Long-term survival outcome after lobectomy in patients with clinical T1 N0 lung cancer

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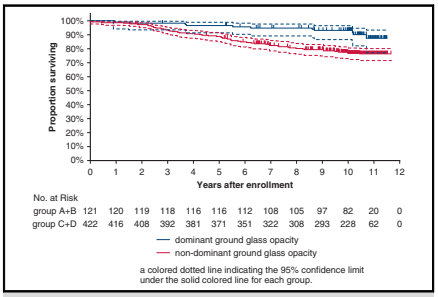
ABSTRACT

Objective: The aim of this study was to assess long-term outcomes after lobectomy in patients with clinical T1 No lung cancer based on thin-section computed tomography.

Methods: We collected the data of patients with pathological adenocarcinoma who had undergone lobectomy. The patients were categorized into 4 groups according to a consolidation tumor ratio and tumor size. Groups A and B included tumors with consolidation tumor ratio ≤0.5 and size ≤3 cm. Group A consisted of tumors ≤2 cm. Group B consisted of the remaining tumors. Groups C and D consisted of tumors with consolidation tumor ratio >0.5. Group C consisted of those with tumors ≤2 cm and Group D consisted of tumors of size 2 to 3 cm. The 10-year overall survival and recurrence-free survival rates were examined.

Results: Among the 543 patients, the 10-year overall survival was 80.4% and the 10-year recurrence-free survival rate was 77.1%. The 10-year overall survival for group A was 94.0%, 92.7% for group B, 84.1% for group C, and 68.8% for group D, and the 10-year recurrence-free survival rate for each group was 94.0%, 89.0%, 79.7%, and 66.1%, respectively. Group A + B showed better overall survival than group C + D (hazard ratio, 2.78; 95% confidence interval, 1.45-5.06) and better 10-year recurrence-free survival (hazard ratio, 2.74; 95% confidence interval, 1.55-4.88). No patient in group A had recurrence.

Conclusions: Those patients with total tumor size ≤3 cm and consolidation tumor ratio ≤0.5 showed excellent prognosis and might be suitable candidates for sublobar resection. If noninferior survival of segmentectomy compared with lobectomy is confirmed in an ongoing Japan Clinical Oncology Group trial, segmentectomy will be included in the standard of care. (J Thorac Cardiovasc Surg 2021;161:281-90)



Clinical T1 No lung cancer with dominant ground glass opacity showed excellent prognosis.

CENTRAL MESSAGE

A 10-year follow-up analysis showed excellent prognosis after lobectomy in patients with clinical T1 No lung cancer with dominant ground glass opacity.

PERSPECTIVE

Patients with a total tumor size ≤3 cm and a consolidation tumor ratio ≤0.5 showed excellent prognosis, indicating potential candidacy for sublobar resection. If the results of the noninferior survival of segmentectomy compared with lobectomy are confirmed in a JCOG trial (data scheduled for release in 2020), segmentectomy will be included in the standard of care for this population.

See Commentaries on pages 291 and 292.

Surgery is the mainstay of treatment for early-stage lung cancer, and lobectomy is the standard procedure for stage I lung cancer.[1] However, it has been reported that some lung cancers with ground glass opacity (GGO), based on thin-section computed tomography (TSCT), will be sufficiently curable by sublobar resection.[2-9] Most lung

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Abbreviations and Acronyms

CT = computed tomography
CTR = consolidation tumor ratio
GGO = ground glass opacity
JCOG = Japan Clinical Oncology Group
OS = overall survival
TSCT = thin-section computed tomography
RFS = recurrence-free survival

Scanning this QR code will take you to the article title page to access supplementary information.

cancers with ground glass nodules are adenocarcinomas, and the appearance of a solid part of the lung tumor from TSCT is known to be closely related to pathological invasive size.[2-4,10]

The Japan Clinical Oncology Group (JCOG) Lung Cancer Surgical Study Group, conducted the JCOG0201 study, a prospective observational study designed to define the radiological criteria on TSCT that could be used to predict the pathological noninvasiveness of clinical stage IA lung cancer.[11] In the JCOG0201 study, to reject the null hypothesis that tumors ≤2 cm in size and consolidation tumor ratio (CTR) ≤0.5 are unable to predict pathologically noninvasive cancers (node negative and no vessel invasion), it was necessary for the lower limit of the 95% confidence interval (CI) of specificity for pathologically noninvasive cancers to be at least 97%, but it was not achieved. In the exploratory analysis, the point estimate of specificity for a pathological diagnosis of noninvasive adenocarcinoma was 98.7% in tumors ≤2 cm in size and a CTR ≤0.25. Thus, the JCOG Lung Cancer Surgical Study Group defined this radiological condition as radiologically noninvasive lung cancer.[11] In the 5-year follow-up, the JCOG0201 study confirmed that not only tumor size ≤2 cm and a CTR ≤0.25, but also a tumor size ≤3 cm with a CTR ≤0.5 of adenocarcinoma was associated with excellent prognosis and 5-year overall survival (OS) rates of 97.1% and 96.7%, respectively.[12] There have been few reports on 5 or more years of follow-up on early-stage lung cancer surgery with preoperative radiological information, but there are some reports of cancer recurring after 5 years postoperatively.[13,14] Therefore, long-term follow-up of patients who have undergone complete resection for lung cancer, including all radiological features is important and will provide useful information for the advancement of cancer treatment.

