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Survival of a surgical series of lung cancer patients with synchronous multiple ground-glass opacities, and the management of their residual lesions☆

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ABSTRACT

Objectives: We reviewed the medical record of a series of patients with synchronous multiple lung cancers (SMLC), in an attempt to identify the optimal treatment strategy for multiple ground-glass opacities (GGOs).

Materials and methods: From 2004 to 2010, 1223 patients underwent complete resection of non-small cell lung cancer. Among these, there were 67 patients (5.5%) with SMLC with at least 1 of the nodules showing GGO appearance. SMLC was divided into the main cancer (MC) which was a main target based on its tumor size or radiological invasiveness and sub-nodules. According to consolidation/tumor ratio (CTR) on thin-section computed tomography, 67 cases were classified into GG-group (MC showing GGO-dominant lesion; CTR $\leq$ 0.5) and GS-group (MC showing solid-dominant lesion; CTR > 0.5).

Results: There were 24 patients in the GG-group (36%) and 43 patients in the GS-group (64%). Surgical resections included 11 sublobar resections (SLs), 32 lobectomies, 19 lobectomy + SLs, and 4 bilobectomies. There were 39 patients with a total of 118 unresected GGOs after the initial surgery. Among them, the frequency of growth was 8% on a per-nodule basis with the median tumor doubling time of 1373 days, and new GGOs emerged in 15 patients (23%). Multivariate analysis demonstrated that larger size of MC and the GS-group was associated with poor prognosis, whereas growth of the residual GGOs, the development of new GGOs, or whether or not all GGOs were treated did not affect survival. The 5-year OS proportions were 95.8% for the GG-group and 68.0% for the GS-group ($p = 0.009$), and 92.4% for a MC of $\leq$25 mm and 53.6% for a MC of >25 mm ($p = 0.008$).

Conclusion: Survival of patients with multifocal GGOs is strongly affected by radiological findings of the MC. Strict surgical control for MC could be most important.

1. Introduction

The widespread use of high-resolution computed tomography (CT) in daily practice and screening has contributed to the frequent detection of ground-glass opacities (GGOs) in asymptomatic patients [1,2]. GGO is defined as a hazy area of increased attenuation in the lung, with preservation of the bronchial and vascular margins, and can be caused by various diseases, such as infections, interstitial diseases, acute alveolar diseases, and neoplasms [3]. GGO lesions are often detected as multiple lesions, and the incidence of multiple primary lung cancers with GGOs has recently increased [4,5].

Abbreviations: CT, computed tomography; GGO, ground-glass opacity; MC, main cancer; SN, sub-nodule; CTR, consolidation/tumor ratio; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; SBRT, stereotactic body radiation therapy; IQR, the interquartile range.

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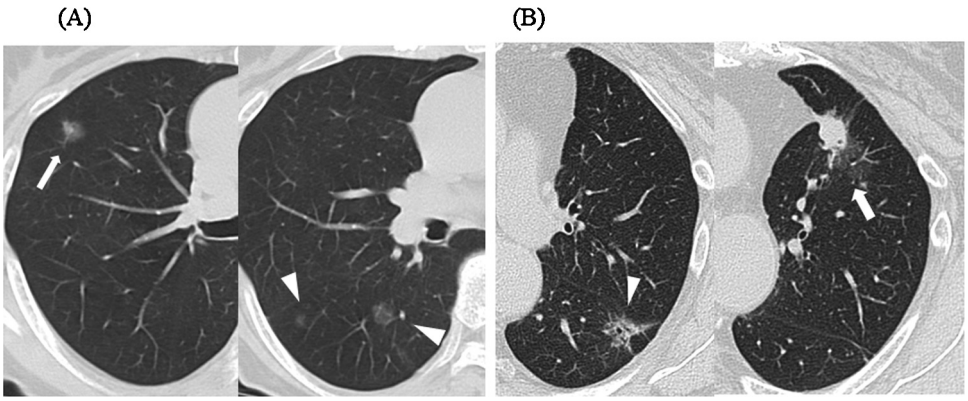

Fig. 1. Typical CT images of synchronous multiple lung lesions. (A) A 71-year-old female patient from the GG-group; the arrow shows the 11-mm MC in the right segment 3 area, and the two arrowheads show a 9-mm and a 5 mm SN in the right segment 6 area, respectively. (B) A 80-year-old female patient of the GS-group; the arrow shows the 41-mm MC in the left segment 3 area, and the arrowhead shows a 23-mm SN in the left segment 6 area.

