CT imaging features regarding ground-glass nodules and solid lesions reflect prognostication of synchronous multiple lung adenocarcinoma

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Abstract

The prognosis of synchronous multiple lung adenocarcinoma (SMLA) dramatically differs due to its nature of multiple primaries or intrapulmonary metastases. This study aimed to assess computed tomography (CT)-reflected SMLA features regarding ground-glass nodules (GGNs) and solid lesions and their correlation with prognostication. One seventy eight SMLA patients who underwent surgical resection were reviewed. According to preoperative CT features, patients were categorized as: multiple GGN (MG) group: MGs without solid lesions; solid plus GGN (SPG) group: one solid lesion and at least one GGN; multiple solid (MS) group: MS lesions, with or without GGNs. Clinical characteristics, disease-free survival (DFS), and overall survival (OS) were retrieved. Largest tumor size ($P < .001$) and lymph-node metastasis prevalence ($P < .001$) were different among three groups, which were highest in the MS group, followed by the SPG group, and lowest in the MG group. Besides, the dominant tumor subtype also varied among the three groups ($P < .001$), while no difference in other clinical characteristics was discovered. DFS was more deteriorative in the MS group compared to the SPG group ($P = .017$) and MG group ($P < .001$), while of no difference between the SPG group and MG group ($P = .128$). Meanwhile, OS exhibited similar treads among the three groups. Besides, after multivariate Cox analyses adjustment, MS versus MG independently correlated with DFS ($P = .030$) and OS ($P = .027$), but SPG versus MG did not. In conclusion, preoperative CT-imaging MS lesions reflect advanced disease features and poor prognosis compared to MG and solid lesion plus GGN in SMLA patients who underwent surgical resection.

Abbreviations: AIS = adenocarcinoma in situ, CT = computed tomography, DFS = disease-free survival, GGNs = ground-glass nodules, IAC = invasive adenocarcinoma, LYN = lymph node, MG = multiple GGN, MIA = minimally invasive adenocarcinoma, MPLA = multiple primary lung adenocarcinoma, MS = multiple solid, OS = overall survival, SMLA = synchronous multiple lung adenocarcinoma, SPG = solid plus GGN.

Keywords: clinical features, ground-glass nodules, prognosis, solid lesions, synchronous multiple lung adenocarcinoma

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths despite the advancements in novel treatment strategies, technologies and drugs.[1–4] Among all lung cancer types, synchronous multiple lung adenocarcinoma (SMLA) is not common that only accounts for <3.7% of all cases.[5] While the treatment of SMLA is difficult to determine due to the perplexity in the identification between multiple primary lung adenocarcinoma (MPLA) and intrapulmonary metastasis.[6–8] Some approaches have been proposed to address this issue, such as histologic and genetic methods through genomic profiling or multiple gene polymorphisms,[9–11] while in most cases, they are only suitable for pathologic/genetic examination through resected tissue samples.

It's interesting to explore whether the features of preoperative imaging would provide some information to reflect the nature of SMLA, although surgery is performed to recognize if it's MPLA or intrapulmonary metastasis, in order to better guild the treatment. According to the current eighth TNM classification, SMLA, characterized by multiple prominent ground-glass nodules (GGNs), should be ruled out from intrapulmonary metastasis.[12] Furthermore, a multiple-center workshop proposes a diagnostic flow for MPLA based on computed tomography CT reflected GGN features and histological examination.[6]

Inspired by the above researches, the current study aimed to assess CT reflected SMLA features regarding GGNs and solid lesions, as well as their correlation with prognostication.

2. Methods

2.1. Patients

With the approval of the Ethics Committee, this study analyzed the data from178 patients with SMLA who underwent surgical resections in our hospital between January 2012 and December 2018. The patients were screened according to the following conditions: diagnosed as synchronous multiple lung cancer; confirmed as lung adenocarcinoma by pathological examination of predominant tumor; more than 18 years old; had the surgical indications (including all solid and sub-solid nodules suspected to be malignant, easily accessible ipsilateral pure GGN, and contralateral GGN with increasing size or solid component during the follow-up period) and received surgical resection; had available preoperative imaging data from CT; had at least one follow-up recording. The patients with other malignancies or cancers were excluded from the study.

2.2. CT screening

Two radiologists independently assessed the CT images; meanwhile, if these two radiologists got inconsistent findings regarding the same CT images, then a third radiologist was invited for reaching the results. A 64-detector row scanner (Brilliance, Philips, USA) was used for generating the CT scans. Initially, collimation of 64×0.625 mm and a FOV of 400 mm were applied for the routine CT scans. To identify the specific lung nodule, the following parameters were set: collimation, 64×0.625 mm; pitch, 0.64; section thickness and interval, 1.0 and 1.0 mm, respectively; 1 to 3 second scan time; matrix, 1024×1024; FOV, 180 mm; 120 kVp; and 300 mA. The reconstruction algorithms for the routine and target CT scans were referred to the previous study.[13]

2.3. Grouping

The preoperative CT images of all patients were collected and reviewed.[6] Based on the CT features (GGN or solid lesion), the patients were divided into three groups, as shown in Figure 1: multiple GGN (MG): CT images showed GGNs (including the pure and part-solid GGNs), but without solid lesions. A typical case with GGN locating at right upper lobe (concomitant lesion) and right middle lobe (main lesion) with clear boundaries (Fig 1A); solid plus GGN (SPG): CT images showed one solid lesion and at least one GGN (including the pure and part-solid GGNs). A typical case with GGN (concomitant lesions) locating at the upper lobe of the right lung with well-defined boundaries; and a solid nodule (main lesion) in the lower lobe of the right lung with pleural traction (Fig 1B); multiple solid (MS): CT images showed MS lesions, with or without GGNs. A typical case with a solid nodule in the upper lobe of the right lung (main lesion), close to the pleura; and a solid nodule (concomitant lesion) locating at the lower lobe of the right lung, which was close to the pleura with pleural traction (Fig 1C).