PATIENTS AND METHODS

JCOG0201 Study

The JCOG0201 study was a prospective, multi-institutional, observational study started in 2002. The study protocol was approved by the JCOG Clinical Trial Review Committee in 2002 and the institutional review board of each participating institution. A total of 811 patients were enrolled in this study from 31 institutions between December 2002 and May 2004. The aim of the study was to determine a definition for radiologically diagnosed early (noninvasive) lung cancer. The primary end point was the specificity for pathologically noninvasive cancers based on the radiological findings using CTR. CTR was defined as the ratio of solid component size to total size of lung tumor on TSCT. The eligibility criteria were suspected or confirmed diagnosis of lung cancer based on plain radiographic film or computed tomographic (CT) scan findings, disease diagnosed to be clinical stage IA (ie, T1 N0 M0) according to the Union for International Cancer Control fifth TNM staging system from contrast-enhanced thoracic CT, tumor center located peripherally (ie, in the outer half of the lung field) found by CT scan, at least 1 dimension of tumor measurable by TSCT, patients aged 20 to 75 years, no prior thoracotomy, feasible pulmonary lobectomy, and written informed consent obtained.

Before surgery, all patients underwent a contrast-enhanced TSCT scan with 1- to 3-mm collimation, particularly focusing on the primary tumor to estimate the size of the entire tumor, including regions with GGO and consolidation. The evaluated factors were the maximum diameters of the tumor and consolidation on the lung window. Noninvasive lung cancer was pathologically defined as a lung adenocarcinoma without nodal involvement, vascular invasion, or lymphatic invasion.

For the final diagnosis, radiological findings based on TSCT were reviewed by 6 reviewers. This centralized radiological review was conducted on patients who were preoperatively or intraoperatively diagnosed with adenocarcinoma. The CT findings concerning the maximum diameter of the tumors and consolidation on the lung window were evaluated by the 6 reviewers, and the final results were decided by consensus. The diameter of the tumor was measured in a horizontal slice of the submitted CT image. The tumor diameter was determined by the maximum axis.

Analysis Population

Of 811 patients, 559 patients had undergone at least a lobectomy, 16 of whom were excluded; 14 patients were ineligible on the basis of postoperative pathologic findings and, for 2 other patients, the maximum tumor size at the time of the central review of the radiological evaluation was unavailable. The remaining 543 patients with adenocarcinoma (67.0%) were analyzed according to the radiological definition for predicting invasive and noninvasive lung cancer using tumor size and CTR. The median number of patients enrolled at each institution was 9 (range, 1-93).

The 543 patients were divided into the following 4 groups using the cutoff definition of a tumor size of 2 or 3 cm with a CTR of 0.25 or 0.5 based on preoperative TSCT: group A, tumor size ≤2 cm and CTR ≤0.25; group B, tumor size ≤3 cm and CTR ≤0.5 excluding group A; group C, tumor size ≤2 cm and CTR >0.5; and group D, tumor size >2 cm and CTR >0.5. Figure 1 illustrates the 4 groups according to tumor size and CTR. Clinicopathological factors, the 10-year OS, and recurrence-free survival (RFS) were compared between groups. Additionally, the number of recurred patients including early (<5 years) and late (≥5 years) recurrence was calculated for each group.

Statistical Analysis

OS was defined as the interval from the date of enrollment to the date of death from any cause. For surviving patients, OS was censored at the last contact date. RFS was defined as the interval from enrollment to initial recurrence or death from any cause. For surviving patients with no recurrence, RFS was censored at the final follow-up visit.

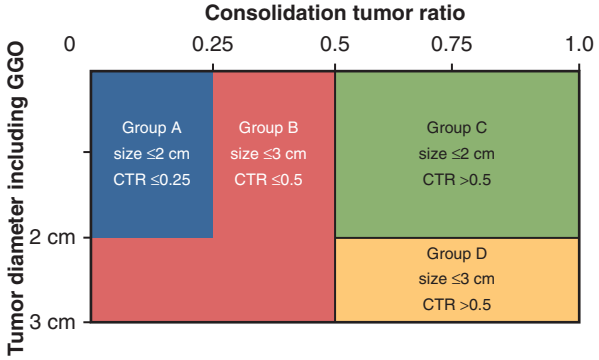


FIGURE 1. Group classifications. Four groups were created according to total tumor diameter, including ground glass opacity (*GGO*), and consolidation tumor ratio (*CTR*). CTR was determined by consolidation size divided by total tumor diameter. Group A, tumors with CTR <0.5 and tumor size ≤2 cm with CTR <0.25; group B, tumors with CTR <0.5 excluded from group A; group C, tumors with CTR >0.5 and tumor size ≤2 cm; and group D, tumors with CTR >0.5 and tumor size 2 to 3 cm.

Recurrence was classified as locoregional, distant, or both. Locoregional recurrence was defined as recurrence within the thoracic cavity on the same side as the primary lesion, resected stump, or lung mediastinal/cervical lymph nodes. Newly emergent pulmonary nodules on the ipsilateral side were included in the classification of locoregional recurrence. Distant recurrence was defined as recurrence in the contralateral thoracic cavity or as extra-thoracic recurrence. Recurrence 5 or more years after surgery was termed late recurrence.

OS and RFS were estimated by the Kaplan-Meier method. A log-rank test was performed to compare OS and RFS between groups. The hazard ratio and 95% CIs were estimated through Cox proportional hazard model. Proportion of cumulative incidence of lung cancer recurrence was estimated by cumulative incidence function. Comparison of cumulative incidence of recurrence between groups were performed by Gray's test. The hazard ratio and 95% CI for the cumulative incidence of recurrence were estimated by Fine & Gray model. All *P* values were 2-sided. All statistical analyses were performed with SAS software, release 9.4 (SAS Institute, Inc, Cary, NC) in the JCOG Data Center.

