Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial

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Summary

Background Lobectomy is the standard of care for early-stage non-small-cell lung cancer (NSCLC). The survival and clinical benefits of segmentectomy have not been investigated in a randomised trial setting. We aimed to investigate if segmentectomy was non-inferior to lobectomy in patients with small-sized peripheral NSCLC.

Methods We conducted this randomised, controlled, non-inferiority trial at 70 institutions in Japan. Patients with clinical stage IA NSCLC (tumour diameter ≤2 cm; consolidation-to-tumour ratio >0·5) were randomly assigned 1:1 to receive either lobectomy or segmentectomy. Randomisation was done via the minimisation method, with balancing for the institution, histological type, sex, age, and thin-section CT findings. Treatment allocation was not concealed from investigators and patients. The primary endpoint was overall survival for all randomly assigned patients. The secondary endpoints were postoperative respiratory function (6 months and 12 months), relapse-free survival, proportion of local relapse, adverse events, proportion of segmentectomy completion, duration of hospital stay, duration of chest tube placement, duration of surgery, amount of blood loss, and the number of automatic surgical staples used. Overall survival was analysed on an intention-to-treat basis with a non-inferiority margin of 1·54 for the upper limit of the 95% CI of the hazard ratio (HR) and estimated using a stratified Cox regression model. This study is registered with UMIN Clinical Trials Registry, UMIN000002317.

Findings Between Aug, 10, 2009, and Oct 21, 2014, 1106 patients (intention-to-treat population) were enrolled to receive lobectomy (n=554) or segmentectomy (n=552). Patient baseline clinicopathological factors were well balanced between the groups. In the segmentectomy group, 22 patients were switched to lobectomies and one patient received wide wedge resection. At a median follow-up of 7·3 years (range 0·0–10·9), the 5-year overall survival was 94·3% (92·1–96·0) for segmentectomy and 91·1% for lobectomy (95% CI 88·4–93·2); superiority and non-inferiority in overall survival were confirmed using a stratified Cox regression model (HR 0·663; 95% CI 0·474–0·927; one-sided p<0·0001 for non-inferiority; p=0·0082 for superiority). Improved overall survival was observed consistently across all predefined subgroups in the segmentectomy group. At 1 year follow-up, the significant difference in the reduction of median forced expiratory volume in 1 sec between the two groups was 3·5% (p<0·0001), which did not reach the predefined threshold for clinical significance of 10%. The 5-year relapse-free survival was 88·0% (95% CI 85·0–90·4) for segmentectomy and 87·9% (84·8–90·3) for lobectomy (HR 0·998; 95% CI 0·753–1·323; p=0·9889). The proportions of patients with local relapse were 10·5% for segmentectomy and 5·4% for lobectomy (p=0·0018). 52 (63%) of 83 patients and 27 (47%) of 58 patients died of other diseases after lobectomy and segmentectomy, respectively. No 30-day or 90-day mortality was observed. One or more postoperative complications of grade 2 or worse occurred at similar frequencies in both groups (142 [26%] patients who received lobectomy, 148 [27%] who received segmentectomy).

Interpretation To our knowledge, this study was the first phase 3 trial to show the benefits of segmentectomy versus lobectomy in overall survival of patients with small-peripheral NSCLC. The findings suggest that segmentectomy should be the standard surgical procedure for this population of patients.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and the incidence has increased over the past two decades.[1] Surgical resection is the gold standard of treatment for early-stage lung cancer, with lobectomy being the standard mode of surgery since 1960.[2] To date, only one randomised controlled trial has compared lobectomy with sublobar resection in

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Research in context

Evidence before this study

We conducted a literature search on PubMed for randomised controlled trials on sublobar resection for early-stage non-small-cell lung cancer (NSCLC) published between Jan 1, 1995, and July 31, 2021, in English. We used the search terms "randomized controlled trial", "early stage", "sublobar resection", and "lung cancer". Additionally, we searched for meeting abstracts of the American Society of Clinical Oncology, World Conference on Lung Cancer, and the European Society of Medical Oncology. Identified published trials included two studies on sublobar resection comparing lobectomy in patients with early-stage NSCLC (one was published in 1995 and the other, CALGB140503: NCT 00499330, had just finished and will be finalised in 2024) and two additional trials involving older adult patients and patients with low respiratory function. To date, only one randomised controlled trial (LCSG821) has compared lobectomy with sublobar resection for overall survival in patients with stage IA lung cancer (maximum tumour diameter ≤3 cm without lymph node metastasis), which was reported by the Lung Cancer Study Group (1995). On the basis of higher death rates and a three-fold increase in local relapses, lobectomy has been the standard mode of surgery, even for early-stage NSCLC. Sublobar resection for early-stage lung cancer is only indicated for selected patients with poor pulmonary reserve or other major comorbidities contraindicating lobectomy. Following the increase of computed tomography screening in the late 90s in Japan, the early detection of small-sized early lung tumours has increased. Japanese clinical oncology groups, specifically the Japan Clinical Oncology Group and the West Japan Oncology Group, conducted three prospective multi-institutional studies to investigate the optimal surgical modality for early-stage NSCLC. JCOG0802/WJOG4607L was a randomised, controlled, non-inferiority trial comparing segmentectomy and lobectomy for radiologically invasive lung cancer, whereas JCOG0804/WJOG4507L and JCOG1211 were non-randomised confirmatory trials of clinical efficacy of sublobar resection for radiologically non-invasive lung cancer.

Added value of this study

To our knowledge, JCOG0802/WJOG4607L is the first randomised trial to show the superiority of segmentectomy over lobectomy in terms of overall survival for early-stage lung cancer. The findings of this study indicate that segmentectomy should be the standard surgical procedure instead of lobectomy for patients with clinical stage IA, small-sized (≤2 cm, consolidation-to-tumour ratio >0·5) peripheral NSCLC.