The detection of synchronous multiple lung nodules may cause the clinical dilemma of how these lesions should be managed. The distinction has important therapeutic and prognostic implications. Although surgical approaches for such multiple lesions depend on their anatomical location, size, and number, as well as the patient's age, and pulmonary function, the decision usually depends on the surgeon's judgment; no standard criteria have been established for the selection of the lesions to be treated, nor the method of management of the residual nodules in cases of synchronous multifocal GGOs. In this study, we retrospectively reviewed the records of a surgical series of lung cancer patients with synchronous multiple lung lesions, proven or suspect for lung cancer, particularly multifocal GGOs, in an attempt to identify the optimal treatment strategy and the management method for the residual and new lesions.

2. Patients and methods

2.1. Patients

From January 2004 to December 2010, a total of 1223 patients underwent complete resection without any preoperative induction therapy for non-small cell lung cancer at our hospital. Among them, 85 patients had either synchronous multiple primary lung cancer or underwent main tumor resection with at least 1 other lesion suspected of lung cancer on preoperative CT scans. Of these, 67 patients (5.5%) who possessed at least one lung lesion showing an area of GGO were included in the study. In the patients who underwent resection for all lung tumors, they were diagnosed as multiple lung cancer with GGO component due to their pathological and clinical characteristics based on the modified Martini and Melamed criteria, the American College of Chest Physicians guidelines, and the theories of the multiclonality of multifocal lepidic-type adenocarcinoma [4,6,7]. The stages of the tumors were determined in accordance with the 7th Edition of the TNM Classification for Lung and Pleural Tumors [8]. This retrospective study was evaluated by the Institutional Review Board of Tokyo Medical University and granted exemption from the requirement for informed consent.

2.2. Radiological evaluation of synchronous multiple lung lesions

CT scans were performed by using a 64-channel MDCT (Light Speed VCT, GE Medical Systems, Milwaukee, WI, USA) with a section thickness of 1.25 mm. Each CT image was acquired within 1 breath hold of about 5 s, after a delay of 70 s during which the contrast media injection took effect.

When collecting and analyzing our data, we firstly divided synchronous multiple lung GGO lesions into two lesions according to the preoperative CT findings; the main cancer (MC) and subnodules (SNs). MC was defined as the main lung cancer to be surgically resected, from its tumor size or radiological invasiveness, and SNs were any other lung lesions.

According to the radiological findings on thin-section CT scan, we examined the ratio of maximum diameter of consolidation to the maximum tumor diameter from the lung window (CTR). The cases were classified into two groups: GG-group and GS-group. The GG-group denotes their MC showing GGO-dominant appearance (CTR $\leq$ 0.5) and the GS-group shows their MC showing solid-dominant appearance (CTR > 0.5), respectively. The radiological criteria of a CTR 0.5 as a cut-off in this study depends on results of several published studies [9–11]. Typical CT findings of patients in the GG-group and the GS-group are shown in Fig. 1A and B, respectively.

2.3. Treatment strategy and postoperative surveillance

In patients with multiple lung lesions, the surgical procedure was determined according to site of lesion, CT findings, estimated postoperative respiratory function, and the presence or absence of preoperative comorbidities. Our basic treatment strategy for synchronous multiple lung lesions was as follows (Supplement Fig. 1): (1) when tumors were in an ipsilateral chest, we tried to resected all lesions larger than 10 mm or radiographical solid-dominant lesions by single-stage surgical treatment. However, for SNs smaller than 10 mm or radiographical GGO-dominant lesions with slow growth, if the extent of the resection was expected to be greater than sublober resection because of the central location or if there were multiple lesions scattered throughout multiple lobes, we decided to perform strict surgical resection of MC and easily accessible SNs by limited resection. (2) When tumors were in contralateral lesions, two-stage surgical treatment was commonly performed. (3) As our strategy throughout the postoperative follow-up period, we performed surgical resection on SNs with a diameter of larger than 10 mm, or with an emerging solid portion. Unless patients were capable of undergoing surgical resection in estimated postoperative respiratory function, we decided not to resect such lesions and instead select SBRT or continuous monitoring of the residual lesions (Supplement Fig. 2).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.02.016.