2.4. Clinical data collection

The clinical data of all patients were obtained from the hospital database, and the detailed data included: demographic information: age, gender, and smoke status; chronic comorbidities: hypertension, hyperlipidemia, and diabetes; disease information: Eastern Cooperative Oncology Group performance status (ECOG PS) score, location of tumor, number of resected tumors, largest tumor size (for the main lesion), lymph node (LYN) metastasis and dominant tumor subtype (adenocarcinoma in situ [AIS], minimally invasive adenocarcinoma [MIA] and invasive adenocarcinoma [IAC]); tumor markers: carcinoembryonic antigen (CEA) and cancer antigen 125 (CA125). Besides, adjuvant chemotherapy after the operation and corresponding regimens were also obtained. In addition, follow-up data of all patients were collected to assess disease-free survival (DFS) and overall survival (OS). The last day of follow-up was December 31, 2020.
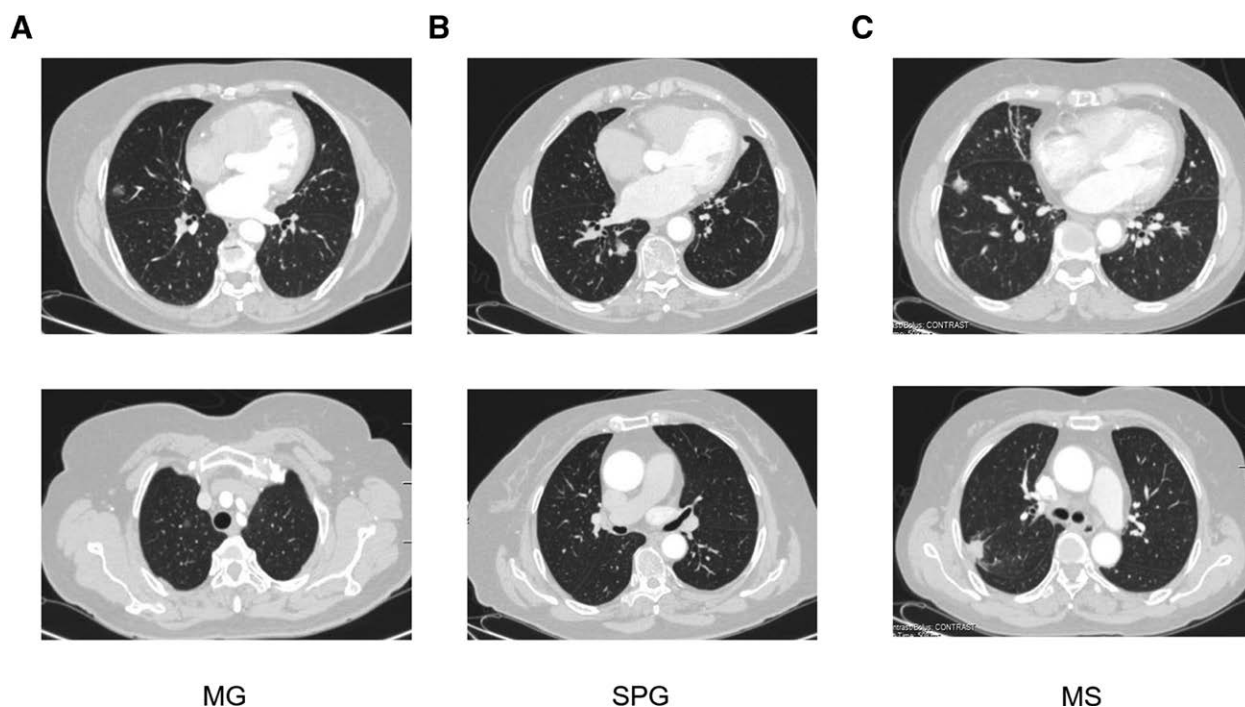

Figure 1. Typical image examples. CT image of MG (A), SPG (B) and MS (C). CT = computed tomography, MG = multiple ground-glass nodule, SPG = solid plus ground-glass nodule.

2.5. Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY) was used for data analysis, and GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, CA) was used to construct graphs. Comparisons of patients' characteristics among groups were determined using one-way analysis of variance (ANOVA) test, Kruskal-Wallis H rank sum test, and Chi-square test. Kaplan–Meier curve and log-rank test were used to compare DFS and OS among groups. Factors affecting DFS and OS were analyzed by Cox proportional hazards regression analyses. Nomogram was plotted based on the potential risk factors in multivariate Cox proportional hazards regression analysis, using the Hmisc, survival, rms, and survcomp packages in R, version 4.0 (http://www.r-project.org). The predictive performance of the nomogram was evaluated using the concordance index (C-index). A P value <0.05 was considered statistical significance.

3. Results

3.1. Clinical characteristics

A total of 178 patients with SMLA were enrolled, aged 61.7 ± 11.5 years, 38.2% were males, and 61.8% were females. 32.0%, 48.3%, and 19.7% of patients presented with disease lesions at the identical lobe, unilateral lobes, and bilateral side, respectively. The number of resected tumors was 2.6 ± 1.1. Besides, the detailed characteristics of enrolled patients are exhibited in Table 1.

3.2. Features among MG, SPG, and MS groups

Most clinical characteristics were of no difference among MG, SPG, and MS groups, such as age, gender, smoke status, chronic complications, ECOG PS, etc. (all $P > .05$). Interestingly, the largest tumor size ($P < .001$) and LYN metastasis prevalence ($P < .001$) were different among three groups, which were highest in the MS group, followed by in SPG group, and lowest in the MG group; besides, dominant tumor subtype also varied among three groups ($P < .001$) (Table 2). In detail, the dominant tumor subtype was AIS/MIA (62.9%) in the MG group, while the dominant tumor subtype was IAC in the SPG group (94.6%) and the MS group (100.0%) (Table 2). Furthermore, according to the diagnostic flow in a previous paper,[6] 93.8% of patients were diagnosed with MPLA, while 6.2% were diagnosed with intrapulmonary metastasis (Table 3).