Implications of all the available evidence

Although lung cancer is a highly malignant disease, according to our results, patients with clinical stage IA, small-sized peripheral NSCLC who receive curative-intent surgery, including lobectomy or segmentectomy, can expect a 5-year overall survival of 90% or higher. The differences in survival outcomes and causes of death between the two groups of this study were not associated with the primary NSCLC but were due to a second primary cancer or other diseases, including respiratory disease or cerebrovascular disease. Compared with segmentectomy, lobectomy for patients with small-sized peripheral early-stage NSCLC appeared to be more invasive (judged by long-term survival) than was formerly believed. The final results of CALGB140503, a large, multicentre, randomised trial similar in setting to our study, will be opened in 2024. The aim of CALGB140503 is to test the hypothesis that sublobar resection (wedge resection or segmentectomy) for peripheral NSCLC (≤2 cm) results in disease-free survival equivalent to that achieved by lobectomy. This trial will provide useful information and could support our conclusions.

the context of overall survival in patients with stage IA lung cancer (in 1995).[3] Given its associated higher death rate and a three-fold risk for local relapses, sublobar resection for early-stage lung cancer has only been indicated for selected patients with poor pulmonary reserve or other major comorbidities contraindicating lobectomy. With the increased frequency of CT screening and advances in diagnostic modalities, including thin-section CT, the early detection rate of small-sized or ground-glass opacity lung tumours has increased. Consequently, the practical indications of sublobar resections have been extended to early-stage lung cancer.[4] Sublobar resections are approved for patients eligible for lobectomy if a small-size peripheral tumour and no lymph node involvement are detected.[5] However, to our knowledge, the benefits of sublobar resection compared with lobectomy have not been shown in randomised controlled trials.

Reportedly, preoperative radiological findings of ground-glass opacity predict prognosis fairly well.[6] To select radiologically non-invasive lung cancer without pathological lymph node involvement or lymphovascular invasion, the Japan Clinical Oncology Group (JCOG) conducted an observational study (JCOG0201) that investigated the association between radiological findings and prognosis in early-stage non-small-cell lung cancer (NSCLC).[7] This study defined radiologically non-invasive lung cancer as having a maximum tumour diameter of 2 cm with a consolidation-to-tumour ratio of 0·25 or less, which was consequently changed to 0·5 or less due to findings of ground-glass opacity predominantly associated with excellent prognoses.[8] Sublobar resection consists of either segmentectomy or wedge resection, and the surgical intensity of these two procedures differs considerably. Segmentectomy refers to anatomical resection with sufficient margins and lymph nodal

assessment, in which margin-positive or nodal metastasis can be assessed during surgery. Therefore, segmentectomy is considered an alternative to lobectomy in terms of curative intensity in oncology and equivalent to wedge resection in terms of preservation of the pulmonary parenchyma in postoperative respiratory function.[9,10]

Given the results of the JCOG0201 and specific features of sublobar resection, JCOG and the West Japan Oncology Group (WJOG) conducted three prospective multi-institutional studies (appendix p 1) to investigate the optimal surgical modality for early-stage NSCLC (JCOG0802/WJOG4607L,[11] JCOG1211,[12] and JCOG0804/WJOG4507L[13]). JCOG0802/WJOG4607L was a randomised, controlled, non-inferiority trial comparing segmentectomy and lobectomy for radiologically invasive lung cancer, whereas JCOG0804/WJOG4507L and JCOG1211 were non-randomised confirmatory trials for radiologically non-invasive lung cancer. After confirming the hypotheses of the three studies, a standard mode of surgery for early-stage NSCLC can be established.

The current study (JCOG0802/WJOG4607L) is the essential part of the three studies and aims to confirm the non-inferiority of segmentectomy, the experimental group, to lobectomy, the standard group, in the context of overall survival in patients with small-sized (≤2 cm; consolidation-to-tumour ratio >0·5) peripheral NSCLC.

Methods

Study design and participants

JCOG0802/WJOG4607L was a multi-institutional and intergroup randomised, open-label, phase 3, randomised controlled trial at 70 institutions in Japan (appendix pp 17–18) designed to support the non-inferiority of segmentectomy for overall survival versus lobectomy, the standard of care, in patients with clinical stage IA small-sized (≤2 cm; consolidation-to-tumour ratio >0·5) peripheral NSCLC. This study was conducted according to the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research. The study protocol was approved by the JCOG and WJOG Protocol Review Committees and the institutional review boards of all participating hospitals. All patients provided written informed consent before enrolment. Full details of the trial have been published previously,[11] and the trial scheme is shown in the appendix (p 2).

The study population included eligible patients aged 20–85 years with an Eastern Cooperative Oncology Group performance score of 0 or 1 and primary, small-sized, invasive peripheral NSCLC (≤2 cm diameter; consolidation-to-tumour ratio >0·5; located in the outer one-third of the pulmonary parenchyma), with clinical stage IA NSCLC confirmed by thin-section CT. At the time of enrolment, the staging was determined according to the seventh edition of the TNM classification of malignant tumours.[14] A two-step registration was used because the radiological eligibility criterion of a complex and histological diagnosis of the tumours was to be determined intraoperatively. Eligibility requirements at first registration included age of 20–85 years, an Eastern Cooperative Oncology Group performance score of 0 or 1, and a tumour deemed a clinically resectable N0 NSCLC suspected lesion. Patients received enhanced thoracic CT within 56 days before the primary registration. Contrast-enhanced thoracic CT had to fulfil the following conditions: a single tumour was shown, NSCLC was suspected, the centre of the tumour was located in the outer third of the lung field, the tumour was not located in the middle lobe, and no lymph node metastasis was evident. Thin-section CT was mandatory and had to fulfil two conditions: a maximum tumour diameter of 2 cm was shown and the tumour had a consolidation-to-tumour ratio of 0·5 or more. The protocol was revised 4 years after the start of enrolment to change the eligibility criterion from a consolidation-to-tumour ratio of 0·25 or more to 0·5 or more, based on the results of the previous JCOG study (JCOG0201), in which the relapse-free survival of patients with a maximum tumour size of 3 cm and a consolidation-to-tumour ratio of 0·5 or less was shown to be good enough (5-year relapse-free survival 95·9%).[15,16] Eligible patients had to have no history of ipsilateral thoracotomy, no previous chemotherapy or radiotherapy for any malignant diseases, an expected postoperative forced expiratory volume in 1 s(FEV1) of 800 mL or more, and a partial pressure of arterial oxygen of 65 torr. Sufficient organ function and written informed consent were required for enrolment. Patients were excluded from the primary registration preoperatively if they met any one of several criteria: (1) active bacterial or fungal infection; (2) simultaneous or metachronous (within the past 5 years) double cancers; (3) women during pregnancy or breastfeeding; (4) interstitial pneumonitis, pulmonary fibrosis, or severe pulmonary emphysema; (5) psychosis; (6) systemic steroidal medication; (7) uncontrollable diabetes; (8) uncontrollable hypertension; or (9) a history of severe heart disease. Intraoperative requirements for the second registration were surgery performed within 28 days of the primary registration, histologically confirmed NSCLC, absence of malignant pleural effusion or pleural dissemination, no nodal involvement, and technical possibility of performing lobectomy, segmentectomy, or lymph node dissection.