Table 1
Patient characteristics.

Factors	Overall (%)	GG-group (CTR ≤ 0.5)	GS-group (CTR > 0.5)	*p*-value
No. of patients	67 (100)	24 (100)	43 (100)	
Age, median (years, IQR)	69 (60–75)	69 (60–76)	69 (60–73)	0.971
Sex				
Male	22 (33)	6 (25)	16 (37)	
Female	45 (67)	18 (75)	27 (63)	0.308
Smoking status				
Never smoker	43 (64)	20 (83)	23 (53)	
Current smoker	6 (9)	0	6 (14)	
Ever smoker	18 (27)	4 (17)	14 (33)	0.031
Detection of lung cancer				
Screening tests	46 (69)	17 (71)	29 (67)	
Incidental	15 (22)	7 (29)	8 (19)	
Symptom	6 (9)	0	6 (14)	0.126
Preoperative pathological diagnosis				
Yes	27 (40)	5 (21)	22 (51)	
TBLB	20	2	19	
CTNB	6	2	4	
Both	1	1	0	
For MC	23	4	19	
For MC and SNs	4	1	3	
No	40 (60)	19 (79)	21 (49)	(Yes vs. no)0.015
History of other malignancies				
Yes	25 (37)	11 (46)	14 (33)	
No	42 (63)	13 (54)	29 (67)	0.281
FEV1.0%, median (%, IQR)	76.0 (72.2–79.9)	77.0 (74.9-80.2)	75.0 (71.0–79.4)	0.314
Comorbidities				
Absent	46 (69)	18 (75)	28 (65)	
Present	21 (31)	6 (25)	15 (35)	0.403
Clinical stage				
IA	49 (71)	20 (83)	29 (67)	
IB	18 (29)	4 (17)	14 (33)	0.159
No. of lesions				
Per-patient, median (IQR)	2 (2–3)	3 (2–7)	2 (2–3)	
2	37 (55)	8 (33)	29 (67)	
3	14 (21)	6 (25)	8 (19)	
≥4	16 (24)	10 (42)	6 (14)	0.008
Size of MC, median (mm, IQR)	25 (16–33)	16 (12–25)	28 (20–35)	0.003
Size of SNs, median (mm, IQR)	10 (7–14)	8 (6–11)	13 (9–19)	<0.001
Imaging characteristics obtained by CT				
All pure GGOs	7 (10)	7 (29)	0	
Others	60 (90)	17 (71)	43 (100)	<0.001
Laterality				
Unilateral	29 (43)	6 (25)	23 (53)	
Same lobe	9	2	7	
Different lobe	10	4	16	
Bilateral	38 (57)	18 (75)	20 (47)	0.078
The coincidence of histology, MC and SNs				
Yes	40 (60)	17 (71)	23 (53)	
No	3 (4)	0	3 (7)	
Not evaluable	24 (36)	7 (29)	17 (40)	(Yes vs. no)0.147

IQR: the interquartile range and FEV1.0: forced expiratory volume in 1 s.

2.4. Statistical analyses

Overall survival (OS) was measured from the date of surgery to the date of death from any cause, or the date on which the patient was last known to be alive. Recurrence-free survival (RFS) time was measured as the interval between the date of surgery and the date of recurrence, or the date of death from any cause, or the date on which the patient was last known to be alive. OS and RFS curves were plotted using the Kaplan–Meier method, and differences in variables were determined using the log-rank test. OS and RFS were assessed by univariate and multivariate analyses using the Cox proportional hazards model. The chi-square test or Student's *t*-test was used to compare proportions and continuous variables. All tests were 2-sided, and p-values < 0.05 were considered to indicate a statistically significant difference between 2 groups. All statistical calculations were performed using the SPSS statistical software package (version 21.0; SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

Median follow-up time of the patients was 58.9 months (range: 1.2–110.8 months). Patient characteristics are summarized in Table 1. There were 24 patients in the GG-group (36%) and 43 patients in the GS-group (64%). The CT data showed all pure GGOs in 7 patients. A comparison of the clinico-radiological data between two groups showed that the GG-group was associated with never smokers ($p = 0.031$), no preoperative pathological diagnosis ($p = 0.015$), larger number of lesions on a per-patient basis ($p = 0.008$), the frequency of patients with all pure GGOs ($p < 0.001$), and smaller tumor size of MC and SN ($p = 0.003$ and $p < 0.001$) compared to the GS-group.

