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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Ten-Year Follow-Up of Lung Cancer Patients with Resected Stage IA Invasive Non-Small Cell Lung Cancer

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ABSTRACT

Objective. The purpose of this study was to assess 10-year follow-up outcomes after surgical resection in patients with stage IA invasive non-small cell lung cancer (NSCLC) based on postoperative pathological diagnosis.

Methods. Patients with stage IA invasive NSCLC who underwent resection between December 2008 and December 2013 were reviewed. Patients were categorized into the pure-ground glass opacity (pGGO), mixed-ground glass opacity (mGGO), and solid groups based on consolidation to tumor ratio (CTR). Postoperative survival and risk of recurrence and developing secondary primary lung cancer were analyzed in each group.

Results. Among the 645 stage IA invasive NSCLC, the 10-year overall survival and recurrence-free survival rate was 79.38% and 77.44%, respectively. The 10-year overall survival for pGGO, mGGO, and solid group of patients was 95.08%, 86.21%, and 72.39%, respectively. The respective recurrence-free survival rate was 100%, 89.82%, and 65.83%. Multivariable Cox regression analysis associated tumor size and GGO components with recurrence and younger age, and tumors with GGO components were associated with longer overall survival. The cumulative incidence curve indicated no recurrence of GGO lung cancer ≥ 5 years postoperatively. Our cohort indicated that the number and stations of dissected lymph node did not influence long-term prognosis of IA invasive NSCLC.

Conclusions. Recurrence of invasive stage IA NSCLC with GGO was more prevalent in patients with tumor size >1 cm and CTR > 0.5, occurring within 5 years after surgery. This will provide important evidence for follow-up strategies in these patients.

Xiongfei Li and Fanfan Fan contributed equally to this paper.

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With 2.2 million newly diagnosed cases and more than 1.8 million deaths annually, lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide.[1–3] The widespread application of low dose computed tomography (CT) in lung cancer screening has resulted in the detection of an increasing number of lung cancer cases with ground glass opacity (GGO) components.[4,5] Nearly 100% of GGO lesions are pathologically confirmed as adenocarcinoma postoperatively.[6] The survival of patients with GGO lung cancer is excellent after complete resection, even in patients harboring a small proportion of GGO components.[7]

Pulmonary adenocarcinoma is classified into adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IAD).[8] Previous studies of the long-term follow-up results of AIS and MIA

adenocarcinoma reported no recurrence of AIS or MIA lung cancer during the 10-year following resection.[6] However, to our knowledge, long-term follow-up results of invasive NSCLC with GGO components have not been reported. In this study, we analyzed the data of a large number of pathological invasive stage Ia NSCLC patients who underwent complete resection to reveal their 10-year follow-up outcomes and recurrence characteristics.

METHODS

Patients

The study analyzed data of consecutive patients with pathological stage IA NSCLC based on the eighth TNM staging system who underwent complete resection at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, between January 2008 and December 2013. Patients with previous history of any cancers or incomplete resection were excluded. Complete resection was defined as resection of all macroscopic tumor tissue and the absence of tumor cells in the surgical margin on microscopic analysis. Clinicopathological characteristics, including age, sex, smoking history, tumor location, CT appearance, operative procedure, pathological eighth TNM stage, pathological subtype, lymphovascular invasion (LVI), time to last follow-up, time to recurrence or death, and sites of initial recurrence, were collected from patients' medical records. Informed consent of the included patients was waived because the study was retrospective.