Randomisation and masking

After confirmation of the eligibility criteria, primary registration was conducted by telephone or fax to the JCOG Data Center from institutions in the JCOG, or by fax to the WJOG Data Center from institutions in the WJOG. After confirmation of the eligibility criteria for the second registration, this registration was conducted by telephone to the JCOG Data Center from institutions in the JCOG, or to the WJOG Data Center from institutions in the WJOG. Eligible patients were randomly assigned (1:1) into the segmentectomy group or the lobectomy group, by the JCOG and WJOG Data

Center, using a minimisation method that balanced the groups according to the institution, histological type (adenocarcinoma or others), sex, age (<70 years or ≥70 years), and thin-section CT findings (consolidation-to-tumour ratio=1 or not). No masking of investigators or patients to treatment allocation was performed.

Procedures

Surgical procedures were performed as described previously.[11,17] In the lobectomy group, lobectomy with hilar and mediastinal lymph node dissection was performed. The resection of more than one lobe was not permitted. If the surgical margin was either less than the maximum tumour diameter or smaller than 20 mm, frozen diagnosis or cytological examination was mandatory for confirming the absence of tumour on the cut end before closing the chest wall. If the margin was positive for tumour cells, additional partial resection was mandatory. In the segmentectomy group, segmentectomy, defined as one segmental resection or a bi-segmental resection (one segment and its additional adjacent segment), with hilar and mediastinal lymph node dissection was performed. Thus, left tri-segmentectomy (S1+S2 plus S3) was considered a bi-segmental resection, but basal segmentectomy, involving the removal of all segments except the apical segment S6 in the lower lobe, was not permitted in this trial because less lung parenchymal is preserved. Dissection of the intersegmental plane was performed by stapling, energy devices, or a combination of the two, depending on the surgeon. The surgical margin was evaluated in the same manner.

In both groups, systematic or selective lymph node dissection[18,19] was mandatory, and nodal sampling was not allowed. Systematic dissection of mediastinal nodes was recommended, but selective dissection was also accepted. Whenever lymph nodal metastases were identified macroscopically during surgery, frozen sections of those lymph nodes were mandatory for diagnosis, and if found positive for tumour cells, a change in the surgical mode was required for complete resection.

The surgical procedure was converted from segmentectomy to lobectomy if lymph node metastasis was confirmed or if the surgical margin was not free of cancer. Completion of the protocol treatment was defined as pathologically complete tumour resection (R0). The definition of video-assisted procedure depended on the institution. Our definition of video-assisted procedure was flexible, such that video-assisted mini-thoracotomy was categorised as video-assisted thoracic surgery. All surgeries were performed by general thoracic surgeons certified by the Japanese Association for Chest Surgery or equivalent as an operator or first assistant.

Postoperative adjuvant chemotherapy with tegafur–uracil and cisplatin plus vinorelbine were recommended for patients with pathological stage IB and pathological stage II or IIIA, respectively. All patients were followed up for at least 5 years. Measurement of tumour markers, chest x-ray, and enhanced chest CT were performed at least every 6 months during the first 2 years and at least every 12 months for the duration of the follow-up allocation.

Outcomes

The primary endpoint was overall survival and the secondary endpoints were postoperative respiratory function (6 months and 12 months), relapse-free survival, proportion of local relapse, adverse events, proportion of completion of segmentectomy, duration of hospital stay, duration of chest tube placement, duration of surgery, amount of blood loss, and the number of automatic surgical staples used. Overall survival was defined as days from randomisation to any cause of death. Relapse-free survival was defined as days from randomisation to relapse or death from any cause, and this outcome was censored on the last day that the patient was alive. Local relapse was defined as tumour relapse in the ipsilateral thorax, which included the resection margin of the lung or bronchus, hilar lymph nodes, mediastinal lymph nodes, and malignant pleural effusion. The difference between the baseline respiratory function and the respiration rate at 6 months and 12 months after surgery was evaluated. In this trial, it was clinically expected that between-group comparisons of the reduction in median FEV1 in the limited resection (segmentectomy) group would differ by more than 10%. A postoperative early complication was defined as a complication occurring within 30 days from surgery. Complications were evaluated using the Common Terminology Criteria for Adverse Events, version 3.0. Efficacy analyses were based on intention-to-treat. Safety analyses, such as adverse events, were conducted only in patients who had lung surgery. The results of adverse events and surgical methods concerning the proportion of segmentectomy completion, duration of hospital stay, duration of chest tube placement, duration of surgery, amount of blood loss, and the number of automatic surgical stalpes used have been previously reported.[17]

Statistical analysis

To calculate sample size, the 5-year overall survival was assumed to be 90% in both groups, and the non-inferiority margin for 5-year overall survival was 85% in the segmentectomy group (corresponding to a hazard ratio [HR] of 1·54). The required sample size to confirm non-inferiority was 1030 (with an expected total number of 131 deaths), with a power of 80%, a one-sided significance level of 0·05, an accrual period of 3 years, and a follow-up period of 5 years. To account for loss at follow-up, the planned total sample size was set at 1100 patients. Two pre-specified interim analyses were conducted after accrual of half of the planned patients and after accrual completion. To keep the study at a

5% one-sided significance level, we used the Lan–DeMets alpha-spending function with an O'Brien–Fleming approach.

This trial was designed to show that segmentectomy is not inferior to lobectomy in terms of overall survival. Therefore, we expected to reach one of four conclusions on the basis of the decision criteria pre-specified in the protocol, considering correlations of overall survival, primary endpoint and respiratory function at 1 year after surgery, and key secondary endpoints in terms of invasiveness (appendix p 38).

First, if segmentectomy was non-inferior and superior to lobectomy with statistical significance in the primary endpoint, we would conclude that segmentectomy should be the new standard treatment. If the upper limit of the CI with multiplicity adjustment for HR estimated by a stratified Cox proportional hazards model was less than 1, superiority was confirmed. Second, if segmentectomy was non-inferior but not superior to lobectomy with statistical significance in the primary endpoint, and segmentectomy was superior to lobectomy in postoperative respiratory function at 1 year after surgery, with a difference of more than 10% in median reduction of FEV1 between the groups, we would conclude that segmentectomy should be the new standard treatment. However, on the basis of a comprehensive review of the other endpoints, we would determine whether lobectomy could remain as one of the standard treatments. Third, if segmentectomy was non-inferior but not superior to lobectomy with statistical significance in the primary endpoint, and segmentectomy was not superior to lobectomy in terms of postoperative respiratory function at 1 year after surgery, we would conclude that lobectomy should remain the standard treatment. However, on the basis of a comprehensive review of the other endpoints, we would determine whether segmentectomy could be considered one of the standard treatments. Fourth, if segmentectomy was not non-inferior and not superior to lobectomy in the primary endpoint and the other endpoints, we would conclude that lobectomy should remain the standard treatment.