RESULTS

Patient Characteristics

The median postoperative follow-up period was 10.1 years (interquartile range, 8.4-10.7 years). The number of patients designated to a group were 35 (6.4%) for group A, 86 (15.8%) for group B, 222 (40.9%) for group C, and 200 (36.8%) for group D. The patients' characteristics in total and for each subgroup are shown in Table 1. More than half of the patients were women (57.4%). The median

TABLE 1. Patient characteristics

Characteristic	All cases (N = 543)	Group A (n = 35)	Group B (n = 86)	Group C (n = 222)	Group D (n = 200)
Men/women	233/310	14/21 (40.0)	34/52 (39.5)	101/121 (45.5)	84/116 (42.0)
Age (y)	62 (35-75)	63 (46-75)	62.5 (44-75)	61 (35-75)	62 (37-75)
Procedure					
Pneumonectomy	1	0	0	0	1 (100)
Lobectomy	534	35 (6.6)	84 (15.0)	217 (40.6)	198 (37.1)
Bilobectomy	8	0	2 (25)	5 (62.5)	1 (12.5)
Maximum tumor size (cm)	2.00 (0.70-3.00)	1.50 (0.90-2.00)	2.20 (1.10-3.00)	1.80 (0.70-2.00)	2.50 (2.10-3.00)
≤1.0	17	5 (29.4)	0	12 (70.6)	0
>1.0-2.0	272	30 (11.0)	32 (11.8)	210 (77.2)	0
>2.0-3.0	254	0	54 (21.3)	0	200 (78.7)
Maximum consolidation size (cm)	1.50 (0-3.00)	0 (0-0.50)	0.80 (0-1.50)	1.50 (0.40-2.00)	2.10 (1.10-3.00)
≤1.0	145	35 (22.7)	69 (47.6)	41 (28.3)	0
>1.0-2.0	276	0	17 (6.2)	181 (65.6)	78 (28.3)
>2.0-3.0	122	0	0	0	122 (100)
Consolidation tumor ratio	0.83 (0-1.00)	0 (0-0.25)	0.39 (0-0.50)	1.00 (0.53-1.00)	0.96 (0.52-1.00)
Pathologic stage					
IA	460 (84.7)	34 (97.1)	84 (97.7)	195 (87.8)	147 (73.5)
IB	28 (5.2)	0	1 (1.2)	9 (4.1)	18 (9.0)
IIA	21 (4.0)	0	0	6 (2.7)	15 (7.5)
IIB	3 (0.6)	0	0	1 (0.5)	2 (1.0)
IIIA	19 (3.5)	0	1 (1.2)	4 (1.8)	14 (0.7)
IIIB	9 (1.7)	1 (2.9)	0	5 (2.3)	3 (1.5)
IV	1 (0.2)	0	0	0	1 (0.5)
Unknown	2 (0.4)	0	0	2 (0.9)	0
pN0	493 (90.8)	35 (10)	85 (98.8)	207 (93.2)	166 (83.0)
pN1	25 (4.6)	0	0	8 (3.6)	17 (8.5)
pN2	23 (4.2)	0	1 (1.2)	5 (2.3)	17 (8.5)
#11 LN metastasis	19 (3.5)	0	0	4 (1.8)	15 (7.5)
#12LN metastasis	22 (4.1)	0	0	6 (2.7)	16 (8.0)

Values are presented as n/n (%), n (%), or mean (range).