3.2. Pathology and treatment

The pathological characteristics of the lesions and the surgical procedures that were performed are summarized in Supplement Table 1. The GG-group was significantly associated with earlier pathological stages ($p = 0.011$). Surgical resections included 11 sublobar resections (SLs), 32 lobectomies, 19 lobectomy + SLs, and 4 bilobectomies. The initial treatment plan consisted of surgery alone in 66 patients (99%) and surgery with stereotactic body radiation therapy (SBRT) in a patient (1%). There were 59 patients (88%) who underwent lymph node resection including 10 systemic dissections, 33 lobe-specific dissections and 16 lymph nodes sampling, and 8 patients (12%) without receiving lymph node confirmation.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.02.016.

3.3. Postoperative surveillance results

The postoperative surveillance results and treatment methods applied for the new lesions are listed in Table 2. Of the 65 patients, 28 patients (42%) had all of their lesions resected, and 39 patients (58%) had residual lesions. Among the 118 residual GGO lesions in the 39 patients, the majority ($n = 99$) did not change in size during the follow-up period. Growth was observed in 9 GGOs, and the median tumor doubling time [the elapsed time (days) $\times \log 2$]/[3 $\times$ log (tumor size at the date of the latest chest CT; mm)/tumor size at the date of the last chest CT; mm)] of these GGOs was 1373 days, with a median amount of growth of 4 mm. During the follow-up period, new GGOs emerged in 15 patients, and the median new nodule size was 9 mm (IQR, 2–45 mm) at the time of the last CT imaging. Six patients (40%) who developed new GGO lesions underwent treatment for the new GGOs, including SBRT (3 patients), resection (2 patient) and intensity-modulated radiation therapy (1 patient).

Table 2
Postoperative surveillance results.

Characteristics	No. of patients (%)
Resection of all lesions	
No	39 (58)
Yes	28 (42)
All lesions in a lobe	9
Lobectomy (one lobe)	8
Segmentectomy	1
Lesions in different lobes, ipsilateral	11
Bilobectomy	4
Lobectomy + segmentectomy	1
Lobectomy + wedge resection	6
Lesions in bilateral lobes	8
Lobectomy + segmentectomy	2
Lobectomy + wedge resection	5
Segmentectomy + wedge resection	1
Fate of untreated residual GGOs	**(No. of GGO lesions)**
No change	99
Size decrease	5
Disappearance	5
Size increase	9
Pathological confirmation of increased GGO	
No	8
Yes	1
Treatment of increased GGO	
No	6
Yes	3
Surgery	1
SBRT	1
Gefitinib	1
Growth rate of residual GGOs showing growth	
Growth in diameter, median (mm, range)	4 (1–42)
Doubling time, median (days, range)	1373 (350–5813)
Emergence of new GGOs	
No	42 (63)
Yes	15 (37)
Size of new GGOs in these patients, median (mm, range)	9 (2–45)
Treatment of new GGOs	
No	9 (60)
Yes	6 (40)
SBRT	3
IMRT	1
Surgery	2
Recurrence	
No	56 (84)
Yes	11 (16)
GG-group	0
GS-group	11
Type of recurrence	
Distant recurrence	8
Local recurrence only from MC	3
Adjuvant chemotherapy	
No	55 (82)
Yes	12 (18)
GG-group	0
GS-group	12

IMRT: intensity-modulated radiation therapy.