Pre-specified subgroup analysis of overall survival was performed according to investigator assessment using a Cox proportional hazards model that included trial regimen, subgroup, and the treatment-by-subgroup interaction term. Subgroup categories with less than 20 deaths were excluded from the analysis.

Overall survival and relapse-free survival were estimated using the Kaplan–Meier method. For the primary analysis, a stratified Cox regression model with two stratification factors was used in the randomisation (histological type [adenocarcinoma or others] and sex) in terms of overall survival, because of the small number of events. Comparisons for this proportion were performed using Fisher's exact test. Wilcoxon's rank-sum test was used to compare postoperative respiratory function at 6 months and 12 months. One-sided p values were calculated for the primary analysis, whereas all other analyses were two-sided. All statistical analyses were performed using SAS (version 9.4).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 10, 2009, and Oct 21, 2014, 1319 patients from 70 institutions in Japan (JCOG, n=44; WJOG, n=26; figure 1) were registered for the study. Of these patients, 1106 patients were randomly assigned at the second registration to receive either lobectomy (n=554) or segmentectomy (n=552). 213 patients were excluded at the secondary registration, mainly because of non-malignant disease diagnosed from intraoperative frozen sections, followed by unspecified histology, hilar or mediastinal nodal involvement found at thoracotomy, and severe pleural adhesion or incomplete lobulation. The characteristics of the two groups were well balanced (table 1). Of the 1106 enrolled patients, 583 (52·7%) patients were men, 422 (38·2%) patients were aged 70 years or older, 968 (87·5%) patients had adenocarcinoma, and 923 (83·5%) patients had pathological stage IA disease (seventh TNM classification). The median tumour diameter was 1·6 cm (range 0·6–2·0), and 553 (50·0%) patients had a consolidation-to-tumour ratio of 1·0. With respect to the pathological nodal status, 1038 (93·9%) patients' cancers were pathological nodal factor (pN)0, 33 (3·0%) were pN1, and 32 (3·0%) were pN2. The complete resection score was R0 in 1099 (99·4%) patients, R1 in three (0·3%), and R2 in two (0·2%). R2 patients were excluded because of macroscopically unresectable tumours, and R1 patients were included in this trial because of microscopically unresectable tumours that did not always result in relapse after surgery. In the segmentectomy group, 22 patients were switched to lobectomies, due to hilar or mediastinal nodal metastasis identified after randomisation in 16 patients, insufficient surgical margins in four patients, intraoperative intrapulmonary metastasis found in the same lobe in one patient, and intraoperative finding deemed technically difficult of segmentectomy in one patient. Additionally, one patient received wide wedge resection due to severe adhesion and pulmonary fibrosis. Three patients had to have a reoperation due to a positive or insufficient surgical margin and pathological incomplete resection; one patient had a positive surgical margin due to micropapillary extension of the tumour, whereas the other two patients had a negative but insufficient surgical margin (<2 cm) based on permanent pathological diagnosis.

Regarding adjuvant therapy, 39 patients received tegafur–uracil, 11 patients received cisplatin plus vinorelbine, and 17 patients received other adjuvant