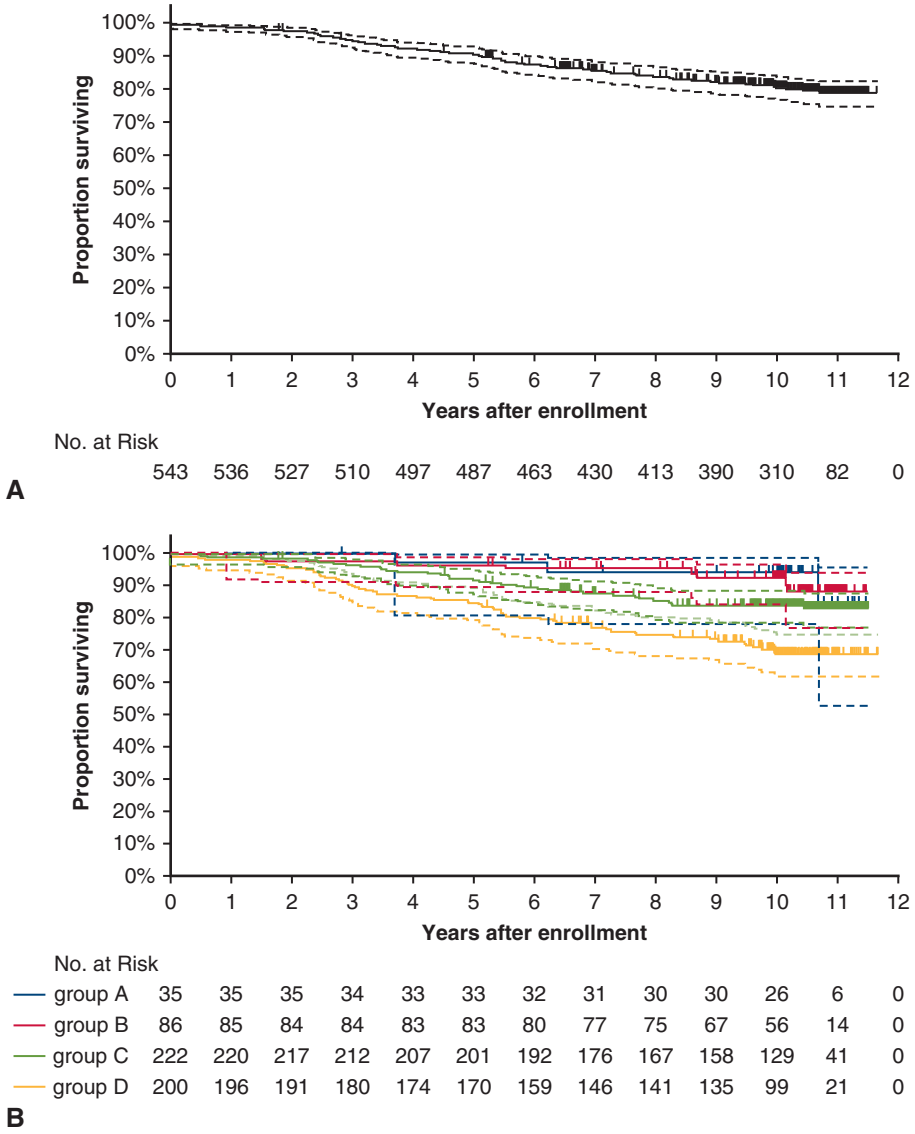


FIGURE 2. Overall survival (OS) curves. The *dotted lines* represent the 95% confidence limits. A, OS for all cases at 10 years was 80.4%. B, OS rate at 10 years for group A, 94.0%; group B, 92.7%; group C, 84.1%; and group D, 68.8%. C, OS curves of combined groups. OS curves for each combined group showed statistically significant difference (groups A + B, tumor size ≤3 cm and CTR ≤0.5 vs groups C + D tumor size ≤3 cm and CTR >0.5; $P = .0011$).

age at the time of surgery was 62 years (range, 35-75 years). These characteristics were similar for all 4 groups. Lobectomy was performed in 98.3% of cases. The mean CTR in groups C and D was 1.00 and 0.96, respectively. Most tumors in both groups were solid-type tumors without radiological GGO. The mean CTR in groups C and D differed considerably from that of groups A and B (0 and 0.39, respectively).

OS at 5 and 10 Years

The OS curves for all patients are shown in Figure 2, *A*. In total, 106 patients died. The OS at 5 and 10 years for the entire group (n = 543) was 90.4% (95% CI, 87.6%-92.6%) and 80.4% (95% CI, 76.7%-83.6%), respectively. In group A, 3 patients died and the 5-year and 10-year OS were 97.1% (95% CI, 80.9%-99.6%) and 94.0% (95% CI, 78.2%-98.5%), respectively. In group B, 8 patients died and the 5-year and 10-year OS were 96.5% (95% CI, 89.6%-98.9%) and 92.7% (95% CI, 84.3%-96.6%). In group C, 35 patients died and the 5-year- and 10-year OS were 91.8% (95% CI, 87.3%-94.8%) and 84.1% (95% CI, 78.4%-88.3%). In group D, 60 patients died and the 5-year and 10-year OS were 85.0% (95% CI, 79.3%-89.3%) and 68.8% (95% CI, 61.6%-74.9%). The OS curves showed significant difference among these 4 groups (Figure 2, *B*) ($P < .0001$).

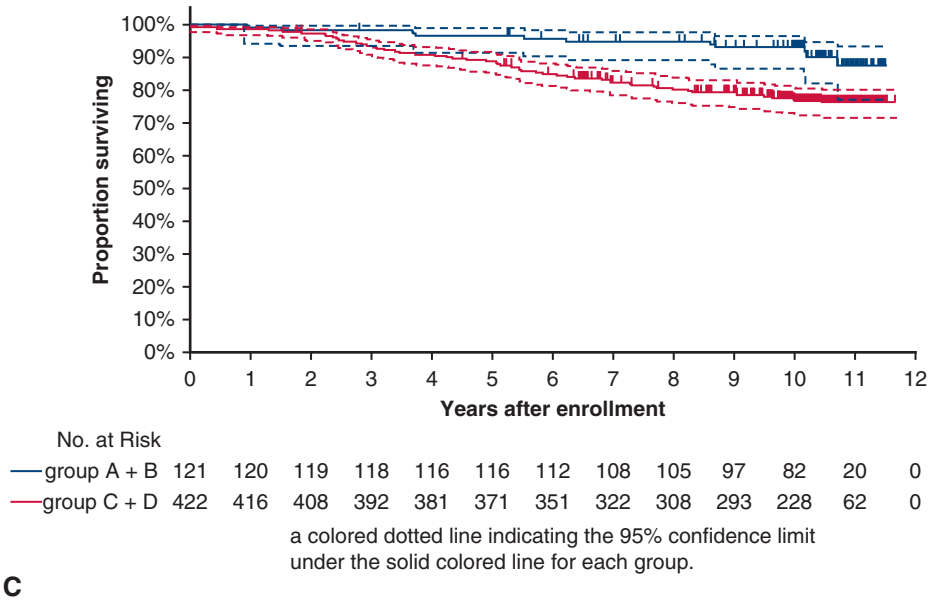


FIGURE 2. Continued.

The 5-year and 10-year OS for group A + B were 96.7% (95% CI, 91.4%-98.7%) and 93.1% (95% CI, 86.7%-96.5%), respectively. The 5-year and 10-year OS for group C + D were 88.6% (95% CI, 85.1%-91.3%) and 76.7% (95% CI, 72.3%-80.6%), respectively. The OS curves between groups A + B and C + D showed a significant difference (Figure 2, *C*) ($P = .0011$). The hazard ratio of group C + D to group A + B was 2.708 (95% CI, 1.450-5.055). In multivariable analysis adjusted by age (<70 years and ≥70 years) and sex, hazard ratio was 2.530 (95% CI, 1.353-4.731).

RFS at 5 and 10 Years

A total of 82 patients had recurrence (locoregional only, 40 patients; distant only, 25 patients; and both types, 17 patients). Among these patients, 13 had recurrence 5 or more years after surgery (ie, late recurrence). Five-year RFS and 10-year RFS in the study group were 84.5% (95% CI, 81.2%-87.3%) and 77.1% (95% CI, 73.2%-80.5%) in all patients (Figure 3, *A*).

