Received: 4 November 2020 | Accepted: 19 January 2021

DOI: 10.1111/1759-7714.13876

ORIGINAL ARTICLE

WILEY

Predictive factors of recurrence after resection of subsolid clinical stage IA lung adenocarcinoma

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Funding information
National Research Foundation of Korea (NRF), Grant/Award Number: grant number: 2018R1D1A1B07043364

Abstract

Background: Ongoing studies are currently investigating the extent of surgical resection required for subsolid cancers. This study aimed to investigate the predictive factors related to recurrence in patients with clinical stage IA subsolid cancer who underwent either lobectomy or sublobar resection.

Methods: This was a prospective multicenter observational study conducted in eight qualifying university teaching hospitals between April 2014 and December 2016. A total of 173 patients with subsolid nodules pathologically confirmed to have primary lung adenocarcinoma and stage IA disease were included in the final analysis. All patients underwent lobectomy, segmentectomy, or wedge resection performed by experienced thoracoscopic surgeons at each site. The surgical procedure was chosen based on the decision of the surgeons involved. The primary endpoint was time to recurrence (TTR).

Results: The study population was 43.9% (76 of 173) male with a mean age of 60.7 years. During the median follow-up period of 5.01 years, nine patients (5%) experienced disease recurrence. In the multivariable analysis, tumor size (size ≥2 cm) (hazard ratio: 73.717, 95% confidence interval [CI]: 3.635–895.036; $p < 0.001$) and stage IA3 (hazard ratio: 62.010, 95% CI: 2.837–855.185; $p < 0.001$) were independent predictors of tumor recurrence. When analyzing the recurrence outcome in patients according to surgical procedure, no significant difference was found in TTR among the three groups (i.e., lobectomy, segmentectomy, and wedge resection; $p = 0.99$).

Conclusions: Patients with radiologically subsolid lung adenocarcinoma measuring <3 cm could be candidates for sublobar resection instead of lobectomy.

KEYWORDS
lobectomy, lung adenocarcinoma, segmentectomy, subsolid nodule, wedge resection

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INTRODUCTION

Computed tomography (CT) is being increasingly used for lung cancer screening, and findings of incidentally detected subsolid nodules (either pure ground-glass nodule [GGN] or part-solid nodule [PSN]) are increasing.[1–3] Patients with stage IA adenocarcinoma observed as subsolid nodules have been reported to have a better prognosis as compared with those that are pure solid adenocarcinoma.[4,5]

Lobectomy demonstrates a great advantage over sublobar resection and has been naturally recommended as the standard surgical procedure for early-stage non-small cell lung cancer (NSCLC).[6] However, there is renewed interest in conducting sublobar resection in selected cases with early-stage NSCLC. Several studies have shown that sublobar resection achieves equivalent surgical outcomes to those of lobectomy in clinical stage IA subsolid lung cancer.[7–9] Previous guidelines from the Fleischner Society recommend the management of persistent subsolid nodules; however, the optimal extent of surgical resection and mediastinal lymph node dissection has yet to be determined.[10, 11] This study aimed to investigate predictive factors related to the recurrence in patients with clinical stage IA subsolid cancer who underwent either lobectomy or sublobar resection.

METHODS

Patient selection

This study was a prospective multicenter observational study conducted in eight qualifying university teaching hospitals. Between April 2014 and December 2016, 250 patients with subsolid nodules indicated for surgical resection under video-assisted thoracoscopic surgery (VATS) were screened and enrolled from the eight sites according to the inclusion criteria. Of the 250 patients from the LOGIS trial,[12] we prospectively enrolled all eligible patients according to the inclusion criteria of the present study as follows: (i) aged more than 20 years, (ii) pulmonary lesion with a GGN component of greater than 50%, (ii) a lesion size of less than 3 cm, (iv) clinical stage IA disease (according to the TNM classification scheme, eighth edition), and (v) pathologically confirmed as having primary lung adenocarcinoma or adenocarcinoma in situ (AIS). The exclusion criteria were as follows: (i) an unwillingness or inability to provide consent, (ii) disease pathologically confirmed as benign or something other than primary lung adenocarcinoma, (iii) patients with synchronous subsolid or pure solid tumors, (iv) patients who were classified as not having stage IA disease, and (v) follow-up loss. The study protocol was approved by the institutional review boards or ethics committees at each participating center and all participants provided their written informed consent.