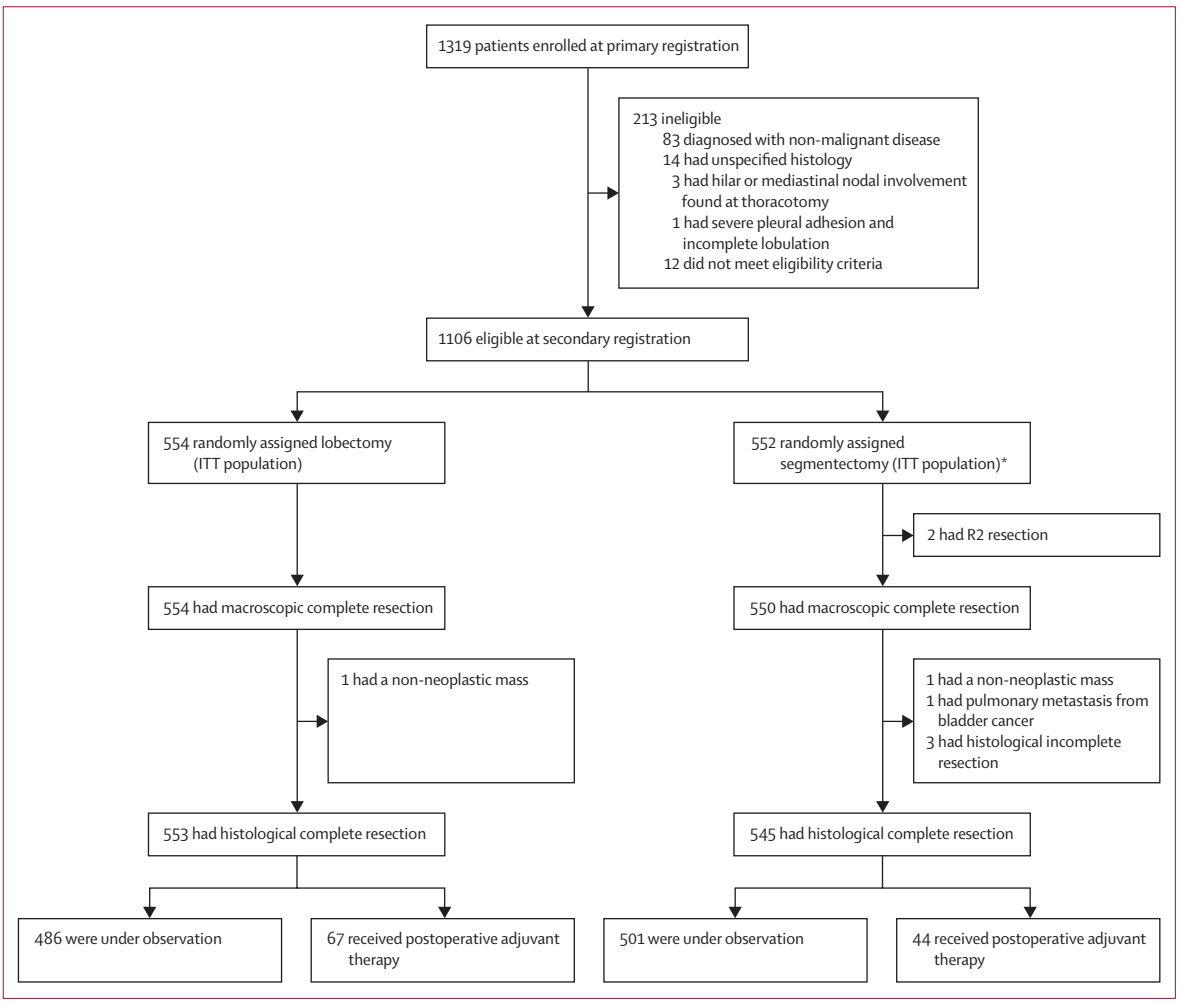

Figure 1: **Trial profile**
Patients under observation were routinely followed up without treatment until relapse. ITT=intention-to-treat. *In the segmentectomy group, 22 patients were switched to lobectomies and one patient received wide wedge resection (see Results).

therapy in the lobectomy group. In the segmentectomy group, 22 patients received tegafur–uracil, 13 patients received cisplatin plus vinorelbine, and 12 patients received other adjuvant therapy.

Immediate adverse events—complications occurring within 30 days from surgery—were previously reported.[17] One or more intraoperative complications of grade 2 or worse occurred in six (1%) patients who had a lobectomy and in nine (2%) patients who had a segmentectomy.[17] No 30-day or 90-day mortality was observed. One or more postoperative complications of grade 2 or worse occurred at similar frequencies in both groups: in 142 (26%) patients who had a lobectomy and 148 (27%) patients who had a segmentectomy.[17] We previously reported that complex segmentectomy was defined as one that required cutting of two or more intersegmental planes.[17] Multivariable analysis showed that predictors of pulmonary complications, including air leak and empyema (grade ≥2), were complex segmentectomy (*vs* lobectomy; odds ratio [OR] 2·07, 95% CI 1·11–3·88; p=0·023) and a pack-year smoking history of 20 or more (2·61, 1·14–5·97; p=0·023).[17] Cutting of two or more intersegmental planes makes segmentectomy more technically difficult than lobectomy, even for certified thoracic surgeons.

Figure 2 shows the overall survival and relapse-free survival for all randomly assigned patients. At a median follow-up of 7·3 years (range 0·0–10·9), the 5-year overall survival was 91·1% (95% CI 88·4–93·2) for lobectomy and 94·3% (92·1–96·0) for segmentectomy (HR 0·663, 95% CI 0·474–0·927; one-sided p<0·0001 for non-inferiority, p=0·0082 for superiority). The 5-year relapse-free survival was 87·9% (95% CI 84·8–90·3) for lobectomy and 88·0% (95% CI 85·0–90·4) for segmentectomy (HR 0·998, 95% CI 0·753–1·323). Improved overall survival was observed consistently across all predefined subgroups, especially in patients who were men, were aged 70 years or older, had solid

	Lobectomy group (n=554)	Segmentectomy group (n=552)*
Age, years	67 (35–85)	67 (32–83)
Sex		
Female	261 (47·1%)	262 (47·5%)
Male	293 (52·9%)	290 (52·5%)
ECOG performance status		
0	541 (97·7%)	542 (98·2%)
1	13 (2·3%)	10 (1·8%)
Smoking history		
Yes	308 (55·6%)	308 (55·8%)
No	246 (44·4%)	244 (44·2%)
Pack years		
≥20	239 (77·6%)	251 (81·5%)
<20	67 (21·8%)	55 (17·9%)
Unknown	2 (0·6%)	2 (0·6%)
Comorbidities		
Presence/absence	275 (49·6%)/ 279 (50·4%)	270 (48·9%)/ 282 (51·1%)
1/2/3/more comorbidities	173 (31·2%)/ 77 (13·9%)/25 (4·5%)	164 (29·7%)/ 77 (13·9%)/29 (5·3%)
Respiratory disease	25 (4·5%)	31 (5·6%)
Cerebrovascular disease	6 (1·1%)	9 (1·6%)
Cardiovascular disease	23 (4·2%)	30 (5·4%)
Liver dysfunction	12 (2·2%)	11 (2·0%)
Renal dysfunction	1 (0·2%)	2 (0·4%)
Hypertension	169 (30·5%)	156 (28·3%)
Diabetes	49 (8·8%)	56 (10·1%)
Other disease	115 (20·8%)	125 (22·6%)
Whole-tumour diameter, cm	1·6 (0·6–2·0)	1·6 (0·6–2·0)
CTR		
0 to ≤0·25	1 (0·2%)	0 (0%)
0·25 to ≤0·5	62 (11·2%)	73 (13·2%)
0·5 to <1	208 (37·6%)	194 (35·1%)
1	283 (51·1%)	285 (51·6%)
FEV1, mL	2260 (1110–4760)	2280 (1010–4900)
FVC, mL	3050 (1370–5990)	3095 (1590–5940)
Pathological type		
Adenocarcinoma	501 (90·4%)	502 (90·9%)
Squamous cell carcinoma	38 (6·9%)	37 (6·7%)
Others	15 (2·7%)	13 (2·4%)
(Table 1 continues in next column)		
(Continued from previous column)		
TNM classification (7th edition)		
pT1a/pT1b	427 (77·1%)/ 51 (9·2%)	453 (82·1%)/ 35 (6·3%)
pT2a/pT2b/pT3	71 (12·8%)/ 0 (0%)/4 (0·7%)	59 (10·7%)/ 1 (0·2%)/2 (0·4%)
Unknown pT status	1 (0·2%)	2 (0·4%)
pN0/pN1/pN2	522 (94·2%)/ 16 (2·9%)/15 (2·7%)	516 (93·5%)/ 17 (3·1%)/17 (3·1%)
Unknown pN status	1 (0·2%)	2 (0·4%)
pM0/pM1a/pM1b	553 (99·8%)/ 0 (0%)/0 (0%)	549 (99·5%)/ 0 (0%)/1 (0·2%)
Unknown pM status	1 (0·2%)	2 (0·4%)
pIA/pIB	455 (82·1%)/ 64 (9·2%)	468 (84·8%)/ 46 (8·3%)
pIIA/pIIB	15 (2·7%)/ 3 (0·5%)	18 (3·3%)/ 1 (0·2%)
pIIIA/pIV	16 (2·9%)/0 (0%)	18 (3·1%)/1 (0·2%)
Unknown p stage	1 (0·2%)	2 (0·4%)
Nodal dissection		
No dissection	0 (0%)	1 (0·2%)
Hilar	9 (1·6%)	17 (3·1%)
Mediastinal, systematic	221 (39·9%)	182 (33·0%)
Mediastinal, selective	324 (58·5%)	352 (63·8%)
Video-assisted thoracic surgery		
Yes	491 (88·7%)	495 (89·7%)
No	63 (21·3%)	57 (20·3%)
Complete resection		
R0/R1/R2	554 (100%)/ 0 (0%)/0 (0%)	550 (99·6%)/ 0 (0%)/2 (0·4%)
Operation time, min	174 (68–567)	201 (90–462)
Blood loss, mL	45 (0–900)	50 (0–800)