3.4. Prognostic analyses

Univariate analyses revealed that 4 factors (age, CTR of MC, size of MC and size of SNs) were significantly associated with OS. Multivariate analysis demonstrated that larger tumor size of MC (hazard ratio [HR]; 3.085, 95% confidence interval [CI]; 1.006–9.463, $p = 0.049$) was a statistically significant predictor of unfavorable OS (Table 3). For RFS, 2 factors (CTR of MC and the resection of all lesions) were identified as statistically significant factors. Sex and size of MC were also marginally significant. On multivariate analysis, a CTR of MC > 0.5 (HR; 9.009, 95%CI; 1.066–64.500, $p = 0.016$) was identified as an independent predictor of unfavorable RFS (Table 4). The 5-year OS proportions according to CTR of MC were 95.8% for the GG-group and 68.0% for the GS-group ($p = 0.009$, Fig. 2A); and for RFS, the proportions were 95.8% and 56.8%, respectively ($p = 0.003$, Fig. 2B). The 5-year OS proportions according to MC size were 92.4% for a MC of $\leq$25 mm and 53.6% for a MC of >25 mm ($p = 0.008$, Fig. 2C); and for RFS, the proportions were 77.7% and 58.6%, respectively ($p = 0.084$, Fig. 2D).

Table 3
Univariate and multivariate analysis of overall survival after the initial operation.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Sex						
Male/female	2.597	0.907–7.463	0.075			
Age (years)	1.056	1.001–1.114	0.045	1.049	0.984–1.119	0.139
No. of lesions per patient	1.391	0.859–2.252	0.180			
Laterality						
Unilateral/bilateral	1.341	0.470–3.831	0.583			
CTR of MC						
GS-group (CTR > 0.5)/GG-group (CTR ≤ 0.5)	9.259	1.208–71.429	0.032	6.993	0.879–55.556	0.066
Resection of all lesions						
Yes/no	2.439	0.814–7.299	0.111			
Emergence of new GGOs						
No/yes	2.358	0.520–10.753	0.266			
Size of MC, median 25 mm	3.974	1.325–11.915	0.014	3.085	1.006–9.463	0.049
Size of SNs, median 10 mm	3.166	0.988–10.150	0.053	1.952	0.550–6.920	0.301
Treatment of all SNs						
Yes/no	1.790	0.561–5.710	0.326			
Treatment timing						
Concurrent/sequential	1.318	0.340–5.102	0.690			
Concurrent/no treatment for residual SNs	1.006	0.289–3.497	0.992			

HR: hazard ratio and CI: confidence interval.

Table 4
Univariate and multivariate analysis of recurrence free survival after the initial operation.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Sex						
Male/female	2.469	0.921–6.617	0.072	2.057	0.675–6.274	0.205
Age (years)	1.042	0.994–1.092	0.087			
No. of lesions per patient	1.359	0.878–2.101	0.169			
Laterality						
Unilateral/bilateral	1.739	0.647–4.671	0.273			
CTR of MC						
GS-group (CTR > 0.5)/GG-group (CTR ≤ 0.5)	10.753	1.414–83.333	0.022	9.009	1.066–64.500	0.035
Resection of all lesions						
Yes/no	3.283	1.139–9.458	0.028	1.114	0.269–4.608	0.882
Emergence of new GGOs						
No/yes	1.289	0.364–4.5677	0.694			
Size of MC, median 25 mm	2.560	0.951–6.894	0.063	1.830	0.674–4.969	0.236
Size of SNs, median 10 mm	2.444	0.847–7.054	0.099			
Treatment of all SNs						
Yes/no	2.207	0.711–6.847	0.171			
Treatment timing						
Concurrent/sequential	1.848	0.500–6.849	0.358			
Concurrent/no treatment for residual SNs	1.527	0.469-4.975	0.483			

HR: hazard ratio and CI: confidence interval.

4. Discussion

In this study, we evaluated the clinicopathological features and long-term outcomes of patients with multifocal GGOs, and the optimal management for the residual and new lesions. For the patients, tumor size and CTR of MC were strongly associated with prognosis, whereas no association was observed between survival and the number of lesions, the emergence of new GGOs, or whether or not all lesions were treated.

Recently, the management of synchronous multiple primary lung cancer has been a particular concern to clinicians because the detection of multiple GGOs has been steadily increasing [4,5]. Several studies addressing this topic have reported similar results, demonstrating a favorable prognosis [5,12–15]. The 5-year OS and RFS proportions of our data were satisfactory and all the patients with multifocal pure GGOs remained alive for 5 years without recurrence, similarly to several previous studies [5,14,15].