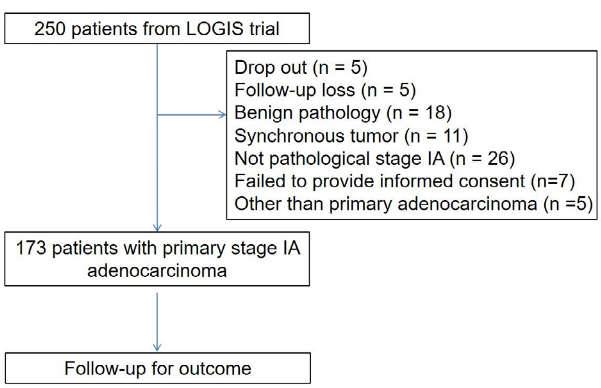

FIGURE 1 Flow chart of patient selection

Finally, 173 patients with subsolid nodules pathologically confirmed to have primary lung adenocarcinoma and pathological stage IA disease (according to the TNM classification scheme, eighth edition), were included for final analysis (Figure 1). All patients underwent thoracoscopic surgery conducted by experienced thoracoscopic surgeons at each site. All data entry, data management, and analyses were coordinated or performed at a data-coordinating center. In our database, the following clinical and pathological characteristics were recorded: age, sex, clinical history including hypertension, diabetes mellitus, hepatitis, cancer (other than lung cancer), surgery (other than lung cancer surgery), heart disease, and smoking, maximum tumor size including GGN component, solid size, stage based on the eighth edition of the TNM classification scheme, surgical method, and pathological type including histological subtype.

Chest CT examinations

All preoperative chest CT examinations were performed using a (at minimum) 16-slice multi-detector single- or dual-source CT scanner. A chest CT was performed in all eligible participants in a craniocaudal direction during inspiration without contrast material enhancement by using the following scan parameters: tube voltage, 120 kV; tube current, 100 mAs, section thickness and interval, 1.0 and 1.0 mm, respectively.

Image and pathology analysis

All image analyses were performed at the data-coordinating center by an experienced board-certificated thoracic radiologist with 10 years of experience in chest CT imaging who was blinded to the clinical and histological findings. TNM staging was based on the eighth edition of the TNM classification proposed by the International Association of Study of Lung Cancer (IASLC).[13]

Subsolid nodules were distinguished depending on the presence of GGN and solid components. Pure GGN was defined as a nodule without a solid component and a PSN was defined as a lung lesion with both a GGN and a solid component.[11] The maximum diameter on the single largest dimension (axial, sagittal, or coronal images) was measured

TABLE 1 Baseline characteristics of 173 patients with pathological stage IA primary lung adenocarcinoma

Variables	Lobectomy (*n* = 63)	Segmentectomy (*n* = 41)	Wedge resection (*n* = 69)	*p*-value
Sex (male %)	23 (36.5)	19 (46.3)	34 (49.2)	0.191
Age (years)	59.84 ± 8.72	61.12 ± 10.68	61.37 ± 11.49	0.534
Hypertension, n (%)	21 (33.3)	17 (41.5)	20 (28.9)	0.627
Diabetes, n (%)	10 (15.8)	9 (21.9)	9 (13.0)	0.590
Hepatitis, n (%)	3 (4.7)	3 (7.3)	5 (7.2)	0.597
Cancer[aa], n (%)	12 (19.0)	15 (36.6)	26 (37.6)	0.039
Surgery[bb], n (%)	29 (46.1)	28 (68.3)	42 (60.8)	0.139
Heart disease, n (%)	4 (6.3)	9 (21.9)	5 (7.2)	0.962
Smoking status				0.222
Current/former, n (%)	16 (25.4)	16 (39.0)	32 (46.4)	
Never, n (%)	47 (74.6)	25 (61.0)	37 (53.6)	
Tumor size, mm	16.88 ± 5.07	15.64 ± 3.47	14.44 ± 5.15	0.019
Solid component, mm	7.24 ± 4.94	4.60 ± 3.24	4.19 ± 3.87	<0.001
Whole tumor volume, mm^3	2408.66 ± 2319.01	1805.94 ± 1372.85	1687.53 ± 2018.48	0.025
Pure GGN	9 (14.3)	11 (26.8)	23 (33.3)	0.029
Part solid nodule	54 (85.7)	30 (73.2)	46 (66.7)	0.025
Location, n (%)				0.007
Right upper lobe	21 (33.3)	8 (19.5)	23 (33.3)	
Right middle lobe	9 (14.3)	0	5 (7.2)	
Right lower lobe	9 (14.3)	6 (14.6)	19 (27.5)	
Left upper lobe	17 (26.9)	21 (51.3)	15 (21.9)	
Left lower lobe	7 (11.2)	6 (14.6)	7 (10.1)	
p-stage				0.066
Stage IA1	12 (19.0)	7 (17.1)	23 (33.3)	
Stage IA2	40 (63.5)	32 (78.0)	41 (59.5)	
Stage IA3	11 (17.5)	2 (4.9)	5 (7.2)	
Histology type				0.259
MIA	12(19.0)	10(24.4)	21 (30.4)	
Invasive adenocarcinoma	51(81.0)	31(75.6)	48 (69.6)	