3.3. Prognostication among MG, SPG, and MS groups

DFS was varied among MG, SPG, and MS groups ($P < .001$) (Fig. 2). Subsequent multiple-group comparisons revealed that DFS was more deteriorative in the MS group compared to the SPG group ($P = .017$) and MG group ($P < .001$), while of no difference between the SPG group and MG group ($P = .128$).

In terms of OS, it was different among MG, SPG, and MS groups as well ($P < .001$) (Fig. 3). Further, multiple-group comparisons disclosed that OS was worse in the MS group compared to the SPG group ($P = .020$) and MG group ($P < .001$), but it was similar between the SPG group and MG group ($P = .431$).

3.4. Prognostic factors

Univariate Cox analysis exhibited that MS versus MG ($P < .001$, HR = 4.334), largest tumor size ($P = .002$, HR = 2.487), LYN metastasis ($P < .001$, HR = 4.024), and dominant tumor subtype IAC ($P = .002$, HR = 2.824) linked with unfavorable DFS, but SPG versus MG ($P = .123$, HR = 1.795) did not correlate with DFS (Fig 4A). Then multivariate Cox analysis was performed to sort independent prognostic factors,

which observed that MS versus MG ($P = .030$, HR = 2.680), hypertension ($P = .008$, HR = 2.380), ECOG PS ($P = .021$, HR = 2.296), identical lobe disease versus bilateral side disease ($P = .040$, HR = 2.421), and LYN metastasis ($P = .011$, HR = 2.796) independently predicted more deteriorative DFS (Fig 4B).

In an aspect of OS, univariate Cox analysis found that MS versus MG ($P < .001$, HR = 5.060), ECOG PS ($P = .039$, HR = 2.172), largest tumor size ($P = .004$, HR = 3.133), LYN metastasis ($P < .001$, HR = 5.633) and dominant tumor subtype IAC ($P = .005$, HR = 4.416) correlated with worse OS, while SPG versus MG ($P = .299$, HR = 1.712) did not relate to OS (Fig 5A). In addition, multivariate Cox analysis discovered that MS versus MG ($P = .027$, HR = 3.695), identical lobe disease versus bilateral side disease ($P = .006$, HR = 4.281), unilateral lobes disease versus bilateral side disease ($P = .023$, HR = 3.136), and LYN metastasis ($P = .047$, HR = 2.779) independently forecasted depraved OS (Fig 5B).

3.5. Nomogram

Nomogram for DFS and OS were established based on the independent prognostic factors, which observed that combining

Table 1	
Patients' characteristics.	
Items	**SMLA patients (N = 178)**
Demographic information	
Age (years), mean ± SD	61.7 ± 11.5
Gender, No. (%)	
Female	110 (61.8)
Male	68 (38.2)
Smoke status, No. (%)	
Never	110 (61.7)
Former	51 (28.7)
Current	17 (9.6)
Chronic comorbidities	
Hypertension, No. (%)	53 (29.8)
Hyperlipidemia, No. (%)	65 (36.5)
Diabetes, No. (%)	33 (18.5)
Disease information	
ECOG PS score, No. (%)	
0	134 (75.3)
1	44 (24.7)
Location of tumors, No. (%)	
Identical lobe	57 (32.0)
Unilateral lobes	86 (48.3)
Bilateral side	35 (19.7)
Number of resected tumors, mean ± SD	2.6 ± 1.1
Largest tumor size (cm), mean ± SD	2.3 ± 1.2
LYN metastasis, No. (%)	39 (21.9)
Dominant tumor subtype, No. (%)	
AIS/MIA	68 (38.2)
IAC	110 (61.8)
Tumor markers	
CEA (ng/mL), median (IQR)	5.2 (2.4–37.0)
CA125 (U/mL), median (IQR)	32.5 (13.1–71.2)
Adjuvant chemotherapy, No. (%)	69 (38.8)
Adjuvant chemotherapy regimen, No. (%)	
NP	34 (19.1)
TP	15 (8.4)
GP	11 (6.2)
DP	9 (5.1)

AIS = adenocarcinoma in situ, CA125 = cancer antigen 125, CEA = carcinoembryonic antigen, DP = docetaxel + cisplatin or carboplatin, ECOG PS = Eastern Cooperative Oncology Group performance status, GP = gemcitabine + cisplatin or carboplatin, IAC = invasive adenocarcinoma, IQR = interquartile range, LYN = lymph node, MIA = minimally invasive adenocarcinoma, NP = navelbine + cisplatin, SD = standard deviation, SMLA = synchronous multiple lung adenocarcinoma, TP = taxol + cisplatin or carboplatin.

Table 2

Comparisons of patients' characteristics among groups.