In the group A, no recurrence was reported and the 5-year and 10-year RFS were 97.1% (95% CI, 80.9%-99.6%) and 94.0% (95% CI, 78.2%-98.5%), respectively. In the group B, 4 patients recurred, including 3 patients with locoregional recurrence and 1 patient with distant recurrence. Two patients developed late recurrence, including 1 patient with locoregional recurrence and 1 with distant recurrence. The 5-year and 10-year RFS for group B were 95.3% (95% CI, 88.1%-98.2%) and 89.0% (95% CI, 79.9%-94.1%). In group C, 33 patients recurred, including 17 patients with locoregional recurrence, 10 patients with distant recurrence, and 6 patients with both types of recurrence. Seven patients developed late recurrence, including 6 patients with locoregional recurrence and 1 with both types of recurrence. The 5-year and 10-year RFS for group C were 86.5% (95% CI, 81.2%-90.3%) and 79.7% (95% CI, 73.6%-84.5%). In group D, 45 patients recurred, including 17 patients with locoregional recurrence, 13 with distant recurrence, and 11 with both types of recurrence. Four patients developed late recurrence including 3 patients with locoregional recurrence and 1 with distant recurrence. The 5-year and 10-year RFS for group D were 75.5% (95% CI, 68.9%-80.9%) and 66.1% (95% CI, 58.9%-72.3%), respectively. The RFS curves among the 4 groups showed significant difference (Figure 3, *B*). The 5-year and 10-year RFS for group A + B were 95.9% (95% CI, 90.3%-98.3%) and 90.5% (95% CI, 83.5%-94.6%), respectively. The 5-year and 10-year RFS for group C + D was 81.3% (95% CI, 77.2%-84.7%) and 73.2% (95% CI, 68.6%-77.3%). The difference in the RFS curve between these 2 groups was significant (Figure 3, *C*) ($P = .0003$). The hazard ratio of group C + D to group A + B was 2.744 (95% CI, 1.545-4.875). In multivariable analysis adjusted by age (<70 years and ≥70 years) and sex, the hazard ratio was 2.564 (95% CI, 1.441-4.562).

Frequency of Early and Late Recurrence Relevant to Tumor Size and CTR

The cumulative incidence curve of recurrence is shown in Figure 4, *A*. At the time of postoperative 5 years, the cumulative incidence rate of recurrence was 0% in group A, 2.3% (95% CI, 0.4%-7.4%) in group B, 11.7% (95% CI, 7.9%-16.4%) in group C and 20.5% (95% CI, 15.2%-26.4%) in group D. At postoperative 10 years, the

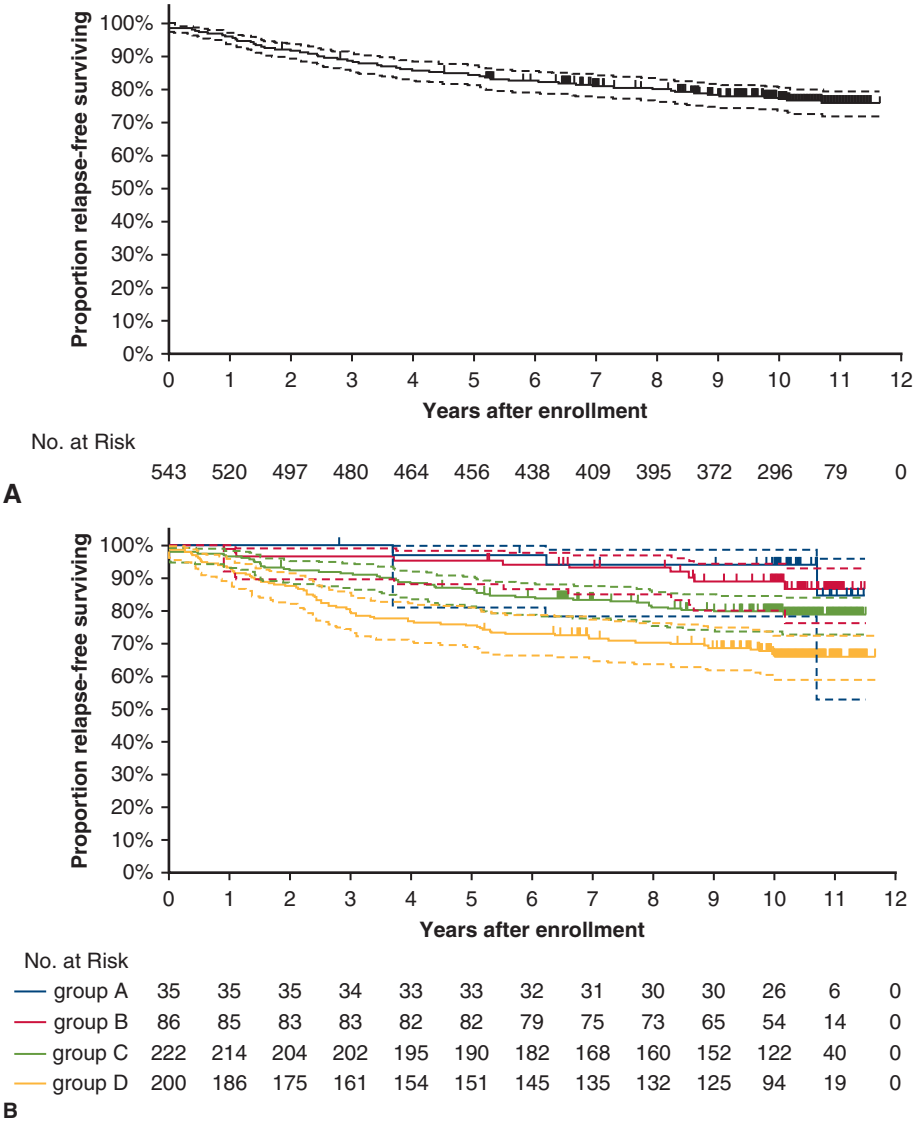


FIGURE 3. Recurrence-free survival (RFS) curves. The *dotted lines* represent the 95% confidence limits. A, RFS rate for all cases at 10 years was 77.1%. B, RFS rate at 10 years was 94.0% for group A, 89.0% for group B, 79.7% for group C, and 66.1% for group D. RFS curves for each group showed statistically significant difference ($P < .0001$). C, RFS curves for each combined group showed statistically significant difference (group A + B, tumor size ≤3 cm and consolidation tumor ratio [CTR] ≤0.5 vs group C + D, tumor size ≤3 cm and CTR >0.5; $P = .0003$).

