 10 and 11) node on frozen section for cN1 tumor suspected of hilar (stations 10 and 11) node metastasis preoperatively.

Randomization
After confirmation of the inclusion criteria for the secondary registration, registration will be made by an on-line system (JCOG Web System) or telephone to the JCOG Data Center. Patients with upper- and lower-lobe tumors will be randomized into arm A (the standard treatment arm for upper- and lower-lobe tumors) or arm B (the experimental treatment arm for upper- and lower-lobe tumors), by a minimization method while balancing the arms with respect to institution, c-Stage (I or II), and histological type (adenocarcinoma or non-adenocarcinoma). NSCLC with an unspecified subtype will be assigned to non-adenocarcinoma. If the patient underwent both a pre- and intra-operative histological diagnosis, the result of intraoperative histology will be preferred. Patients with middle-lobe tumors will not be randomized and will be assigned to arm C to undergo right middle lobectomy plus SND.

Treatment methods
The scheme of this study is shown in Fig. 1.

In arm A, upper or lower lobectomy plus SND will be performed. Nodal sampling is not allowed.

The SND area in the mediastinum includes stations 2 R, 4 R and 7 for right upper-lobe tumors, 2 R, 4 R, 7, 8 and 9 for right lower-
lobe tumors, 4 L, 5, 6 and 7 for left upper-lobe tumors, and 4 L, 5, 6, 7, 8 and 9 for left lower-lobe tumors according to both the International Association for the Study of Lung Cancer (IASLC) node map in the eighth edition of the TNM classification (16) and the usual procedure in Japanese clinical practice (8,9,11,12).

In arm B, upper or lower lobectomy plus LND will be performed. Nodal sampling is not allowed. The LND area in the mediastinum includes stations 2 R and 4 R for right upper-lobe tumors, 7, 8 and 9 for right lower-lobe tumors, 4 L, 5 and 6 for left upper-lobe tumors, and 7, 8 and 9 for left lower-lobe tumors. When lymph node metastasis in a hilar (stations 10 and 11) or mediastinal area is suspected macroscopically, the involved node should be picked up and subjected to intra-operative frozen-section analysis. If metastasis is identified pathologically, the surgical procedure will be converted to lobectomy plus SND. For lower-lobe tumors assigned to LND, dissection of hilar station 10 node, which is far from the inferior mediastinum, can be omitted except for cN1 (station 10) disease and intra-operatively station 10-positive disease.

Patients in arm C will undergo middle lobectomy plus SND. The mediastinal dissection area should include stations 2 R, 4 R, 7, 8 and 9. Nodal sampling is not allowed. The SND and LND areas in each lobe are shown in Table 1.

To assure that the assigned surgical procedures are performed properly, the procedures will be centrally reviewed by photograph in selected patients. In all of the arms, postoperative adjuvant chemotherapy is not mandatory, but is recommended according to clinical guidelines in Japan if the pathological findings reveal a tumor with pathological (p-) stage of IA3 or higher. For tumors of p-Stage IA3, IB, or IIA (UICC-TNM ver. 8), oral UFT for 2 years is recommended. For tumors of p-Stage II B-IIIA (UICC-TNM ver. 8), four cycles of intravenous cisplatin-based regimens are recommended according to the predetermined regimen at each institution (cisplatin plus vinorelbine, docetaxel or gemcitabine). Each patients will be encouraged to receive post-operative adjuvant chemotherapy within 56 days after surgery.

Follow-up
All registered patients who fulfill the second registration criteria will be followed-up for 10 years. The patients will be checked by physical and imaging examinations using chest X-ray every 6 months until postoperative 5 years or by enhanced CT scans every 1 year until postoperative 10 years.