Items	MG (n = 105)	SPG (n = 37)	MS (n = 36)	P value
Demographic information				
Age (years), mean ± SD	61.2 ± 11.3	62.3 ± 12.2	62.4 ± 11.5	0.826
Gender, No. (%)				0.133
Female	71 (67.6)	21 (56.8)	18 (50.0)	
Male	34 (32.4)	16 (43.2)	18 (50.0)	
Smoke status, No. (%)				0.061
Never	71 (67.6)	22 (59.5)	17 (47.2)	
Former	29 (27.6)	10 (27.0)	12 (33.4)	
Current	5 (4.8)	5 (13.5)	7 (19.4)	
Chronic comorbidities				
Hypertension, No. (%)	28 (26.7)	14 (37.8)	11 (30.6)	0.439
Hyperlipidemia, No. (%)	35 (33.3)	15 (40.5)	15 (41.7)	0.569
Diabetes, No. (%)	18 (17.1)	7 (18.9)	8 (22.2)	0.794
Disease information				
ECOG PS score, No. (%)				0.144
0	84 (80.0)	27 (73.0)	23 (63.9)	
1	21 (20.0)	10 (27.0)	13 (36.1)	
Location of tumors, No. (%)				0.092
Identical lobe	31 (29.5)	8 (21.6)	18 (50.0)	
Unilateral lobes	51 (48.6)	21 (56.8)	14 (38.9)	
Bilateral side	23 (21.9)	8 (21.6)	4 (11.1)	
Number of resected tumors, mean ± SD	2.5 ± 0.9	2.7 ± 1.2	2.8 ± 1.4	0.324
Largest tumor size (cm), mean ± SD	1.8 ± 0.9	2.5 ± 1.2	3.3 ± 1.4	**<0.001**
LYN metastasis, No. (%)	3 (2.9)	13 (35.1)	23 (63.9)	**<0.001**
Dominant tumor subtype, No. (%)				**<0.001**
AIS/MIA	66 (62.9)	2 (5.4)	0 (0.0)	
IAC	39 (37.1)	35 (94.6)	36 (100.0)	
Tumor markers				
CEA (ng/mL), median (IQR)	5.1 (2.2–34.3)	3.3 (1.7–37.8)	10.7 (2.7–45.0)	0.229
CA125 (U/mL), median (IQR)	28.9 (12.7–78.9)	28.1 (12.0–62.0)	43.2 (21.1–72.7)	0.356

AIS = adenocarcinoma in situ, CA125 = cancer antigen 125, CEA = carcinoembryonic antigen, ECOG PS = Eastern Cooperative Oncology Group performance status, GGN = ground glass nodule, IAC = invasive adenocarcinoma, IQR = interquartile range, LYN = lymph node, MG = multiple ground glass nodule, MS = multiple solid, MIA = minimally invasive adenocarcinoma, SD = standard deviation, SPG = solid plus ground glass nodule.

Table 3

Diagnosis.

Items, No. (%)	MPLA	Intrapulmonary metastasis
SMLA patients (N = 178)	167 (93.8)	11 (6.2)
MG (n = 105)	105 (100.0)	0 (0.0)
SPG (n = 37)	37 (100.0)	0 (0.0)
MS (n = 36)	25 (69.4)	11 (30.6)

GGN = ground glass nodule, MG = multiple ground glass nodule, MPLA = multiple primary lung adenocarcinoma, MS = multiple solid, SPG = Solid plus ground glass nodule.

MS versus MG, hypertension, ECOG PS, identical lobe disease versus bilateral side disease, and LYN metastasis exhibited a C-Index of 0.763 (95%CI 0.690–0.836) for DFS estimation (Fig 6A). Then combining MS versus MG, identical lobe disease versus bilateral side disease, and LYN metastasis presented a C-Index of 0.833 (95%CI 0.764–0.902) for OS estimation (Fig 6B).

4. Discussion

SMLA frequently affects females (accounting for 60%–80% cases) and never smokers (accounting for 30%–80% cases), which is typically catheterized as IAC with lepidic-predominant type, MIA or AIS.[14] The general 5-year OS ranges from 65% to 80% in SMLA patients receiving local treatment only, and the prognosis varies significantly within SMLA subgroups, with MPLA patients having a favorable prognosis compared with intrapulmonary metastasis.[15–17] Previously, some methods for categorizing the features of SMLA have been proposed, including histological examinations of multiple markers, gene mutations, or even more directly, judging from the survival profile.[18] Preoperative MG frequently indicates a satisfactory survival profile in SMLA patients, which may indicate MPLA; while the coexistence of one or more solid lesions plus GGN remains hard to define its survival profile, implying MPLA or intrapulmonary metastasis may be integrated into these patients.[6,18] So as to clarify this issue, more efforts are needed.

In our present study, we divided SMLA patients into three groups (MG, SPG, and MS groups), then investigated the differences among them, discovering that the largest tumor size, LYN metastasis prevalence, and dominant tumor subtype were varied among the three groups, while other clinical characteristics differed. The possible explanation was that patients with MS indicated a higher possibility of intrapulmonary metastasis than MPLA, and the intrapulmonary metastasis reflected enhanced tumor growth ability and more invasive nature of tumors, resulting in increased largest tumor size, LYN metastasis prevalence, and dominant tumor subtype IAC compared to patients with MG, SPG.[14,18] Our significant findings were also partially less than a previous study,[6] which might result from the patients' heterogeneity and relatively small samples in our study.

A previous paper proposed a diagnosis flow for MPLA and intrapulmonary metastasis in SMLA patients,[6] which included GGN-associated CT features, tumor histological subtype of AIS or MIA, major subtype or variant difference, lepidic background, and genetic features. Following that diagnosis flow, our present study identified 93.8% MPLA patients and 6.2% patients with intrapulmonary metastasis. In the MG and SPG
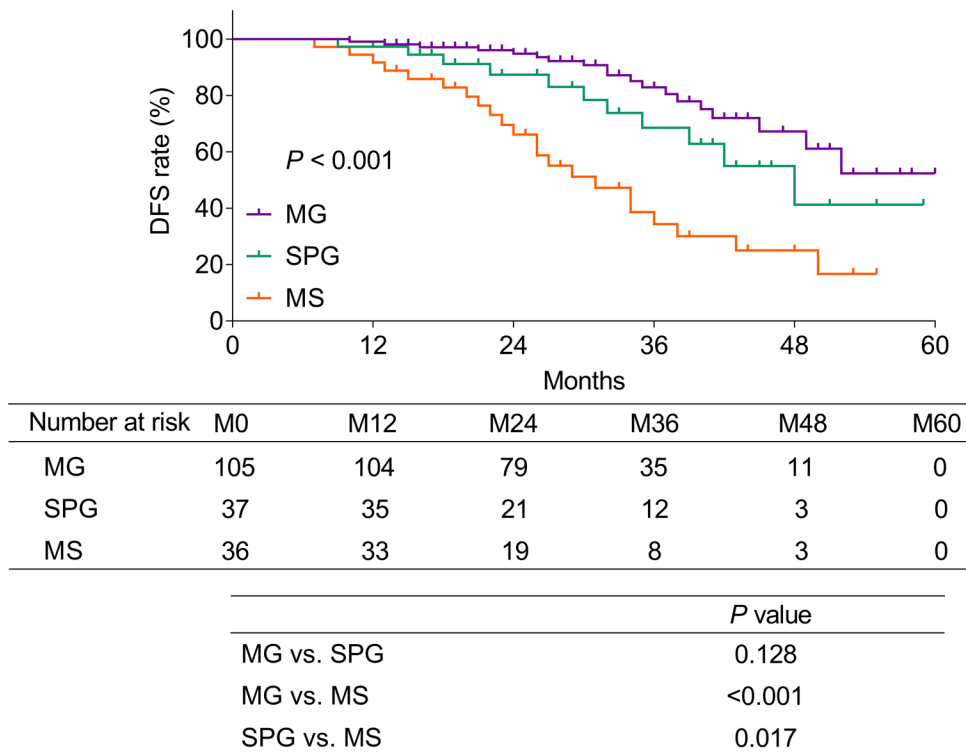
Figure 2. Comparison of DFS by K-M curve. DFS = disease-free survival.