Data are n (%) or median (range). CTR=consolidation-to-tumour ratio. ECOG=Eastern Cooperative Oncology Group. FEV1=forced expiratory volume in s. FVC=forced vital capacity. p=pathological. pM=pathological metastasis. pN=pathological nodal factor. pT=pathological tumour factor. *The segmentectomy group included one wide wedge resection and 22 lobectomies, which were converted from segmentectomies.

Table 1: **Patient characteristics on enrolment**

tumours, and had non-adenocarcinomas in the segmentectomy group (figure 3). We confirmed the results for overall survival and relapse-free survival using per-protocol and as-treated sensitivity analyses (appendix 3–6).

The locoregional and distant sites of the first relapse are listed in the appendix (7–8). Significantly more locoregional relapses occurred in patients who had segmentectomy (n=58, 11%) than in those who had lobectomy (n=30, 5%; p=0·0018); however, the total relapse pattern, including patients who had distant relapse plus those who had both distant and logoregional relapse, was similar in the segmentectomy and lobectomy groups.

Table 2 summarises the causes of death among the enrolled patients. Slightly more patients died due to other diseases in the lobectomy group than in the segmentectomy group. Furthermore, other cancer-related deaths, including second primary lung cancer, were more frequent in patients who had a lobectomy (n=31, 6%) than in those who had a segmentectomy (n=12, 2%). Furthermore, the number of patients who died of respiratory or cerebrovascular causes was slightly higher in the lobectomy group than in the segmentectomy group. However, the incidences of second cancers were

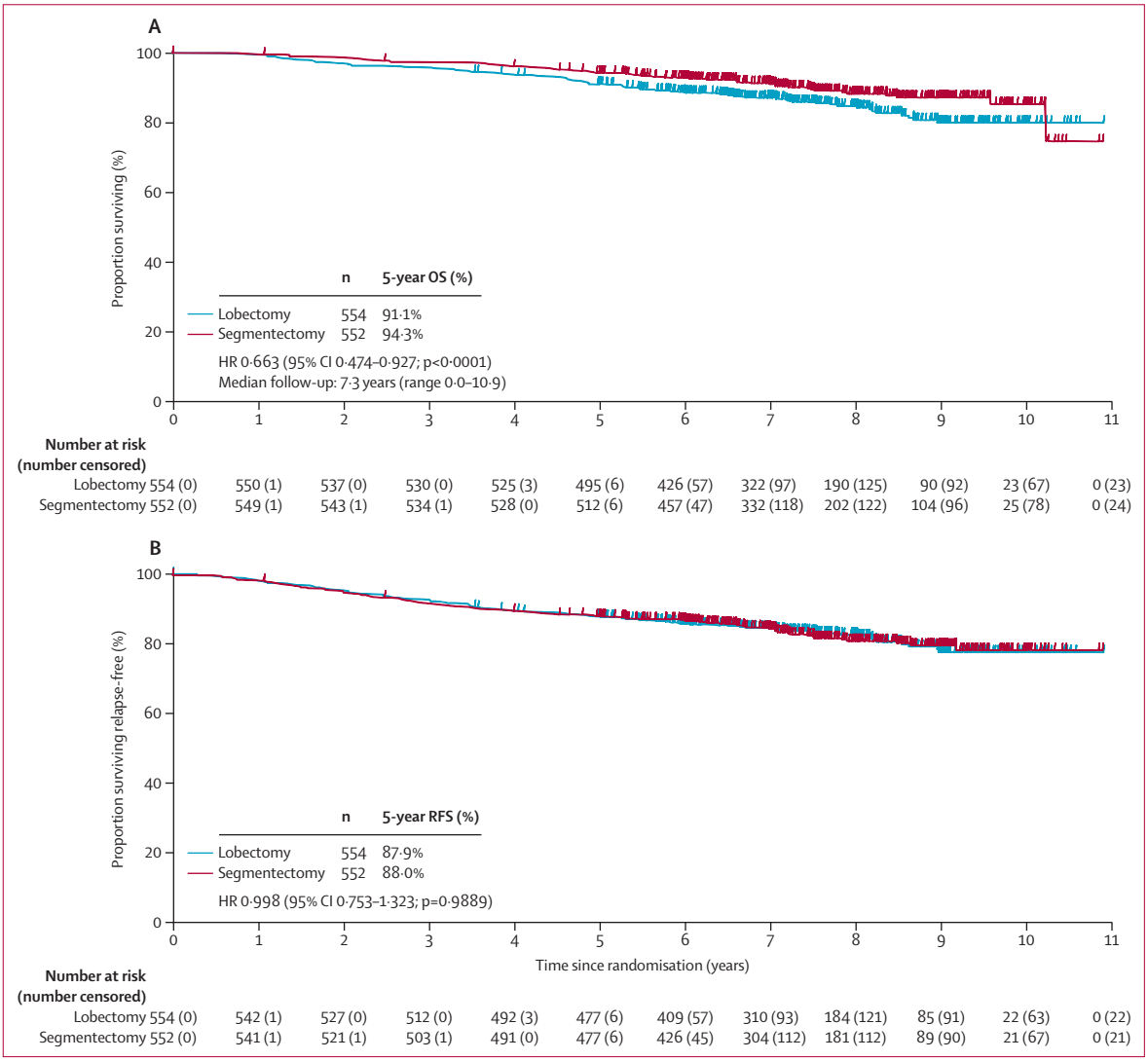

Figure 2: **Kaplan–Meier estimates of overall survival (A) and relapse-free survival (B)**
HR=hazard ratio. OS=overall survival. RFS=relapse-free survival.

similar (88 [15·9%] in the lobectomy group *vs* 84 [15·2%] in the segmentectomy group). Among second cancers, the incidences of second primary lung cancer were 36 versus 43 and other cancers were 70 versus 69 in the lobectomy group and the segmentectomy group, respectively. The incidences of carcinomas in situ were also similar (appendix pp 9–10).