Note: Values are presented as mean ± standard deviation or patient number with (%).
Abbreviations: GGN, ground-glass opacity; MIA, minimally invasive adenocarcinoma.
[a]History of cancer included all cancers other than lung cancer.
[b]History of surgery included surgery other than lung cancer surgery.

on a lung window and recorded for determining the size of the solid component and whole target nodule. For quantitative volume analysis, commercialized software (AVIEW Research) was used to measure the whole tumor volume. The lesion segmentation was performed on a lung window setting (width, 1500 HU; level, −600 HU) images. The whole volume of interest (VOI) of the target lesion was isolated by semi-automatic segmentation. If the segmented border of the target lesion was incorrect, the reviewer manually corrected the VOI according to the border of the target lesion on slices including the target lesion on axial images. When the observer approved the definition of the margin, the program automatically calculated the tumor volume.

The postoperative pathological diagnosis was made according to the IASLC/American Thoracic Society/European Respiratory Society classification as adenocarcinoma in situ, minimally invasive adenocarcinoma, or invasive adenocarcinoma which was further divided into lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, solid predominant, and invasive mucinous adenocarcinoma. The predominant pattern was defined as the pattern with the largest percentage (not necessarily 50% or higher).[14]

Follow-up protocol

All patients were followed up from the day of surgery. They were examined physically and underwent chest CT covering cervical to abdominal lesions every 3–6 months for the first two years. Thereafter, they were examined physically and by chest CT every six months during the third year and then once per year for subsequent years up to five years. The primary endpoint of the present study was time to recurrence

(TTR), which was defined as the time from the day of surgery to the day of first recurrence. Local recurrence was defined as disease recurrence at the surgical resection margin, ipsilateral hilum, and/or mediastinum. All other sites of failure were considered distant recurrences. Patients who died from other causes during the study period were considered to be censored with no event when calculating TTR. Observations were censored at the last follow-up at which the patient was alive or lost to follow-up.

Statistical analysis

The differences between categorical variables were analyzed by chi-squared test. Differences between continuous variables were analyzed by the one way ANOVA test or Kruskal-Wallis test. A Cox proportional-hazards regression model was used to evaluate the risk factors for lung cancer-related recurrence among the different surgical methods. Statistically significant findings on univariate analysis were subsequently included in the multivariate analysis. Only variables with p-values of less than 0.20 during univariate analysis were added to the final multivariate models to prevent model overfitting. From the Cox proportional-hazards model, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with using Firth correction. Concordance (C) statistics were used to compare the predictive prognosis among the models.[15] Survival curves were estimated by the Kaplan–Meier method according to the three different surgical groups.

TABLE 2 Univariate analysis using a Cox proportional-hazards regression model

	Time-to recurrence			
Characteristic	**HR**	**95% CI**		***p* value**
Age	1.056	0.982	1.135	0.143
Sex (male)	0.623	0.157	2.475	0.503
Hypertension	1.689	0.351	8.134	0.513
Diabetes	1.406	0.176	11.249	0.748
Hepatitis	1.093	0.049	24.501	0.952
Cancer	1.643	0.341	7.912	0.536
Surgery	5.897	0.739	47.230	0.095
Heart disease	0.890	0.022	8.871	0.523
Smoking[a]	1.501	0.402	5.601	0.546
Tumor size, cm				
Size < 2 cm	1 (ref)			
Size ≥ 2 cm	63.404	3.161	971.714	<0.001
Subsolid nodule subtype				
Pure GGN	1 (ref)			
Part-solid nodule	2.093	0.259	16.938	0.489
Solid size, mm				
Size < 6 mm	1 (ref)			
Size ≥ 6 mm	2.245	0.559	9.012	0.254
Tumor volume (*100), mm^3				
Volume < 10	1 (ref)			
Volume ≥ 10	11.012	0.559	220.872	0.017
Surgery				
Lobectomy	1 (ref)			
Segmentectomy	0.839	0.153	4.613	0.840
Wedge resection	0.864	0.190	3.935	0.851
Stage				
Stage IA1	1 (ref)			
Stage IA2	0.867	0.005	25.373	0.623
Stage IA3	47.787	2.211	832.707	<0.001
Histology type				
MIA	1 (ref)			
Invasive adenocarcinoma	2.723	0.341	21.776	0.345

Abbreviations: AIS, adenocarcinoma in situ; CI, confidence interval; GGN, ground-glass opacity; HR, hazard ratio; MIA, minimally invasive adenocarcinoma.
[a]smoking included all former and current smokers.