Radiological and Histological Evaluation

Thin section CT scans were independently reviewed by two radiologists for GGO and solid appearance. For cases with different results, the two radiologists re-reviewed and discussed the data and then reached a consensus. Adenocarcinoma subtypes were classified on the basis of the lung adenocarcinoma (LADC) classification systems of the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society were applied to classify adenocarcinoma subtypes.[8] Acinar pattern-predominant adenocarcinoma (APA), papillary pattern-predominant adenocarcinoma (PPA), and invasive mucinous adenocarcinoma were classified as intermediate-grade LADC. Micropapillary pattern-predominant adenocarcinoma (MPA) and solid pattern-predominant adenocarcinoma (SPA) were classified as high-grade LADC. All pathological findings were reviewed by two experienced pathologists, and disagreement was resolved through re-review and discussion. The definition of metachronous secondary primary lung cancer (SPLC) followed our previous study.[9,10]

Follow-Up Strategy

Follow-up started from the date of surgery. Physical examination, chest CT scans, ultrasonography of the abdominal, cervical, and supraclavicular regions, as well as CT scans or magnetic resonance imaging (MRI) of the brain were performed every 6 months for 3 years after surgery, every 8 months from years 3 to 5, and annually for subsequent years. The application of ultrasonography of the abdominal, cervical, and supraclavicular regions and MRI of brain is used to detect evidence of possible recurrence of lung cancer at these sites. We do not perform PET scans for periodic reexamination, This is based on the comprehensive consideration of its high cost and the risk of overtesting.

In addition, bone scans were performed every year. Overall survival (OS) was defined as the time between the day of surgery and the day of death or last follow-up. Recurrence-free survival (RFS) was counted from the day of surgery to the date of first recurrence or last follow-up. Patients who died from other causes were considered to be censored with no event when calculating RFS.

Statistical Analysis

Characteristic differences between groups were compared by Pearson's chi-square test or Fisher's exact test as appropriate, and the Kaplan-Meier method was used to estimate OS and RFS, with log-rank tests to evaluate significant differences. All p-values were t-sided; $p < 0.05$ was considered statistically significant. Univariate and multivariate analyses were performed with Cox regression analysis using SPSS version 22.0 (SPSS Inc, Chicago, IL), and variables were excluded sequentially if the alpha error was ≥ 0.05. All statistical analysis was performed by using IBM SPSS 24.0 (IBM, Armonk, NY), GraphPad Prism 9.0 (GraphPad, San Diego, CA), and RStudio software version 2022.07.1+554 (Posit, Boston, MA).

RESULTS

Patient Characteristics

The clinicopathological characteristics of the 645 patients with resected stage IA invasive NSCLC are listed in Table 1. Of these 645 patients, 62 (9.61%) were categorized as pure-GGO (pGGO), 217 (33.64%) as mixed-GGO (mGGO) group, and 366 (56.74%) as solid.

Among the 645 patients, 432 (66.98%) were ≤65 years and 213 (33.02%) were >65 years. There was no significant difference between the three groups. Of the 645 patients, 345 (53.49%) patients were female. The pGGO and mGGO patients included more female patients than the solid group. Of the total patients, 445 (68.99%) were

TABLE 1 Clinicopathologic characteristics of patients with invasive stage IA NSCLC