Number at risk	M0	M12	M24	M36	M48	M60
MG	105	104	79	35	11	0
SPG	37	35	21	12	3	0
MS	36	33	19	8	3	0

	P value
MG vs. SPG	0.128
MG vs. MS	<0.001
SPG vs. MS	0.017
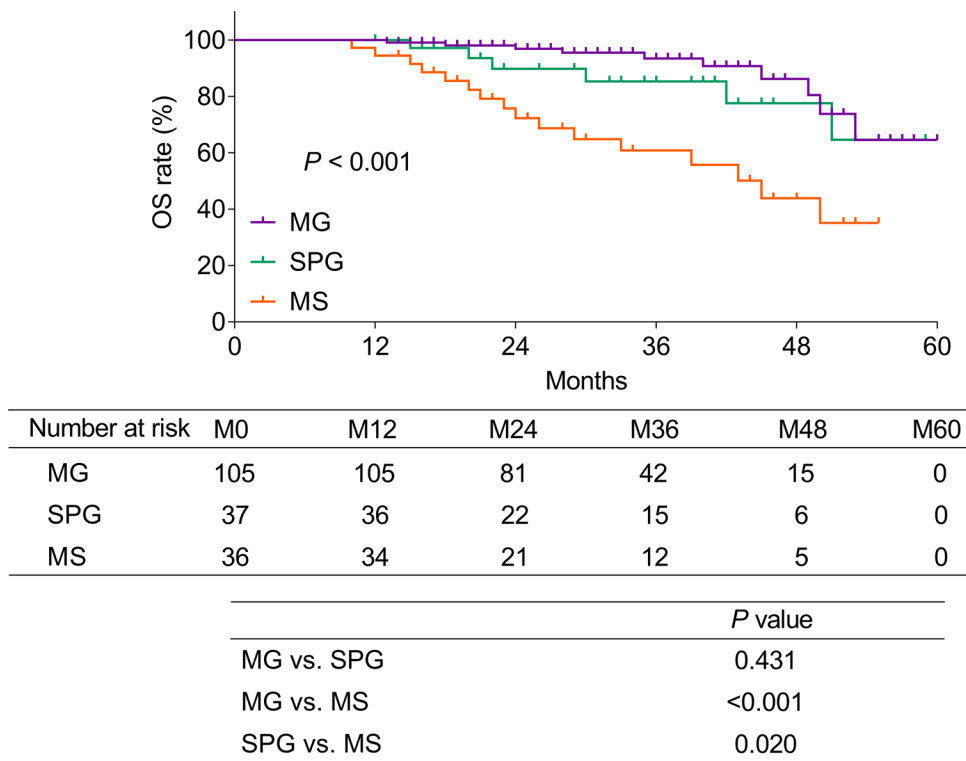
Figure 3. Comparison of OS by K-M curve. OS = overall survival.

Number at risk	M0	M12	M24	M36	M48	M60
MG	105	105	81	42	15	0
SPG	37	36	22	15	6	0
MS	36	34	21	12	5	0

	P value
MG vs. SPG	0.431
MG vs. MS	<0.001
SPG vs. MS	0.020

A

Univariate Cox's proportional hazards regression analysis for DFS

Variables	P value	HR (95%CI)
Group		
MG	Reference	
SPG	0.123	1.795 (0.853-3.774)
MS	**<0.001**	4.334 (2.343-8.016)
Age (>60 years vs. ≤60 years)	0.504	1.220 (0.680-2.189)
Gender (male vs. female)	0.573	1.171 (0.677-2.025)
Smoke status		
Never	Reference	
Former	0.730	1.115 (0.601-2.067)
Current	0.776	1.135 (0.473-2.725)
Hypertension (yes vs. no)	0.248	1.401 (0.791-2.483)
Hyperlipidemia (yes vs. no)	0.648	1.141 (0.648-2.009)
Diabetes (yes vs. no)	0.851	1.066 (0.547-2.077)
ECOG PS score (1 vs. 0)	0.116	1.642 (0.884-3.052)
Location of tumors		
Bilateral side	Reference	
Unilateral lobes	0.301	1.408 (0.736-2.693)
Identical lobe	0.152	1.750 (0.813-3.765)
Number of resected tumors in individual patients (≥3 vs. <3)	0.124	1.575 (0.883-2.810)
Largest tumor size (≥2 cm vs. <2 cm)	**0.002**	2.487 (1.407-4.397)
LYN metastasis (yes vs. no)	**<0.001**	4.024 (2.319-6.984)
Dominant tumor subtype (IAC vs. AIS/MIA)	**0.002**	2.824 (1.450-5.499)
CEA (abnormal vs. normal)	0.251	1.388 (0.793-2.429)
CA125 (abnormal vs. normal)	0.123	1.543 (0.890-2.676)