TABLE 3 Multivariate analysis using a Cox proportional-hazards regression model

	Time-to recurrence			
Model 1	**HR**	**95% CI**		***p* value**
Surgery				
Lobectomy	1 (ref)			
Segmentectomy	0.839	0.153	4.613	0.840
Wedge resection	0.864	0.190	3.935	0.851
	Time-to recurrence			
Model 2	**HR**	**95% CI**		***p*-value**
Surgery				
Lobectomy	1 (ref)			
Segmentectomy	2.368	0.443	12.664	0.304
Wedge resection	1.241	0.27	5.704	0.765
Tumor size, cm				
Size < 2 cm	1 (ref)			
Size ≥ 2 cm	73.717	3.635	895.036	<0.001
	Time-to recurrence			
Model 3	**HR**	**95% CI**		***p*-value**
Surgery				
Lobectomy	1 (ref)			
Segmentectomy	0.935	0.174	5.017	0.932
Wedge resection	1.176	0.258	5.373	0.822
Tumor volume (*100), mm^3				
Volume < 10	1 (ref)			
Volume ≥ 10	11.447	0.559	234.245	0.016
	Time-to recurrence			
Model 4	**HR**	**95% CI**		***p*-value**
Surgery				
Lobectomy	1 (ref)			
Segmentectomy	1.06	0.188	5.982	0.948
Wedge resection	1.146	0.239	5.494	0.864
Solid size, mm				
Size < 6 mm	1 (ref)			
Size ≥ 6 mm	2.319	0.547	9.84	0.254
	Time-to recurrence			
Model 5	**HR**	**95% CI**		***p*-value**
Surgery				
Lobectomy	1 (ref)			
Segmentectomy	3.882	0.641	23.519	0.141
Wedge resection	1.258	0.27	5.867	0.751
Stage				
Stage IA1	1 (ref)			
Stage IA2	0.841	0.005	22.722	0.599
Stage IA3	62.01	2.837	855.185	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

Their comparisons were performed by using the log-rank test. Here, p-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using commercial software (R version 3.3.2 from the R Foundation for Statistical Computing and MedCalc version 12 from MedCalc).

TABLE 4 C-statistics for the prediction of disease recurrence

Model	C-statistics for model with disease recurrence		
	C-index	Difference (95% CI)	Model comparison *p*-value
Model 1: Surgery	0.516	NA	NA
Model 2: Surgery + tumor size	0.718	0.202 (−0.015, 0.419)	0.041
Model 3: Surgery + tumor volume	0.565	0.049 (−0.018, 0.117)	0.754
Model 4: Surgery + solid size	0.523	0.007 (−0.075, 0.089)	0.871
Model 5: Surgery + stage	0.740	0.224 (−0.079, 0.527)	0.032

Note: Model comparison between Model 1 vs. Model 2, Model 1 vs. Model 3, Model 1 vs. Model 4 and Model 1 vs. Model 5.