The correlation between GGOs detected by CT and their pathology has been widely studied [11,16–19]. Most adenocarcinomas with a favorable prognosis, namely, AIS, MIA, or the lepidic subtype, were observed by radiography as pure or mixed GGOs [14,20]. Our study also showed that part-solid tumors with solid-dominant appearance on CT had a higher malignant potential compared with GGO-dominant tumors notwithstanding synchronous

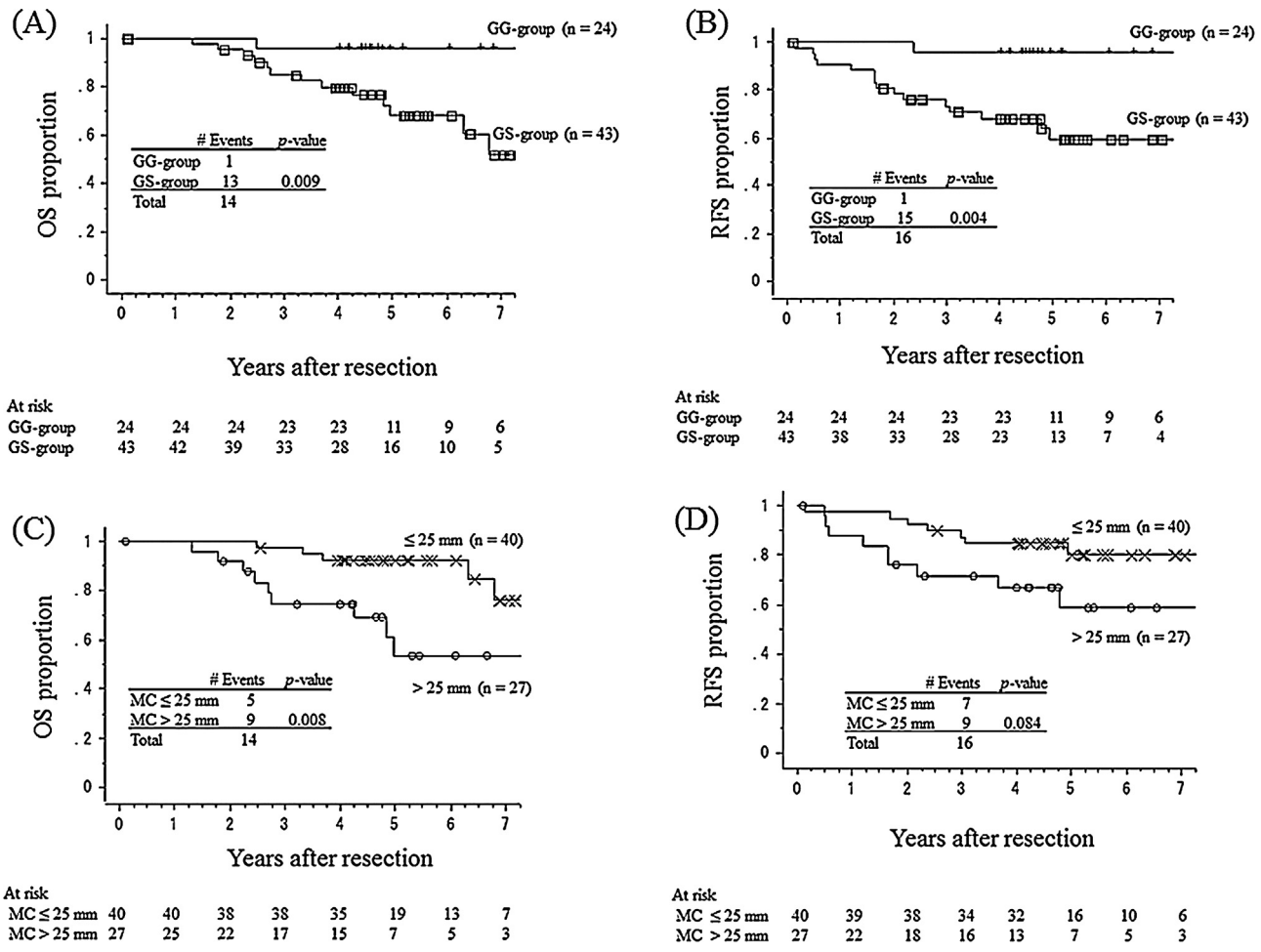

Fig. 2. (A) Overall survival curves of the GG-group and the GS-group. (B) Recurrence-free survival curves of the GG-group and the GS-group. (C) Overall survival curves of patients with a MC > 25 mm and those with a MC ≤ 25 mm. (D) Recurrence-free survival curves of patients with a MC > 25 mm and those with a MC ≤ 25 mm.