rate was 0% in group A, 4.9% (95% CI, 1.6%-11.1) in group B, 14.7% (95% CI, 10.3%-19.7%) in group C, and 22.5% (95% CI, 17.0%-28.6%) in group D.

Within 5 years after surgery, the recurrence was noted in none for group A (35 cases), 2 for group B (86 cases), 26 for group C (222 cases), and 41 for group D (200 cases). A comparison of the 4 groups showed that the proportion of recurrence was higher in the subgroup with the higher CTR. Figure 4, *B*, shows the distribution of the recurrent cases according to tumor size and CTR in 10 years. All of the recurrent cases had a tumor size of ≥1 cm, and most of them showed a CTR of 1. Recurrence was noted more frequently in patients with a CTR of >0.5, especially in those with a CTR of >0.8; a higher CTR tended to be associated with a higher proportion of recurrence.

Five or more years after surgery, the recurrence for each group was none for group A, 2 cases for group B, 7 cases for group C, and 4 cases for group D. The most frequent type of late recurrence was locoregional in 10 of all 13 cases. Figure 4, *C*, shows the distribution of recurrence according to size and CTR 5 or more years after surgery. The tumor size of lung cancer in all recurred patient was >1.5 cm, but the proportion of recurrence did not associate with larger tumor sizes. Most of the cases of late recurrence had a higher CTR.

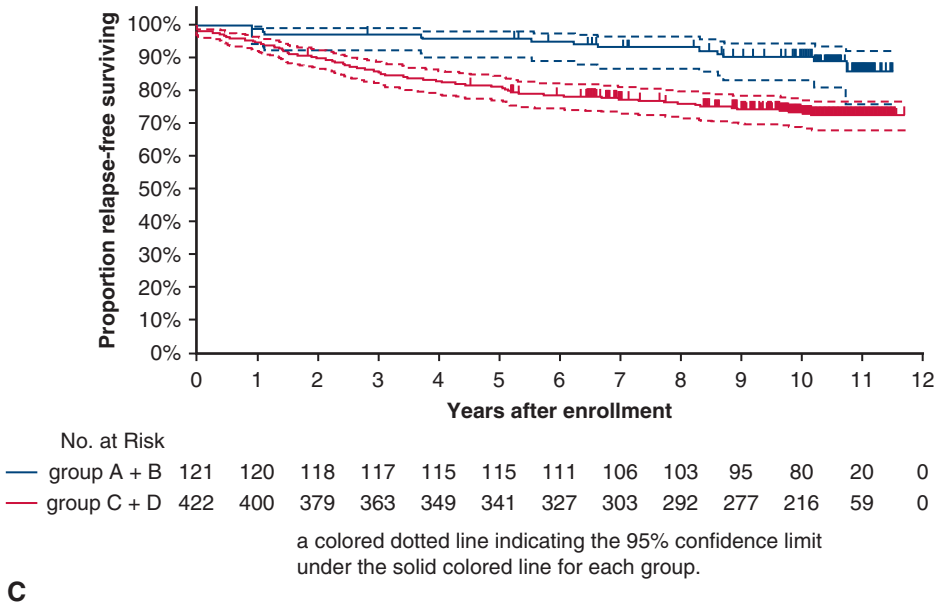


FIGURE 3. Continued.

DISCUSSION

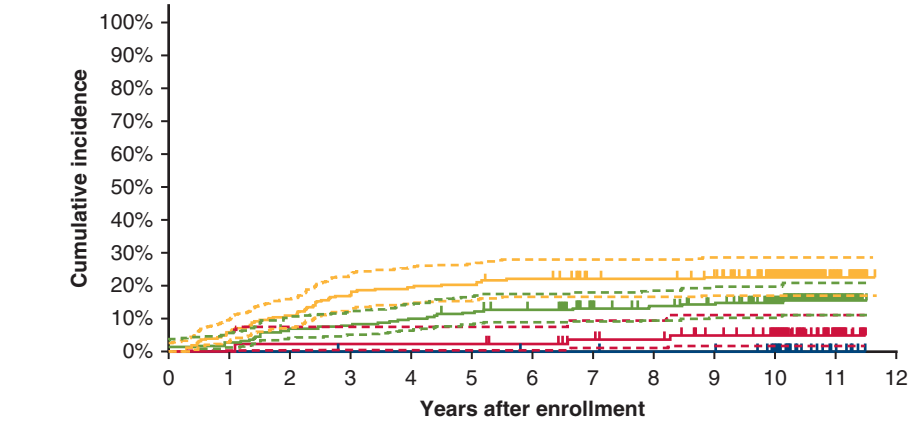
This is the first prospective trial of a long-term follow-up of 10 years after lobectomy for patients in Japan with clinical T1 N0 lung cancer. This study shows the results of a long-term prognosis after lobectomy and the characteristics leading to recurrence. Follow-up data for patients with a tumor size of ≤2 cm and a CTR of ≤0.25 showed no recurrence after more than 10 years after surgery. In addition, patients with total tumor size ≤3 cm and CTR ≤0.5 showed excellent prognosis. In terms of 10-year OS rate after lobectomy, patients of tumor size ≤2 cm and a CTR of ≤0.25 and tumor size 2 to 3 cm and CTR ≤0.5 showed similar good outcome (Figure 5). This indicates that these patients might be suitable candidates for sublobar resection.