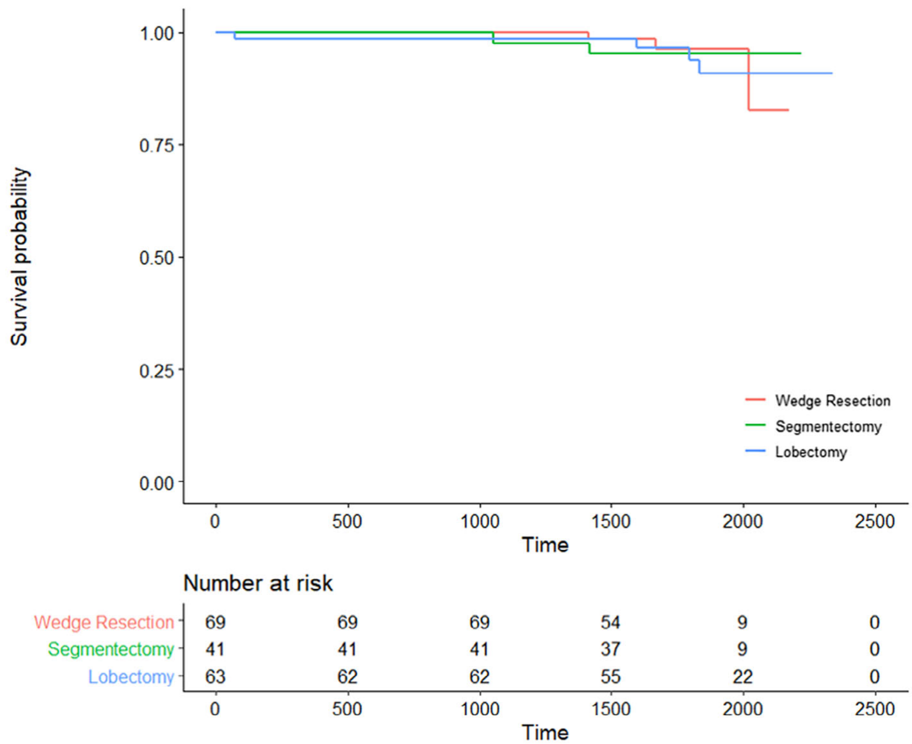

FIGURE 2 Time to recurrence in patients with adenocarcinoma presented as subsolid nodule stratified according to surgical procedure

RESULTS

Patient characteristics

Overall, the study population consisted of 173 patients with clinicopathological stage IA primary lung adenocarcinoma; among these, 43.9% (76 of 173) were male with a mean age of 60.7 years. The clinical characteristics of the patient population according to surgical procedures are listed in Table 1. In the lobectomy group, history of cancer was significantly lower compared to segmentectomy and wedge resection groups ($p = 0.039$). The tumor size, solid component and volume were higher in the lobectomy group than segmentectomy and wedge resection groups (all $p < 0.001$). The lobectomy group had higher part-solid nodules than segmentectomy and wedge resection groups ($p < 0.001$), whereas the wedge resection group had higher pure GGN than segmentectomy and lobectomy groups ($p < 0.001$).

Recurrence outcome

During the median follow-up period of 5.01 years (interquartile range: 4.33–5.45 year), nine patients experienced disease recurrence: ipsilateral or contralateral lung ($n = 6$), brain ($n = 2$), and LN (mediastinum) ($n = 1$). Disease recurrence was confirmed by means of biopsy or surgery in four (44%) patients, while the remaining five (56%) patients were confirmed by means of CT, MRI or PET scan.

When patients were divided into lobectomy, segmentectomy, and wedge resection subgroups, three patients with disease recurrence underwent wedge resection, two underwent segmentectomy, and four underwent lobectomy. The pathological TNM stage of the nine patients with disease recurrence was stage IA3. All patients were confirmed to have invasive adenocarcinoma (five with papillary predominant and four with acinar predominant).

In a univariate Cox regression analysis, tumor size (size ≥ 2 cm) (HR: 63.404, 95% CI: 3.161–971.714; $p < 0.001$), tumor volume (volume ≥ 10[*100] mm3) (HR: 11.012, 95% CI: 0.559–220.872; p = 0.017) and stage IA3 (HR: 47.787, 95% CI: 2.211–832.707; $p < 0.001$) were deemed predictors of disease recurrence (Table 2). To determine the prognostic predictors between surgical procedures, we constructed several models with additional parameters. All variables met a proportional-hazards assumption. In models 2 and 5, tumor size (size ≥ 2 cm) (HR: 73.717, 95% CI: 3.635–895.036; $p < 0.001$) and stage of IA3 (HR: 62.01, 95% CI: 2.837–855.185; $p < 0.001$) were independent predictors of tumor recurrence (Table 3).

The incremental benefit of additional parameters was assessed using C-statistics as shown in Table 4. With regard to disease recurrence, the benefits of tumor size (model 2) and stage (model 5) were significant as compared with the surgical procedure (model 1) (C-index: 0.718 vs. 0.516, and 0.740 vs. 0.516, respectively; all $p < 0.05$).

When analyzing the recurrence outcomes among patients according to surgical procedures, the log-rank test revealed no significant difference in RFS among the three groups (i.e., lobectomy, segmentectomy, and wedge resection; p = 0.99) (Figure 2).