B

Backward stepwise multivariate Cox's proportional hazards regression analysis for DFS

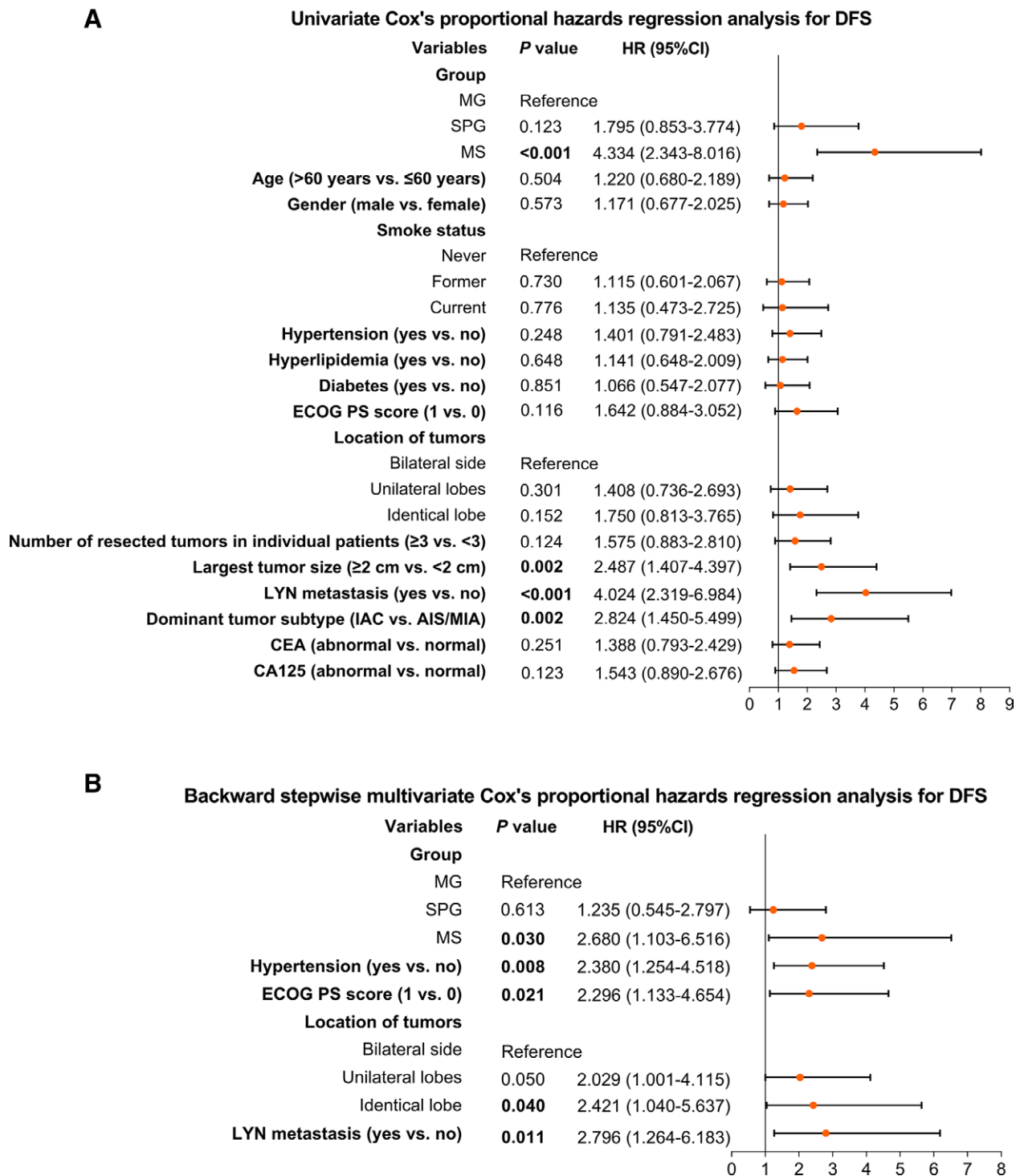| Variables	P value	HR (95%CI)
Group		
MG	Reference	
SPG	0.613	1.235 (0.545-2.797)
MS	**0.030**	2.680 (1.103-6.516)
Hypertension (yes vs. no)	**0.008**	2.380 (1.254-4.518)
ECOG PS score (1 vs. 0)	**0.021**	2.296 (1.133-4.654)
Location of tumors		
Bilateral side	Reference	
Unilateral lobes	0.050	2.029 (1.001-4.115)
Identical lobe	**0.040**	2.421 (1.040-5.637)
LYN metastasis (yes vs. no)	**0.011**	2.796 (1.264-6.183)