Characteristics	All (n = 645)	Pure GGO (n = 62)	Part-solid (n = 217)	Solid (n = 366)	*p*
Age (year)					0.584
≤65	432 (66.98)	43 (69.35)	150 (69.12)	239 (65.30)	
>65	213 (33.02)	19 (30.65)	67 (30.88)	127 (34.70)	
Sex					< 0.001
Female	345 (53.49)	41 (66.13)	146 (67.28)	158 (43.17)	
Male	300 (46.51)	21 (33.87)	71 (32.72)	208 (56.83)	
Smoking history					< 0.001
Never	445 (68.99)	48 (77.42)	175 (80.65)	222 (60.66)	
Ever	200 (31.01)	14 (22.58)	42 (19.35)	144 (39.34)	
Size (cm)					< 0.001
0–1	79 (12.25)	17 (27.42)	34 (15.67)	28 (7.65)	
1–2	354 (54.88)	38 (61.29)	138 (63.59)	178 (48.63)	
2–3	212 (32.87)	7 (11.29)	45 (20.74)	160 (43.72)	
Operative procedure					< 0.001
Wedge	31 (4.81)	7(11.29)	16 (7.37)	8 (2.19)	
Segmentectomy	4 (0.62)	0(0.00)	4 (1.84)	0 (0.00)	
Lobectomy	610 (94.57)	55(88.71)	197 (90.78)	358 (97.81)	
Tumor location					< 0.001
Peripheral	628 (97.36)	62(100.00)	217 (100.00)	349 (95.36)	
Central	17 (2.64)	0(0.00)	0 (0.00)	17 (4.64)	
DLNN (median)	14				< 0.001
≤14	349 (54.11)	40 (64.52)	132 (60.83)	177 (48.36)	
>14	296 (45.89)	22 (35.48)	85 (39.17)	189 (51.64)	
DLNS (median)	6				0.001
≤6	431 (66.82)	43 (69.35)	165 (76.04)	223 (60.93)	
>6	214 (33.18)	19 (30.65)	52 (23.96)	143 (39.07)	
Histological type					< 0.001
LPA/APA/PPA/IMA	518 (80.31)	62 (100.00)	212 (97.70)	244 (66.67)	
MPA/SPA	48 (7.44)	0 (0.00)	5 (2.30)	43 (11.75)	
SQCC	79 (12.25)	0 (0.00)	0 (0.00)	79 (21.58)	
Lymphovascular invasion					0.026
Yes	14 (2.17)	0 (0.00)	1 (0.46)	13 (3.55)	
No	631 (97.83)	62 (100.00)	216 (99.54)	353 (96.45)	

nonsmokers. The pGGO and mGGO patients included significantly more nonsmokers than the solid group (Table 1).

Of 645 patients, 79 (12.25%), 354 (54.88%), and 212 (32.87%) comprised the T ≤1 cm, 1 cm < T ≤ 2 cm, and 2 cm < T ≤ 3 cm groups, respectively. The tumor sizes of pGGO and mGGO patients were significantly smaller than the solid group of patients, including solid adenocarcinoma carcinoma (ADCC) and squamous cell carcinoma (SQCC) patients. The number of dissected lymph nodes (DLNN) and station counts of dissected lymph nodes (DLNS) were counted and their median counts were 14 and 6. Statistical analyses indicated that patients solid group had more DLNN and DLNS. Among all the patients, LVI was present in 14 (2.17%) and 631 (97.83%) were negative (Table 1).

Ten-Year Follow-Up Data (Comparison and 10-Year Survival Rate

Kaplan-Meier analysis indicated that the 10-year RFS rate of all invasive stage IA NSCLC patients was 77.44% (Fig. 1A). The 10-year OS rate was 79.38% (Fig. 1B). The 10-year RFS rates were 100% in the pGGO group, 89.82% in the mGGO group, and 65.83% in the solid group (Fig. 2A). The log-rank tests indicated that the 10-year RFS rates differed significantly between the three groups of patients (pGGO vs. mGGO group, $p = 0.033$; mGGO vs. solid group, $p < 0.001$; pGGO vs. solid group, $p < 0.001$) (Fig. 2A). The 10-year OS rates were 95.08% in the pGGO group, 86.21% in the mGGO group, and 72.39% in the solid group (Fig. 2B). Log-rank analysis indicated that the 10-year OS