Study design and statistical analysis
This trial is mainly designed to confirm that lobectomy plus LND is not inferior to lobectomy plus SND in terms of OS (part 1). If lobectomy plus LND is to be non-inferior and less-invasive parameters including adverse events (AEs), blood loss, and length of hospital stay are not qualitatively increased from the predicted values (5% of Grade 3 AEs, blood loss of 100 ml, and hospital stay of 10 days), lobectomy plus LND will be the preferred treatment for c-Stage I–II NSCLC locating in upper and lower lobes. We assumed a 5-year OS of 70% in each arm and a non-inferiority margin of 5.5% for lobectomy plus LND compared to lobectomy plus SND. According to Schoenfeld and Richter’s method (17), a sample size of 705 patients in each will be needed to observe a total of 579 of the required events, 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 total sample size of the second registration was set at 1450 patients to account for patients lost to follow-up. We estimated that 15% of the patients would be ineligible at the second registration. Thus, the target sample size at the first registration was set at 1700 patients.

In part 2, the survival and mode of nodal metastasis of c-Stage I–II NSCLC in the middle lobe will be investigated. If OS of patients with middle-lobe NSCLC is worse than that of upper- and lower-lobe NSCLC patients, a more effective postoperative treatment strategy will be planned for a future study. Patients will be accrued until the enrollment for part 1 is complete.

Interim analysis and monitoring
We plan to conduct two interim analyses. The first will be performed after half of the planned 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 planned 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 (18). 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 the JCOG Data Center to evaluate the study progress and improve the quality of data.

Participating institutions (from north to south)
(1) Sendai Medical Center, (2) Tohoku University Hospital, (3) Yamagata Prefectural Central Hospital, (4) Ibaragi Prefectural Central Hospital and Cancer Center, (5) Tochigi Cancer Center, (6) Gunma Prefectural Cancer Center, (7) National Cancer Center Hospital East, (8) Chiba Cancer Center, (9) Chiba University, Graduate School of Medicine, (10) National Cancer Center Hospital, (11) Kyorin University faculty of Medicine, (12) Tokyo Medical University Hospital, (13) Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, (14) Keio University Hospital, (15) Cancer Institute Hospital of Japanese Foundation for Cancer Research, (16) Juntendo University Hospital, (17) Nippon Medical School Hospital, (18) St. Marianna University School of Medicine, (19) Kanagawa Cancer Center, (20) Yokohama Municipal Citizen’s Hospital, (21) Yokohama City University Medical Center, (22) Niigata Cancer Center Hospital, (23) Niigata

| Table 1. Dissection area of mediastinal lymph nodes in each lobe |
|-------------------|-----------------|-----------------|-----------------|
| Right lung         |                  | Left lung        |                  |
| RUL               | RML             | LUL             | LLL             |
| SND 2R, 4R, 7      | 2R, 4R, 7, 8, 9 | 2R, 4R, 7, 8, 9 | 4 L, 5, 6, 7    |
| LND 2R, 4R         | (→)             | 7, 8, 9         | 4 L, 5, 6       |
|                   |                 |                 | 7, 8, 9         |

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; SND, systematic nodal dissection; LND, lobe-specific nodal dissection.
University Medical and Dental Hospital, (24) Kanazawa University School of Medicine, (25) Shizuoka Cancer Center, (26) Aichi Cancer Center Hospital, (27) Nagoya University School of Medicine, (28) Kyoto University Hospital, (29) Osaka University School of Medicine, (30) Osaka Medical Center for Cancer and Cardiovascular Diseases, (31) Osaka Prefectural medical Center for Respiratory and Allergic Diseases, (32) Kinki-chuo Chest Medical Center, (33) Osaka City General Hospital, (34) Hyogo Cancer Center, (35) Kurashiki Central Hospital, (36) Okayama University Hospital, (37) Kure Medical Center, (38) Hiroshima University Hospital, (39) Shikoku Cancer Center, (40) National Kyushu Cancer Center, (41) Nagasaki University Hospital, (42) Kumamoto University Medical School, (43) Kumamoto Chuo Hospital, and (44) 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.

Abbreviations
JCOG-LCSSG Japan Clinical Oncology Group-Lung Cancer Surgical Study Group
NSCLC non-small cell lung cancer
SNL systematic nodal dissection
LND lobe-specific nodal dissection
OS overall survival
RFS relapse-free survival

References