Figure 4. Cox analysis for DFS. Univariate (A) and multivariate (B) Cox proportional hazards regression analysis for DFS. DFS = disease-free survival.
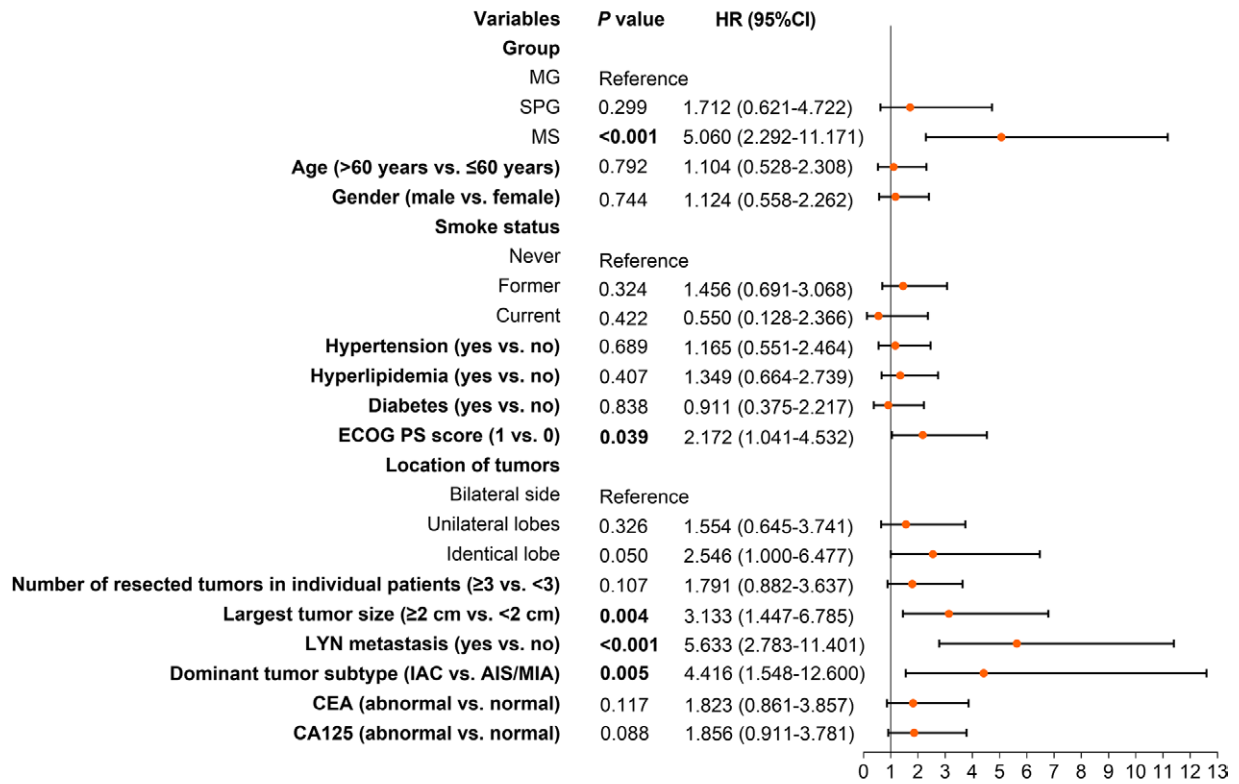
groups, 100% of cases were categorized as MPLA; in the MS group, 69.4% of cases were classified as MPLA and 30.6% as intrapulmonary metastasis.

Since it's a recognized way to categorize SMLA in accordance with its survival profile,[6,18] which may provide some information for its nature as MPLA or intrapulmonary metastasis. A previous study reported that MPLA patients who underwent surgical resection with or without adjuvant chemotherapy achieved 1-year OS of 96.6% and 3-year OS of 74.2%.[19]

Another study observed that MPLA patients with at least 3 lesions who underwent one-stage resection realized 3-year DFS of 88.9% and 3-year OS of 94.7%.[20] However, the SMLA patients with intrapulmonary metastasis have obviously lower survivals rates.[21,22] In our present study, we discovered that patients with MS exhibited more depraved DFS and OS compared to patients with SPG or MG, while patients with SPG and patients with MG had similar outcomes. It was worth noting that we also adjusted the results via multivariate analyses,

A

Univariate Cox's proportional hazards regression analysis for OS

Variables	P value	HR (95%CI)
Group		
MG	Reference	
SPG	0.299	1.712 (0.621-4.722)
MS	**<0.001**	5.060 (2.292-11.171)
Age (>60 years vs. ≤60 years)	0.792	1.104 (0.528-2.308)
Gender (male vs. female)	0.744	1.124 (0.558-2.262)
Smoke status		
Never	Reference	
Former	0.324	1.456 (0.691-3.068)
Current	0.422	0.550 (0.128-2.366)
Hypertension (yes vs. no)	0.689	1.165 (0.551-2.464)
Hyperlipidemia (yes vs. no)	0.407	1.349 (0.664-2.739)
Diabetes (yes vs. no)	0.838	0.911 (0.375-2.217)
ECOG PS score (1 vs. 0)	**0.039**	2.172 (1.041-4.532)
Location of tumors		
Bilateral side	Reference	
Unilateral lobes	0.326	1.554 (0.645-3.741)
Identical lobe	0.050	2.546 (1.000-6.477)
Number of resected tumors in individual patients (≥3 vs. <3)	0.107	1.791 (0.882-3.637)
Largest tumor size (≥2 cm vs. <2 cm)	**0.004**	3.133 (1.447-6.785)
LYN metastasis (yes vs. no)	**<0.001**	5.633 (2.783-11.401)
Dominant tumor subtype (IAC vs. AIS/MIA)	**0.005**	4.416 (1.548-12.600)
CEA (abnormal vs. normal)	0.117	1.823 (0.861-3.857)
CA125 (abnormal vs. normal)	0.088	1.856 (0.911-3.781)

B

Backward stepwise multivariate Cox's proportional hazards regression analysis for OS

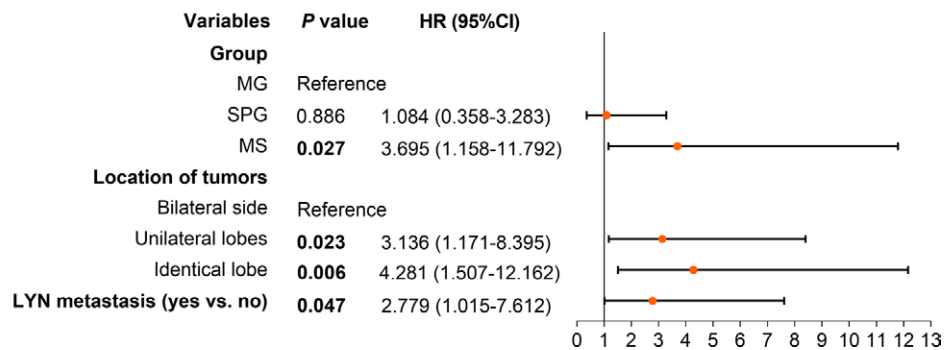| Variables	P value	HR (95%CI)
Group		
MG	Reference	
SPG	0.886	1.084 (0.358-3.283)
MS	**0.027**	3.695 (1.158-11.792)
Location of tumors		
Bilateral side	Reference	
Unilateral lobes	**0.023**	3.136 (1.171-8.395)
Identical lobe	**0.006**	4.281 (1.507-12.162)
LYN metastasis (yes vs. no)	**0.047**	2.779 (1.015-7.612)