Patients with tumors sized ≤2 cm and CTRs ≤0.25 showed no recurrence in the 10 years of follow-up. For this small size tumor, wide wedge resection is easy to perform. Based on the results of excellent prognosis at the 5-year follow-up of the JCOG0201 study, a prospective clinical study (JCOG0804/WJOG4507L) confirming the efficacy of wide wedge resection with sufficient surgical margin has already been carried out.[15] This trial has also planned to conduct a 10-year follow-up.

On the other hand, the long-term outcome for lung cancer patients with a tumor between ≤3 and >2 cm and a CTR between ≤0.5 and >0.25 (4 patients recurred [3.3%]) was nearly equivalent to the outcome for patients with tumors sized ≤2 cm and CTRs ≤0.25. This excellent prognosis is consistent with the results of a previous study.[12] Of these 4 patients with recurrence, 2 died of lung cancer associated with distant and mediastinal lymph-node metastases. The other 2 cases had pulmonary metastases but were still alive at the end of the follow-up period. Because they survived for a prolonged period after recurrence, the possibility of a second primary lung cancer cannot be ruled out. Patients who met this definition and were treated by lobectomy had quite excellent outcomes. Therefore, lobectomy may not be necessary for these patients considering that the less invasive nature of their tumors met the criteria. Regarding tumors sized up to 3 cm, it is harder to have enough of a surgical margin than tumors up to 2 cm in size. Thus, segmentectomy may be a suitable procedure if an adequate surgical margin is obtained. The JCOG1211 trial is ongoing to confirm the safety and efficacy of segmentectomy for this population and the main analysis is scheduled to be reported in 2020.[16]

Patients with a CTR >0.5 clearly had a higher rate of recurrence than those with a CTR ≤0.5. In a patient cohort with tumor size ≤2 cm and CTR >0.5, a phase III trial has been ongoing to confirm the noninferiority of segmentectomy compared with lobectomy (JCOG0802/WJOG4607L).[17] Tumor size >2 cm and CTR >0.5 have been found to associate with recurrence and sublobar resection is not suitable for tumors of this size.

The examination of long-term prognosis only in pathologic stage I in the JCOG0201 study showed that patients with positive vascular and/or pleural invasion tended to have a poor prognosis.[18] A tumor of size ≤2 cm and CTR <0.25 found from preoperative TSCT can almost rule out such cases with positive vascular and/or pleural invasion so, in this study, the prognosis was clearly excellent. On the other hand, frequent recurrence was seen in tumors sized ≤2 cm and CTR >0.5. In CALBG140503, a multi-institutional phase III study to compare lobectomy and

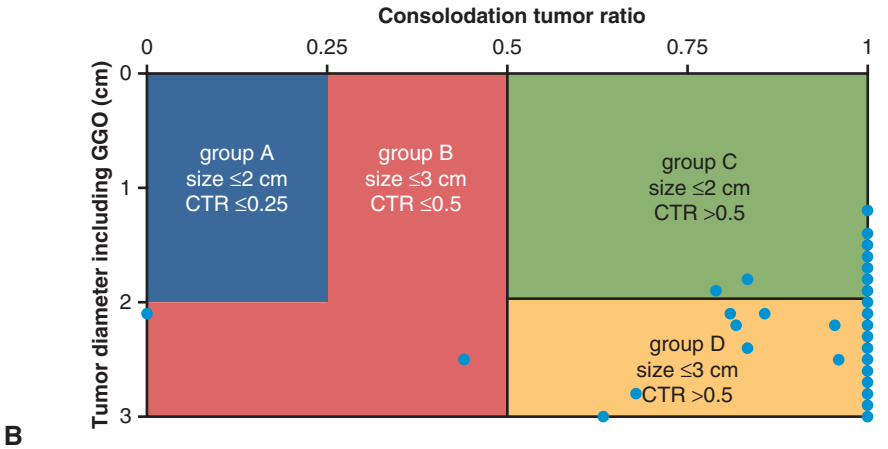


No. at Risk

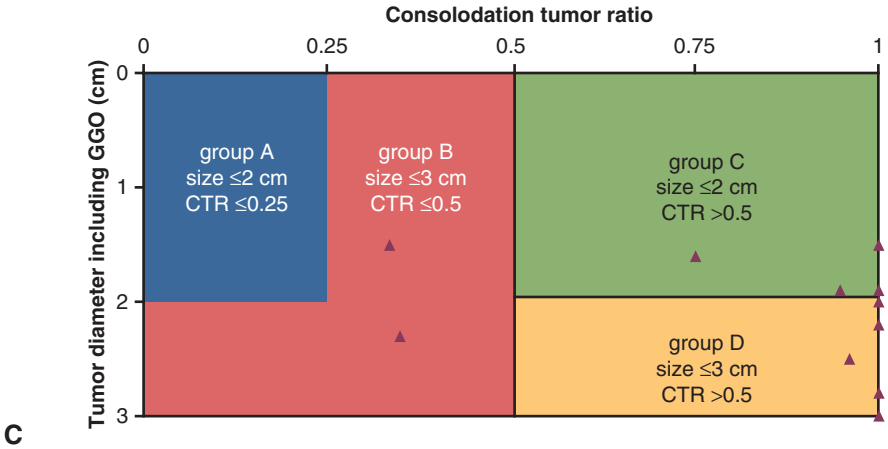
group A	35	35	35	34	33	33	32	31	30	30	26	6	0
group B	86	85	83	83	82	82	79	75	73	65	54	14	0
group C	222	214	204	202	195	190	182	168	160	152	122	40	0
group D	200	186	175	161	154	151	145	135	132	125	94	19	0

A

a colored dotted line indicating the 95% confidence limit under the solid colored line for each group.