multiple lung lesions. Barsky et al. [4] demonstrated the increasing incidence of lepidic-type tumors, with 25% showing multifocality; most of these tumors have shown independent clonality upon genetic analyses, suggesting that limited resection should be recommended. On the other hand, Girard et al. and Chung et al. tried to prove the multiclonality of these tumors using genomic analyses [21,22]. Most multifocal GGOs are considered to be multiple and distinct primary disease clones. A growing hypothesis, known as field cancerization, suggests that carcinogenic exposure or genetic factors affect tissues or organs, causing many cells in the same area to become transformed [23,24]. In addition, a history of lung cancer or extrapulmonary malignancies was speculated to be a significant predictive factor for the formation of nonsolid nodules, from analyzing the natural history of GGOs [25,26]. Further research from both clinical and genetic viewpoints is therefore needed to understand more clearly the pathophysiology of synchronous multiple lung cancers.

The appropriate treatment and surveillance methods for the residual or new GGOs remain controversial. The surgical procedure was generally determined according to site of lesion, CT findings, estimated postoperative respiratory function, and the presence or absence of preoperative comorbidities. In the current study, patients had relatively normal forced expiratory volume in 1 s and less comorbidities. Those factors were considered to be far more important in making a decision to treatment for the residual or new lesions. We investigated the fate of the residual GGOs, and growth was observed in 9 of the 118 GGOs (7.6%) during the follow-up period of this study. The frequency of pure GGO nodule growth in the literature was in the range of 0–46.0% [5,20,25–27], and several authors reported that a history of lung cancer, attenuation value of CT, initial nodule size, and a newly developed solid portion can be helpful in predicting their future growth [20,25,26]. Chang et al. [20] demonstrated that 91.7% of growing GGOs were surgically validated, and all lesions were confirmed as lung cancer. Cho et al. [27] showed that a persistent, stable, and pure GGO has a 59% chance of a cancer diagnosis. Moreover, Matsuguma et al. [25] demonstrated that the growth of part-solid and pure GGO lesions occurred even after 5 years, which suggests that we should appropriately judge treatment timing for SNs by the postoperative surveillance throughout the patient's life. The present study found that a nodule size of ≥10 mm in a SN was marginally associated with poor OS (HR; 3.166, 95%CI; 0.988–10.150, $p = 0.053$). The findings of our present study as well as previous studies demonstrate that GGO lesions should be divided into 2 subgroups; 1 that requires immediate treatment, and another that can be observed for an extended period without treatment. It is important to develop a prediction method for the development of invasive cancers using clinical data, as well as biomarkers to identify the optimal target population. These data also may justify a clinical strategy of strict local control of MC and easily accessible SNs by limited resection or SBRT, and monitoring of the residual GGOs.

The limitation of this study is its retrospective nature. First, the follow-up CT scan protocol and the follow-up duration were heterogeneous. Second, we did not perform tissue confirmation of SNs

on every study patient. Third, distinguishing additional primary tumors from pulmonary metastases was practically difficult. However, as multifocal GGO-dominant lung cancers are considered as showing the multiclonality, almost all the cases with GG-group is expected not to be satellite nodules from primary tumor. In part-solid multiple lung cancers, tumors of similar histologic subtype or those of similar histology in the presence of metastasis in intervening regional or mediastinal lymph nodes were exhaustively excluded based on the morphology-based diagnostic criteria [7].

In conclusion, there appears to be a difference in the biology between multifocal GGO-dominant tumors and solid-dominant tumors. We found that the survival of patients with synchronous multifocal GGOs is strongly affected by radiological CT findings of the MC. Regarding the residual and new lesions detected in this study, we will continue to carefully observe their course for longer than 10 years, to obtain further information on multifocal GGOs.

Conflict of interest statement

All authors declare that they have no conflicts of interest associated with this study.

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