Figure 5. Cox analysis for OS. Univariate (A) and multivariate (B) Cox proportional hazards regression analysis for OS. OS = overall survival.

and observed similar findings. This could provide evidence that SPG and MG have similar survival, indicating MPLA features, whereas MS has extremely worse survival, indicating intrapulmonary metastasis features.

Several limitations could be mentioned in our study: firstly, because SMLA was rare in our hospital, the sample size was relatively small; secondly, the follow-up duration could be extended further to investigate the OS; thirdly, a validation cohort for nomogram analysis could be enrolled in the future studies; fourthly, only SMLA patients who underwent surgical resection were enrolled in this study, therefore the findings might not be applicable to SMLA patients receiving other therapies; fifthly, the follow-up of the pure GGN was indicated to present a higher likelihood of growth in older population, while the lack of follow-up for the pure GGN was another limitation of this study.[23]

In conclusion, preoperative CT-imaging MS lesions reflects advanced disease features and poor prognosis compared to MG and solid lesion plus GGN in SMLA patients who underwent surgical resection.

Author contributions

Conceptualization: Jieli Kou.
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Supervision: Jieli Kou, Yang Yu.
Writing – original draft: Jieli Kou, Xiaofei Gu, Yang Yu.
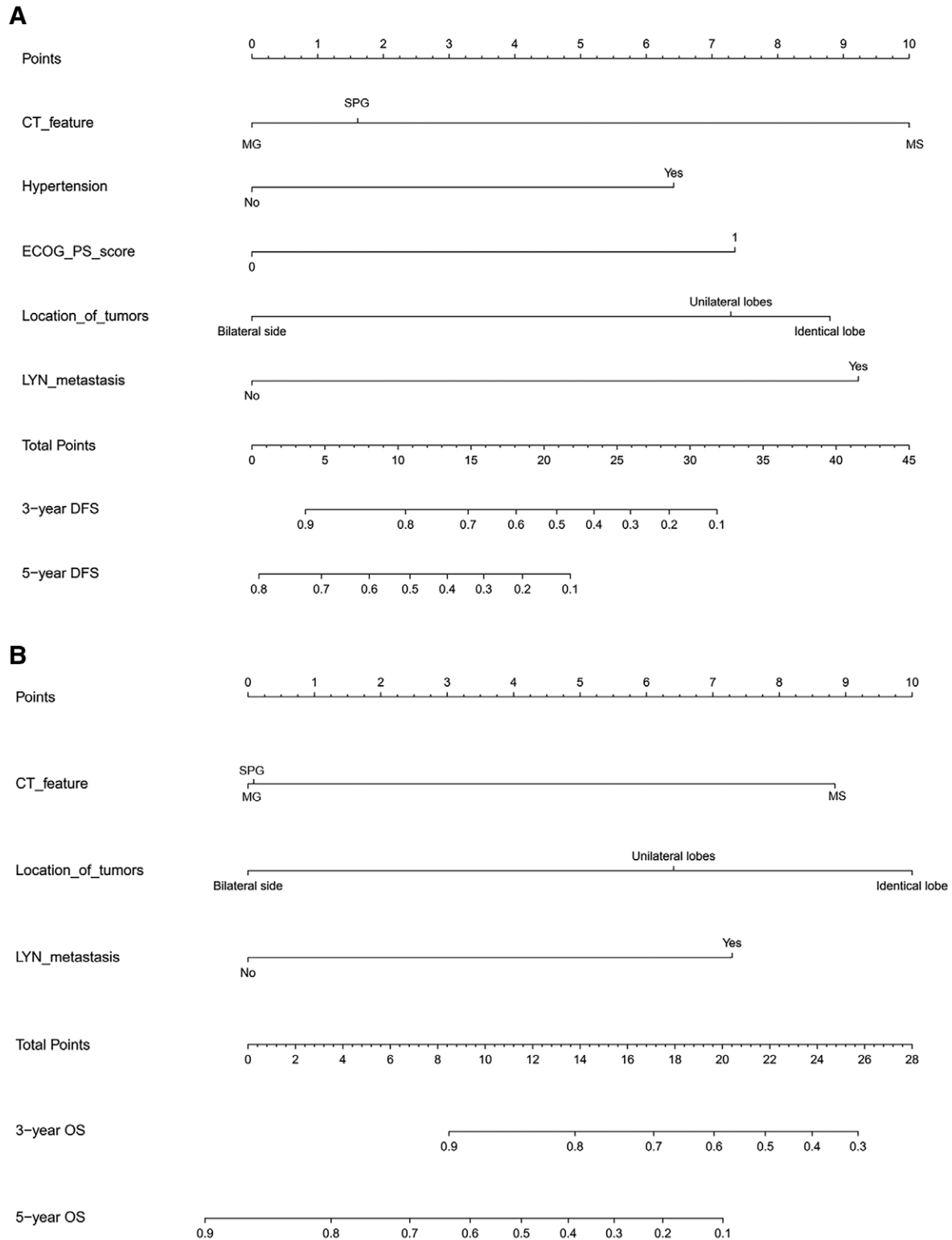**Writing – review & editing:** Jieli Kou, Shugang Zheng

A

B

Figure 6. Nomogram analysis. Nomogram analysis involving independent prognostic factors for estimating DFS (A) and OS (B). DFS = disease-free survival, OS = overall survival.

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