B



C

FIGURE 4. Frequency of recurrence in the 4 groups according to size and consolidation tumor ratio (*CTR*). The *dotted lines* represent the 95% confidence limits. A, Cumulative incidence curves of recurrence of 4 groups. (Gray's test $P < .0001$). B, Recurrent cases within 5 years postoperatively (n = 69). *Blue circles* indicate recurrent cases. There was much overlap of cases at CTR = 1. C, Recurrent cases after 5 years (n = 13) (*red triangles*). Most of the cases of late recurrence had a high CTR but some exist with a lower CTR. *GGO*, Ground glass opacity.

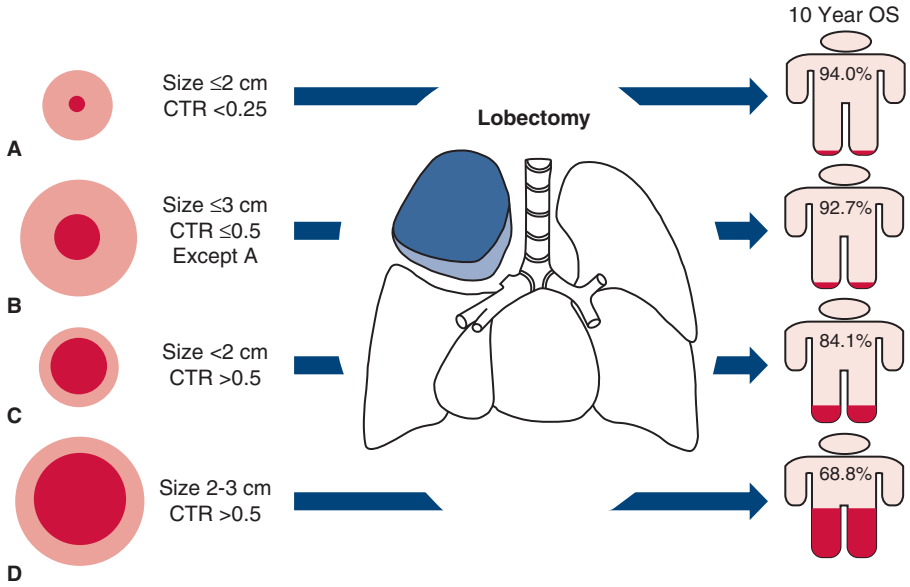


FIGURE 5. Long-term survival outcome after lobectomy in patients with clinical T1 N0 lung cancer. The 10-year overall survival of group A, tumor size ≤2 cm, and consolidation tumor ratio (*CTR*) <0.25 and group B, tumor size ≤3 cm, and CTR <0.5 showed excellent prognosis. For tumors with CTR >0.5, larger size >2 cm showed worse outcome than <2 cm. *OS*, Overall survival.

sublobar resection for tumors sized ≤2 cm, only total tumor size, and not consolidation size, was used as the allocation factor.[19] This can influence the outcome after surgery, and the results of a clinical trial need to be interpreted carefully.

Usually, most cases of recurrence develop within 5 years after surgery, and so the follow-up period is often up to 5 years after surgery.[20] However, the risk of recurrence continues after more than 5 years after surgery with a reported rate of recurrence of 4.8% to 18%.[13,14] In this study, late recurrence—5 years or more after surgery—was found in 15.9% of all recurrent cases among patients with clinical stage IA lung cancer who had, at the least, undergone a lobectomy. When assessing the efficacy of lung cancer treatment, the follow-up period needs to be carefully considered.

The results of our study suggest that the preoperative estimation of CTR to evaluate the malignant potential of a tumor would be useful when selecting candidates for sublobar resection from the viewpoint of long-term prognosis. Ongoing clinical trials conducted by the JCOG Lung Cancer Surgical Group are expected to provide further clarification in the next several years.

Limitations

It is extremely difficult to distinguish between pulmonary metastases and newly emergent lung nodules of secondary lung cancer after surgery. In some patients with a single pulmonary nodule, such lesions were resected and diagnosed pathologically to distinguish them. However, the final evaluation of recurrence or secondary lung cancer was made on the basis of the judgment of the clinicians at each facility in the case of the same pathological type. Some of the recurrence data in this report are estimated recurrence rates rather than true recurrence rates.

CONCLUSIONS

From a 10-year follow-up after lobectomy, none of the cases of radiologically noninvasive lung cancer, defined as tumor size ≤2 cm with CTR ≤0.25, recurred. A tumor size ≤3 cm with CTR ≤0.5 also associated with excellent outcomes. If noninferior survival of segmentectomy compared with lobectomy is confirmed in an ongoing JCOG trial projected to be reported in 2020, segmentectomy will be included in the standard of care for this population.

Conflict of Interest Statement

Dr Ito had relevant financial activities outside the submitted work and received seminar presentation fees from Johnson and Johnson, Covidien Japan, Novartis, and AstraZeneca. Dr Suzuki had relevant financial activities outside the submitted work and received research grants and lecture fees from Ethicon, Medtronic, Taiho, and Eli Lilly. Dr Aokage had relevant financial activities outside the submitted work and received editorial supervisory and seminar presentation fees from Covidien Japan; video presentation, seminar presentation, and product development consultation fees from Johnson and Johnson; writing and seminar presentation fees from Taiho Pharma; lecture presentation and chair fees from Ono Pharmaceutical Co, Ltd, and lecture presentation fees from Mochida Pharmaceutical Co, Ltd, MSD, and AstraZeneca. All other authors have nothing to disclose with regard to commercial support.

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