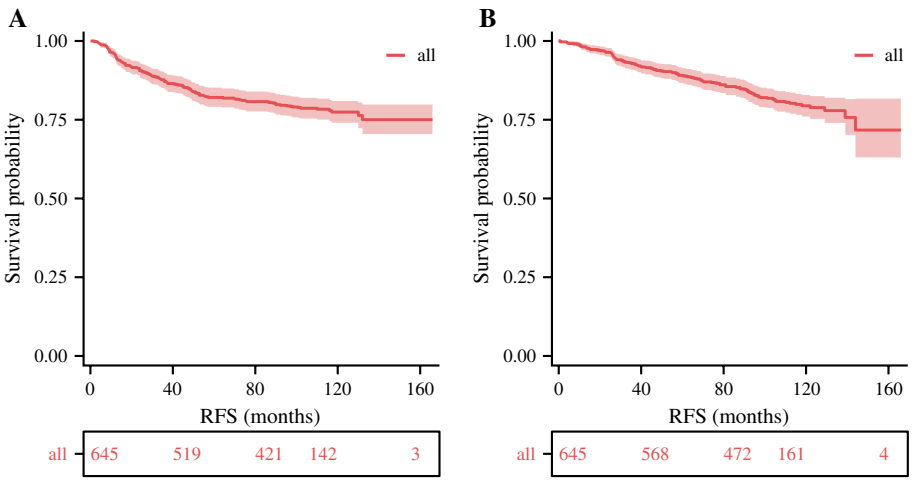

FIG. 1 Recurrence-free survival (**A**) and overall survival (**B**) of patients with invasive stage IA NSCLC

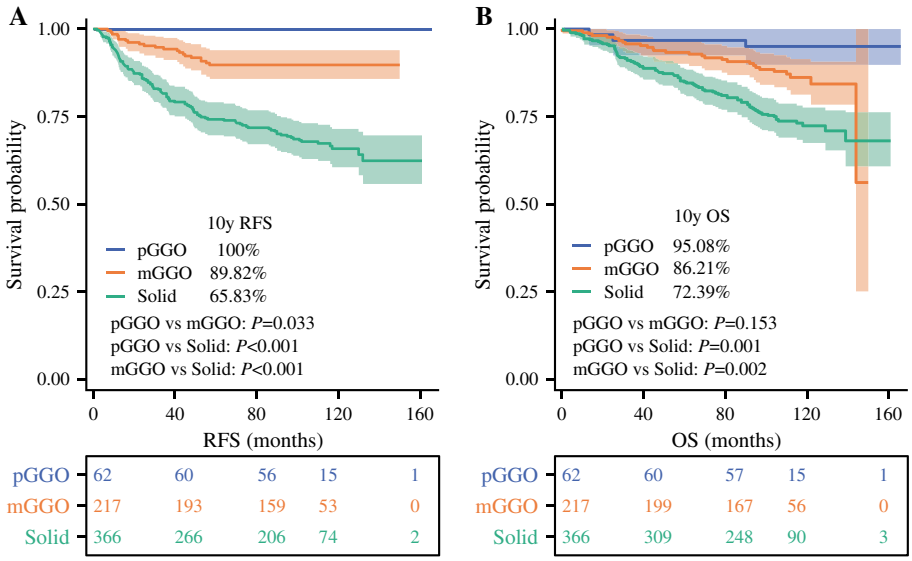

FIG. 2 Recurrence-free survival (**A**) and overall survival (**B**) of patients according to the appearance of ground-glass opacity (GGO) components

rates differed significantly for the pGGO versus mGGO group ($p = 0.052$), mGGO versus solid group ($p < 0.001$), and pGGO versus solid group ($p < 0.001$) (Fig. 2B).

Prognostic Factors for NSCLC During the 10-Year Follow-Up

Cox proportional hazard analyses were performed to further evaluate the prognostic factors in the postoperative decade for IA invasive NSCLC patients. In the analyses for recurrence-free survival, all pGGO patients were excluded because pGGO patients did not have any recurrence. According to the results of univariate analyses, all variables whose p value was < 0.05, including smoking history, histology type, T stage, lymphovascular invasion, surgical type, GGO, and tumor location were incorporated into sequential multivariate analyses. Multivariate analyses with T1a comprising the reference group revealed that concerning pathological tumor size, T1b (hazard ratio [HR] = 1.793 (0.821–3.916), $p = 0.091$; T1c (HR = 2.493 (1.134–5.479), $p = 0.003$), and GGO components (HR =0.307 (0.188–0.500), $p < 0.001$) were independently significant prognostic factors for RFS in invasive stage I NSCLC (Table 2). Concerning OS, after univariate analyses, significant variables, including age, sex, smoking history, histology type, T stage, lymphovascular invasion, and GGO, were incorporated into sequential multivariate analyses. Multivariate analyses indicated that age (HR = 2.008 (1.405–2.871), $p < 0.001$) and GGO components were significant independent prognostic factors for OS in invasive stage IA NSCLC (Table 3).