Among the patients with relapse, 18 (49%) of 37 patients in the lobectomy group were alive at the 5-year follow-up (range 0·3–9·0; however, in the segmentectomy group, 35 (68%) of 51 patients were alive at the same time point (at median time to relapse, 2·5 years and 2·7 years [range 0·0–9·2], respectively). 80% (35 of 44) of patients with tumour relapse received treatment for relapse in the lobectomy group, whereas in the segmentectomy group, 93% (62 of 67) of patients who had relapsed received intensive treatment, including reoperation in 13 patients, radiotherapy in 13 patients, chemotherapy in 32 patients, and chemoradiotherapy in four patients. Regarding second primary lung cancer, additional intensive resections were performed in 32 (89%) of 36 patients with second primary lung cancer in the segmentectomy group compared with 19 (63%) of 30 in the lobectomy group (appendix 11–12).

The median reductions in FEV1 were 10·4% (range 4·7–16·6) at 6 months and 8·5% (3·5–14·8) at 12 months for segmentectomy (p<0·0001), and 13·1% (7·0–20·5) at 6 months and 12·0% (5·6–18·8) at 12 months for lobectomy (p<0·0001; appendix 13–14). Differences in the proportions of median FEV1 reduction between the segmentectomy and lobectomy groups were 2·7% at 6 months and 3·5% at 12 months, which did not reach the predefined threshold for clinical significance of 10% at 1 year follow-up.

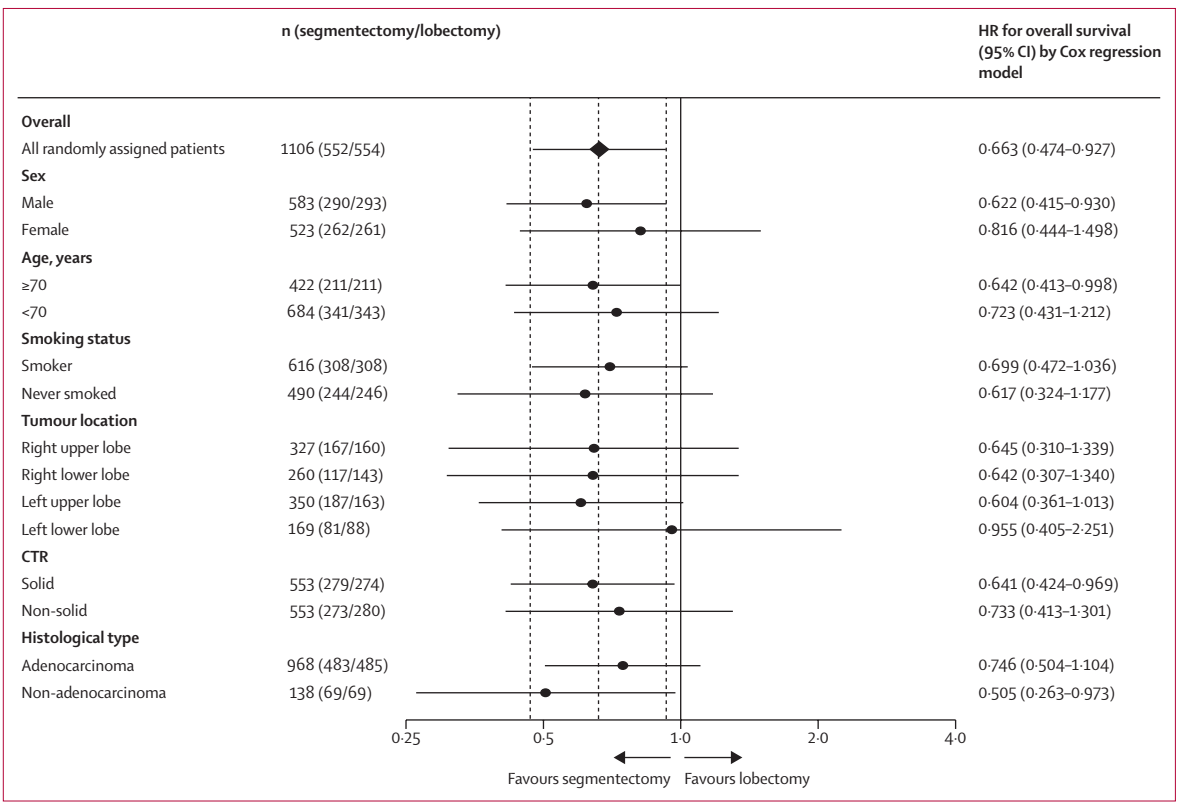

Figure 3: **Subgroup analyses of overall survival**
The middle vertical dashed line indicates the median, and the outer dashed lines indicate the 95% CI for the overall HR (all patients). An HR less than 1 implies a lower risk of overall survival after segmentectomy versus lobectomy. CTR=consolidation-to-tumour ratio. HR=hazard ratio.

Discussion

Our study showed segmentectomy to be non-inferior and superior to lobectomy with regards to overall survival. Therefore, in accord with our pre-defined decision criteria, we concluded that segmentectomy should be the standard surgical procedure, rather than lobectomy, for patients with small-sized (≤2 cm, consolidation-to-tumour ratio >0·5) peripheral NSCLC, even though we did not find the expected evidence of superiority in postoperative respiratory function in the segmentectomy group. The superiority of segmentectomy to lobectomy in terms of overall survival was consistent across all predefined subgroups. However, locoregional relapses occurred more frequently in the segmentectomy group, although no significant difference was reported in the overall relapse-free survival. This finding was somewhat unexpected. Death from other cancers (including second primary lung cancer), respiratory disease, and cerebro-vascular disease, occurred more frequently in the lobectomy group than in the segmentectomy group. By contrast, the incidences of second other cancers and second primary lung cancers in both groups were similar, and incidences of carcinomas in situ were also similar. We additionally assessed types of comorbidities. No significant differences in comorbidities, including those related to respiratory, cerebrovascular, and cardiovascular disease, were observed between the two groups at the time of enrolment. Excessive deaths in the lobectomy group were attributed to more deaths due to cancers in other organs and respiratory or cerebrovascular diseases.