DISCUSSION

In this study, we found that radiologically subsolid lung cancer in patients measuring less than 3 cm had an excellent surgical outcome regardless of surgical procedures, subsolid nodule subtype and solid component size. In addition, the TTR was not significantly different among the various surgical procedures (i.e., whether the patients underwent lobectomy, segmentectomy, or wedge resection). The findings in this study may help to guide surgical procedure selection in patients with clinical stage IA adenocarcinoma observed as subsolid nodules.

On the basis of the current evidence, the standard surgical treatment for primary lung cancer is still lobectomy, even though several trials to date have explored the use of sublobar resection for lung cancer.[7–9, 16–18] One previous study using a national cancer database in the United States demonstrated that patients who underwent sublobar resection for stage IA NSCLC had poorer oncological outcomes.[19] On the other hand, a previous meta-analysis demonstrated that patients with tumors measuring less than 2 cm located peripherally with favorable histopathology and with GGN on CT imaging might be candidates for sublobar resection instead of lobectomy.[20] Our study results were consistent with these findings. In our study, there was no recurrence among patients with tumors that were smaller than 2 cm regardless of surgical procedures, subsolid nodule subtype and solid component size. We found that tumor size larger than 2 cm and stage IA3 were independent risk factors of disease recurrence in patients with clinical stage IA subsolid adenocarcinoma.

Regarding part-solid tumors, several studies have previously demonstrated that solid component size correlates more accurately with tumor invasiveness and prognosis than maximum tumor size.[4,21,22] Currently, the size of the solid component is applied to the category T stage for part-solid lung cancers according to the eighth edition of the TNM classification scheme of lung cancer because the solid component is regarded as the invasive component.[23] However, our study showed that solid component size was not an independent predictor of tumor recurrence. Our results appear to be inconsistent with the results of several previous studies.[4,21,22] The reason why our results were different from previous studies may be related to our exclusion of pure solid tumor when considering the effect of solid component size. Although the solid component in a PSN by CT has a greater chance of having an invasive component on histological examination, the solid area could also represent a benign scar or a fibrous scar.[24] In addition, managing PSNs with several solid components can be a challenge because there is currently no consensus regarding how the solid components of these lesions should be measured.

There is still no strong evidence based on a randomized controlled trial for the extent of surgical resection for subsolid nodules. However, the results of this study validate and support the NCCN guideline (version 5, 2020) recommendation to guide surgical procedure selection in patients with clinical stage IA adenocarcinoma observed as subsolid nodules.

We acknowledge that there are some limitations and biases in our study. First, this study did not proceed with a randomized controlled investigation. For surgical methods, patients were not evenly assigned to lobectomy, segmentectomy, or wedge resection. In addition, the nodal sampling was not uniformly performed in each center. In the lobectomy and segmentectomy groups, all patients underwent mediastinal lymph node dissection. However, in the wedge resection group, 24 (34.2%) patients did not undergo mediastinal lymph node dissection. Second, the recurrence rate was very small. Only nine patients experienced disease recurrence. Therefore, depending on the recurrence rate, these results may be affected. To reduce the bias from low recurrence rate, we applied Firth correction when calculating 95% CI. Third, there was not enough follow-up time after surgery to evaluate overall survival. The median follow-up period was 5.01 years (interquartile range: 4.33–5.45 years). In this study, we evaluated the TTR instead of overall survival because in stage I disease more patients died from causes other than from cancer during the follow-up period.

In conclusion, radiologically subsolid lung adenocarcinoma measuring <3 cm could be candidates for sublobar resection instead of lobectomy. In our study, subsolid lung cancer measuring smaller than 3 cm had excellent surgical outcome regardless of surgical procedures, subsolid nodule subtype and solid component size. In addition, the TTR was not significantly different among the various surgical procedures of lobectomy, segmentectomy, or wedge resection in patients with clinical stage IA adenocarcinoma observed as subsolid nodules. While these results need to be replicated in larger randomized controlled studies, our results validate subjects eligible for sublobar resection recommended by NCCN 2020 guideline and provide the surgeon with a rationale for choosing a less-extensive surgical alternative for clinical stage IA adenocarcinomas observed as subsolid nodules without compromising patient outcomes.

ACKNOWLEDGMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education (grant number: 2018R1D1A1B07043364).

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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How to cite this article: Im DJ, Lee SM, Han K, et al. Predictive factors of recurrence after resection of subsolid clinical stage IA lung adenocarcinoma. *Thoracic Cancer*. 2021;12:941–948. https://doi.org/10.1111/1759-7714.13876