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

The cumulative incidence curve of recurrence is shown in Fig. 3A. At postoperative 5 years, the cumulative incidence

TABLE 2 Univariate and multivariable Cox regression analysis of factors associated with recurrence-free survival for invasive stage IA lung cancer patients

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (>65 vs. ≤ 65 years)	1.088(0.761–1.556)	0.643		
Sex (male vs. female)	1.402(0.996–1.973)	0.052		
Smoking history	1.454(1.026–2.060)	0.035		
Histology type				
LPA/APA/PPA/IMA	Ref			
MPA/SPA	2.054(1.241–3.401)	0.005		
SQCC	1.277(0.788–2.069)	0.321		
T stage				
T1a	Ref		Ref	
T1b	1.958(0.897–4.274)	0.091	1.793(0.821-3.916)	0.143
T1c	3.231(0.897–7.062)	0.003	2.493(1.134-5.479)	0.023
Lymphovascular invasion	2.892(1.348–6.202)	0.006		
Surgical type				
Sub-lobe resection	Ref			
Lobectomy	3.778 (0.935–15.267)	0.062		
GGO (yes vs. no)				
Solid	Ref		Ref	
mGGO	0.274 (0.172–0.437)	< 0.001	0.307 (0.188–0.500)	< 0.001
Tumor location				
Peripheral	Ref			
Central	2.269 (1.110–4.639)	0.025		

TABLE 3 Univariate and multivariable cox regression analysis of factors associated with overall survival for invasive stage IA lung cancer patients

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (>65 vs. ≤65 years)	2.001 (1.400–2.859)	< 0.001	2.008(1.405–2.871)	< 0.001
Sex (male vs. female)	1.673 (1.166–2.400)	0.005		
Smoking history	1.627 (1.132–2.337)	0.008		
Histology type				
LPA/APA/PPA/IMA	Ref			
MPA/SPA	1.978 (1.142–3.426)	0.015		
SQCC	1.653 (1.016–2.690)	0.043		
T stage				
T1a	Ref			
T1b	1.313 (0.670–2.573)	0.428		
T1c	2.303 (1.174–4.519)	0.015		
Lymphovascular invasion	2.730 (1.198–6.222)	0.017		
Surgical type				
Sub-lobe resection	Ref			
Lobectomy	1.866 (0.689–5.055)	0.220		
GGO				
Solid	Ref		Ref	
mGGO	0.484 (0.316–0.739)	0.001	0.483 (0.316–0.739)	0.001
pGGO	0.163 (0.051–0.514)	0.002	0.162 (0.051–0.511)	0.002
Tumor location				
Peripheral	Ref			
Central	1.987 (0.874–4.519)	0.101		