Despite a two-fold increase in local relapses that was probably due to lesser resection in the segmentectomy

	Lobectomy group (n=554)	Segmentectomy group (n=552)
Total deaths	83	58
Lung cancer death	28	26
Other death	52	27
Other cancer (including second primary lung cancer)	31	12
Non-malignant disease	21	15
Respiratory disease	8	4
Cerebrovascular disease	7	2
Cardiovascular disease	4	4
Other diseases	2	5
Unknown	3	5

141 patients died during the follow-up period. *At median follow-up of 7·3 years (range 0·0–10·9).

Table 2: **Summary of causes of death during follow-up***

group, more patients survived in this group during the 5-year follow-up than in the lobectomy group. We found that additional intensive resections and therapies for treating relapse or second primary lung cancer were performed more frequently in patients after segmentectomy compared with lobectomy. We speculate that segmentectomy, which preserves more lung parenchymal than does lobectomy, might have contributed to the more extensive treatment for not only relapse of the primary lung cancer and second primary lung cancer but also possibly for other cancers and other lethal disease that might be present, resulting in overall survival being significantly exceeded, despite the higher local relapse rate in this trial. Attribution of the increased number of deaths in the lobectomy group to non-malignant causes, including respiratory disease and cerebrovascular disease, is not directly supported by these data.

Intraoperative lymph node assessment and identification of the appropriate surgical margins are both essential if thoracic surgeons select sublobar resection, even in early-stage lung cancer.[20] Although 22 segmentectomies were converted to lobectomy in the segmentectomy group due to lymph node metastasis, insufficient surgical margins, and other reasons, local relapses, including 11 surgical margins and two bronchial stumps, continued to occur in the segmentectomy group. Furthermore, in the first relapse, ipsilateral or contralateral mediastinal lymph nodal relapse occurred more frequently in the segmentectomy group than in the lobectomy group. Thus, a more detailed analysis of radiological and pathological findings and surgical procedures in each case is required to obtain information on how to judiciously select patients and to understand how to improve segmentectomies.

This study has some limitations. Detailed evaluation of treatment intensities for miscellaneous second primary cancers was not feasible; such assessments are complicated. As this study was an unblinded trial, unavoidable bias probably existed; however, the outcomes that were used could be objectively assessed. Furthermore, reasons for improved survival among patients who had segmentectomy versus those who had lobectomy still need to be clarified.

Although lung cancer is a highly malignant disease, according to our results, patients with clinical stage IA small-sized peripheral NSCLC who receive surgery with curative intent, including lobectomy or segmentectomy, can expect a 5-year overall survival of 90% or higher. The differences in survival outcomes and causes of death between the two groups of this study were not associated with the primary NSCLC, but were instead due to a second primary cancer or other diseases. Compared with segmentectomy, lobectomy for patients with small-sized peripheral early-stage NSCLC appeared to be more invasive (judged by long-term survival) than was formerly believed. Thoracic surgeons need to pursue not only a curative intent but also a surgical procedure that is the least invasive, and reserve the possibility of more extensive treatment for upcoming life-threatening diseases, such as second primary cancer, respiratory disease, or cerebrovascular disease. We believe that attention to these aspects of treatment will lead to long-term survival benefits for all patients with early-stage lung cancer.

To our knowledge, JCOG0802/WJOG4607L is the first and only randomised trial to show the superiority of segmentectomy over lobectomy in overall survival for early-stage lung cancer. These results indicate that segmentectomy should be the standard surgical procedure for patients with small-sized peripheral NSCLC.

Contributors

HS, MO, MT, RN, TM, S-IW, and HA designed the trial and interpreted the data. KS, KA, TA, JO, IY, HI, NO, MY, and NI recruited patients and collected the data. MW, KN, HF, and SN analysed the data. The first draft of the manuscript was prepared by HS and was based on the authors' comments on the manuscript outline. Thereafter, the first draft was critically reviewed and revised by all authors. All authors had full access to the data, verified the underlying data, and contributed to data interpretation and review, revision, and approval of the report.

Declaration of interests

HS reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from MSD, Boehringer Ingelheim, Ethicon, Covidien, Chugai Pharmaceutical, Astellas Pharma, Fujifilm Medical, and Bristol Myers Squibb. MO reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from MSD, Ethicon, Covidien, Chugai Pharmaceutical, ONO Pharmaceutical, AstraZeneca, and Bristol Myers Squibb. MT reports grants from Boehringer Ingelheim Japan, MSD, AstraZeneca, ONO Pharmaceutical, MSD, Bristol Myers Squibb, and Eli Lilly Japan; consulting fees from AstraZeneca, Chugai Pharmaceutical, MSD, and Novartis; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Johnson & Johnson Japan, AstraZeneca, Eli Lilly Japan, Chugai Pharmaceutical, Taiho Pharmaceutical, Medtronic Japan, ONO Pharmaceutical, MSD, Bristol Myers Squibb, and Teijin Pharmaceutical. KS reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Boehringer Ingelheim, Ethicon, Covidien, Chugai Pharmaceutical, Astellas Pharma, Intuitive, and Bristol Myers Squibb. KA reports consulting fees from TAIHO pharma, Olympus medical, AstraZeneca, Covidien, Johnson & Johnson, and Care-net; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from MSD, Mochida Pharmaceutical, Johnson & Johnson, Covidien, Chugai Pharmaceutical, Bristol Myers Squibb, Eli-lilly, and Teijin healthcare. IY reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from MSD, Boehringer Ingelheim, Ethicon, Covidien, Chugai Pharmaceutical, Astellas Pharma, Fujifilm Medical, and Bristol Myers Squibb. NI reports grants from AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, Pfizer, Taiho Pharmaceutical, Eli Lilly, ONO Pharmaceutical, Bristol-Meyers Squibb, MSD, Nihon Medi-Physics, Teijin Pharmaceutical, Kyowa Kirin, Sanofi, Eisai, Astellas Pharma, Shionogi, Daiichi-Sankyo, and Roche Diagnostics; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, Pfizer, Taiho Pharmaceutical, Eli Lilly, ONO Pharmaceutical, Bristol-Meyers Squibb, MSD, Nihon Medi-physics, Teijin Pharmaceutical, Johnson & Johnson, and Olympus Corporation. MW reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Chugai Pharmaceutical and Johnson & Johnson. HF reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Chugai Pharmaceutical. TM reports

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Data sharing

Qualified researchers can request access to study documents (including the clinical study report, the study protocol with any amendments, and the statistical analysis plan) that support the methods and findings reported in this Article.

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