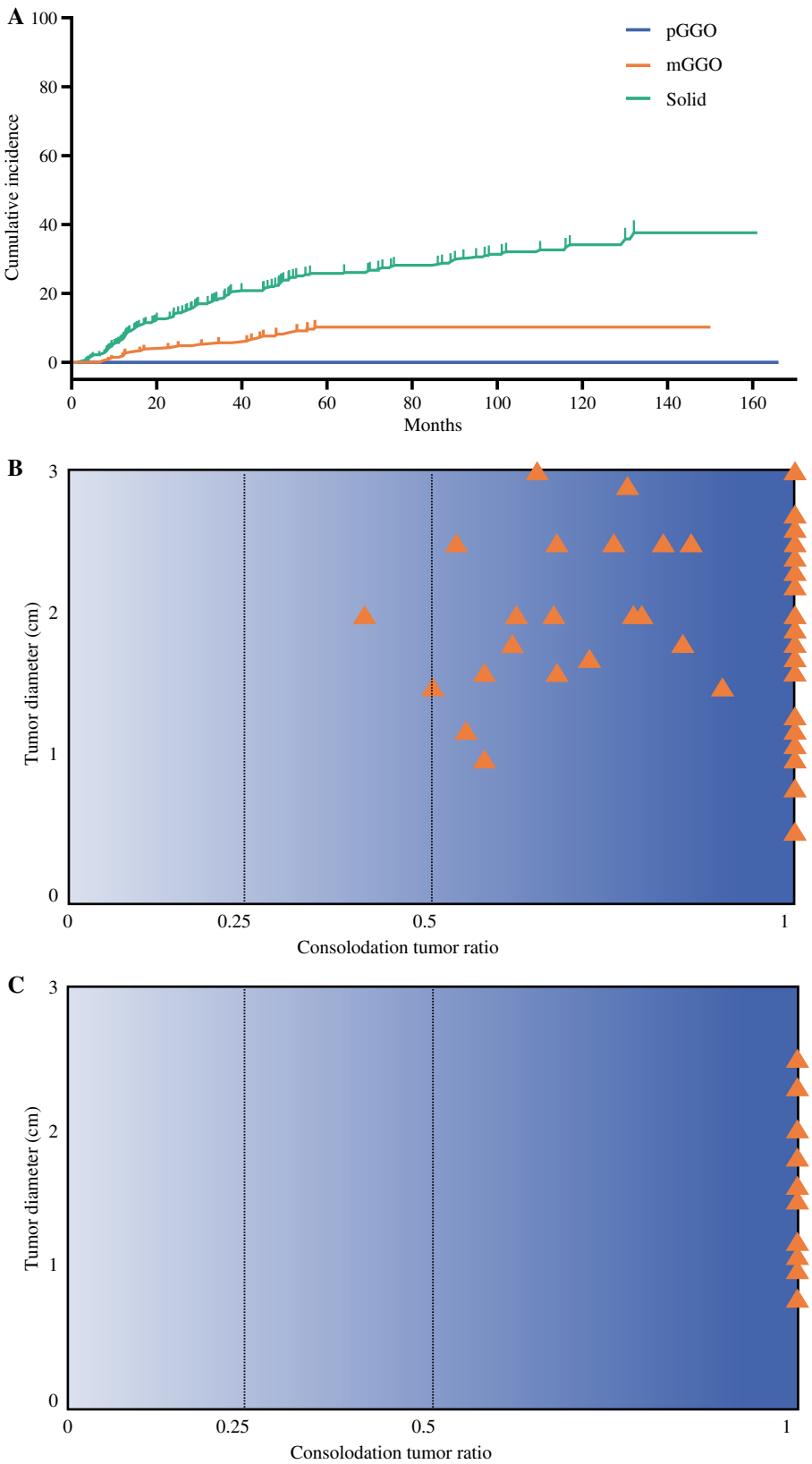

FIG. 3 Frequency of recurrence in the three groups according to size and consolidation tumor ratio (CTR). **A** Cumulative incidence curves of recurrence of three groups. **B** Recurrent cases within 5 years postoperatively (pGGO = 0; mGGO = 19; Solid = 86). Red triangles indicate recurrent cases. **C** Recurrent cases after 5 years (pGGO = 0; mGGO = 0, Solid = 23) (red triangles)

rate of recurrence was 0%, 10.18%, and 25.74% in the pGGO, mGGO, and solid group, respectively. The respective rates at postoperative 10 years were 0%, 10.18%, and 34.17%.

Within 5 years after surgery, recurrence was noted in none of the pGGO patients (62 cases), 21 mGGO patients (217 cases), and 89 solid patients (366 cases). Comparison of the three groups showed that the proportion of recurrence was higher in the solid subgroup within 5 years after surgery. Figure 3B presents the distribution of the recurrent cases according to tumor size and CTR. For GGO patients, recurrence was more frequent in patients with a CTR > 0.5 and tumor size > 1 cm.

Five or more years after surgery, recurrence was noted for none of the pGGO and mGGO patients and for 23 patients in the solid group. Figure 3C shows the distribution of recurrence according to size and CTR ≥ 5 years after surgery. No recurrence occurred in pGGO and mGGO patients. When recurrence occurred, most tumors exceeded 1 cm in size (Fig. 3C).

Site and Pattern of Recurrence

We counted the sites of recurrence in patients with lung cancer in S Table 1. Among them, lung is the most common site of recurrence, followed by brain with 17 cases and bone with 16 cases. Further analyses indicated that there were significantly more locoregional recurrence than distant recurrence (S Table 1). Furthermore, we counted the respective recurrence sites and patterns of lung cancer patients within and after 5 years of surgery. S Table 2 showed that lung is the most common recurrence site within 5 years, followed by brain and bone. Five or more years after surgery, there were no recurrences in the pGGO and mGGO groups. Likewise, the lung is the most common site of recurrence, and there were more locoregional recurrences.

Characteristics of SPLC

During the follow-up period, only 20 (3.1%) patients were observed to develop SPLC. Ten years after surgery, the risks of pGGO, mGGO, and solid patients were 6.96%, 5.01%, and 2.77%, respectively. Additionally, the incidence of developing SPLC had no significantly statistical difference between three groups (S Fig. 1).

Influence of DLNN and DLNS

To investigate the effect of intraoperative lymph node dissection on the long-term prognosis of patients, we counted the number and stations of dissected lymph node during the operation. The median counts of dissected lymph node number (DLNN) and dissected lymph node stations (DLNS) were 14 and 6. In terms of the DLNS, we divided patients into DLNS ≤ 6 and DLNS > 6 groups, and survival analyses were performed and found that RFS and OS had no statistical difference between DLNS ≤ 6 and DLNS > 6 groups in all patients, pGGO, mGGO, and solid tumor patients (S Fig. 2). About DLNN, patients were divided into DLNN ≤ 14 and DLNN > 14 groups, and survival analyses indicated that there were no significantly statistical difference of RFS and OS between DLNN ≤ 14 and DLNN > 14 groups in all patients, mGGO, and solid tumor patients (S Fig. 3). However in pGGO group, DLNN ≤ 14 had better OS than DLNN > 14 group. However, only three patients reached the outcomes of follow-up; two of them died with other nonneoplastic diseases, and there were only 22 pGGO patients in DLNN > 14 group. Therefore, it is not conclusive whether the number of lymph nodes dissected affects the long-term prognosis of pGGO patients

DISCUSSION

Previous research has established that GGO lung cancers were typically characterized as noninvasive or minimally invasive low grade adenocarcinomas with a favorable prognosis following surgery.[9,11–13] This study enrolled invasive stage IA NSCLC patients harboring GGO components. Their long-term prognosis after surgical treatment and characteristics leading to recurrence were investigated and clarified. Concerning clinical features, patients with GGO lung cancer (including pGGO and mGGO) comprised more women and nonsmokers, and featured tumors of smaller size. These findings are consistent with those of previous studies.[11,14]

Our cohort indicated that the lymphovascular invasion rate of IA invasive NSCLC was 2.17%, further analysis found that the lymphovascular invasion rates of pGGO and mGGO patients were 0% and 0.46%, which were significantly lower than solid patients (3.39%). Another study reported that the lymphovascular invasion rate of IB NSCLC were 5.7%.[15] These results indicated that as lung cancer became more advanced in stage, their lymphovascular invasion rate increased.

Cox regression analyses revealed age as a significant prognostic factor for OS but not for RFS. Previous studies also showed that old age was associated with worse OS and not with RFS. Consistent with previous research, this study also confirmed the association of the GGO-component with better RFS and OS.[16]

Regarding 10-year survival, Ito et al. analyzed data of 548 clinical T1N0 lung cancer patients and reported 10-year OS and RFS rate of 80.4% and 77.1%, respectively.[14] These values are consistent with our results (10-year OS, 79.38%; 10-year RFS, 77.44%), although there may have been

patients with preinvasive cancers with better prognosis and pathological N1 patients with worse prognosis.

Li et al. reported that the 10-year RFS and OS rate of pGGO patients was 100% and 96.9%, respectively.[9] Although the study they included some AIS and MIA patients who had excellent prognosis, we also observed highly favorable survival for patients with invasive pGGO lung cancer, with 100% RFS and 95.08% OS, and no lung cancer-related death 10 years after surgery.

Previous descriptions of no recurrence at the 10-year follow-up in patients with tumors ≤ 2 cm in size and CTRs ≤ 0.25 had no recurrence in the 10 years of follow-up was confirmed in our study.[14] For small-sized tumors, wedge resection is easy to perform and a sufficient surgical margin is left to ensure R0 resection. In contrast, the long-term outcome for lung cancer patients with CTRs ≤ 0.5 to > 0.25, in which two patients (2.4%) recurred was nearly equivalent to the outcome for patients with CTRs ≤ 0.25. This excellent prognosis is consistent with the results of a previous study.[17] In the two patients with recurrence, bone metastasis developed. Both patients were still alive at the end of the follow-up period.

This study indicated that patients with CTR > 0.5 clearly had a significantly higher recurrence rate than those with CTR ≤ 0.5, consistent with previous study.[14] In our cohort, the recurrence in patients with CTR > 0.5 mainly involved tumors > 1 cm. There was one patient with recurrence among 16 GGO patients whose tumor size ≤ 1 cm and CTR > 0.5 (6.25%). In comparison, GGO patients with CTR > 0.5 and tumor size > 1 cm had significantly more recurrence with 16.22% recurrence rate. Ito et al. also reported these patients had higher recurrence rate than those with a tumor size ≤ 1 cm and CTR > 0.5.[14] For patients with CTR > 0.5 and tumors > 2 cm and ≤ 3 cm in size, sublobar resection may not be a suitable procedure, because it was difficult to achieve a suitable surgical margin.[18,19] For patients with CTR > 0.5 and tumor size > 1 cm to ≤ 2 cm, recurrence was still high and similar to the rate for patients with tumor size > 2 cm and ≤ 3 cm. The choice of surgical procedure for these patients should still be cautious, Although the JCOG0802 clinical trial confirmed the noninferiority of segmentectomy compared with lobectomy for patients with tumor size ≤ 2 cm and CTR > 0.5, which also indicated segmentectomy group, had nearly twice the rate of local relapse compared to the lobectomy group (10.5% vs. 5.4%).[20,21]

The American Society of Clinical Oncology (ASCO) guidelines released in 2019 state that lung cancer patients receiving radical surgical treatment should receive postoperative follow-up examinations every 6 months for 2 years after surgery and once a year thereafter.[22] In the present study, no late recurrences were evident (≥5 years after surgery) in the mGGO patients. Considering the excellent RFS, the interval of follow-up should be extended more appropriately than routine for pGGO patients after surgery and also for mGGO after 5 years following surgery.

There were some limitations and biases in our study. First, this was a single-center retrospective study and selection bias could not be avoided. Second, few individuals underwent sublobar resection and the long-term outcomes of IA patients who underwent wedge or segmentectomy remained uncertain.

CONCLUSIONS

No recurrence was observed in pGGO patients, even in patients with invasive pathological components, 10 years after surgery. Recurrences of invasive stage IA NSCLC with mGGO were concentrated in patients with tumors >1 cm and CTR >0.5, and occurred within 5 years postoperatively. This will provide important evidence for follow-up strategies in these patients.

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DISCLOSURE The authors declare that they have no conflict of interest.

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