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The role of the ground-glass opacity ratio in resected lung adenocarcinoma

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Abstract

OBJECTIVES: The goal of this study was to investigate the role of the ground-glass opacity (GGO) ratio in lung adenocarcinoma in predicting surgical outcomes.

METHODS: Patients who underwent surgical resection for pulmonary adenocarcinoma between January 2004 and December 2013 were reviewed. The clinical data, imaging characteristics of nodules, surgical approaches and outcomes were analysed with a mean follow-up of 87 months.

RESULTS: Of 789 enrolled patients, 267 cases were categorized as having a GGO ratio ≥0.75; 522 cases were categorized as having a GGO ratio <0.75. The gender, tumour differentiation, epidermal growth factor receptor mutation, smoking habits, lymphovascular space invasion, tumour size, maximum standard uptake value and carcinoembryonic antigen levels were significantly different in the 2 groups. In the group with a GGO ratio ≥0.75, 63.3% of the patients underwent sublobar resection (18.8% with a GGO ratio < 0.75, P <0.001). These patients had fewer relapses (2.2% for GGO ratio ≥0.75, 26.8% for GGO ratio <0.75, P < 0.001) and a better 5-year survival rate (95.5% for GGO ratio ≥0.75, 77.4% for GGO ratio <0.75, P < 0.001). None of the patients with a GGO ratio ≥0.75 had lymph node involvement. The multivariable Cox regression analysis revealed that a GGO ratio <0.75 was an independent factor for postoperative relapse with a hazard ratio of 3.96.

CONCLUSIONS: A GGO ratio ≥0.75 provided a favourable prognostic prediction in patients with resected lung adenocarcinoma. Sublobar resection and lymph node sampling revealed a fair outcome regardless of tumour size. However, anatomical resection is still the standard approach for patients with tumours with a GGO ratio <0.75, size >2 cm.

Keywords: Lung cancer • Ground-glass opacity • Surgery

INTRODUCTION

Lung cancer remains a leading cause of cancer-related deaths worldwide. With the development of computed tomography (CT) scans of the chest, low-dose CT has become more sensitive in detecting early-stage lung cancers [1]. More and more small nodules have been identified in CT scan screening. The incidence of nodules with ground-glass opacity (GGO) in a screened population ranges from 0.2% to 0.5% [2]. The diagnosis of GGO includes focal infection, fibrosis, precancerous lesions (adenomatous hyperplasia) and adenocarcinoma. The goal of the surgical management of GGO lesions is to obtain tissue proof and accurate staging. Some studies have reported that a GGO ratio provides a favourable prognostic value in a small lung adenocarcinoma detected by CT scan [3, 4]. GGO-dominant lung adenocarcinoma represents a homogeneous group with non-invasive characteristics. Retrospective studies have showed that sublobar resection in patients with early-stage lung cancer had outcomes similar to those obtained in patients who had an anatomical resection [5, 6]. The theoretical advantage of limited resection includes preservation of pulmonary function and reduction of perioperative morbidity. However, there are no robust data from randomized trials that demonstrate better long-term outcomes following sublobar resection or the role of lymph node dissection. De Zoysa *et al.* [7] concluded that lobectomy was still the principal strategy for treatment of early-stage cancer in physiologically suitable patients. However, that review article did not focus on pulmonary nodules with a GGO component. Adenocarcinoma subtype and lymph node status are the most important prognostic factors [8]. Pure GGO or GGO mixed with a small area of solid attenuation results in a good prognosis. A high GGO ratio on a CT scan is predictive of better overall survival

(OS) and disease-free survival (DFS). The cut-off point of the GGO ratio in the determination of a surgical outcome (anatomical or sublobar resection) was inconsistent in different studies [3]. The association between GGO ratio, grade of tumour differentiation and epidermal growth factor receptor (EGFR) status has not been elucidated. The surgical procedure of sublobar resection, such as wedge resection versus segmentectomy and lymph node dissection versus lymph node sampling for pulmonary nodules with a GGO component, remains controversial. Our goal was to clarify the role of the GGO ratio in early-stage lung adenocarcinoma regarding clinical characteristics and surgical outcome.

PATIENTS AND METHODS

All patients who underwent anatomical resections for clinical early-stage (I and II) non-small-cell lung cancer (NSCLC) at the Tri-Service General Hospital, Taiwan, between January 2004 and December 2013 were reviewed retrospectively. This study was approved by the institutional review board of our hospital (TSGHIRB 1-105-05-010). The patients underwent preoperative staging workups, including chest CT scans, positron emission tomography (PET) and abdominal ultrasonography. PET was performed for the assessment of mediastinal lymph node or bone metastases. We excluded patients who had received neoadjuvant chemotherapy and those with synchronous or metachronous lung cancers and non-adenocarcinoma. Determination of cancer stage was based on the tumour–node–metastasis classification (7th edition) of the American Joint Committee on Cancer [9]. A total of 789 patients who underwent surgical resection and mediastinal lymph node dissection for lung adenocarcinoma were enrolled. The anatomical resection included the procedures of lobectomy, bilobectomy and pneumonectomy. The sublobar resection included wedge resection and segmentectomy.

All images were acquired within a single academic medical centre using a Philips multidetector CT system (Philips Healthcare, Brilliance 64, Amsterdam, Netherlands). The images were photographed with a section thickness ranging from 1 to 2.5 mm using both a mediastinum (width, 350 HU; level, 30 HU) and lung window (width, 1500 HU; level, -600 HU). Tumour size was measured in the largest cross-section by averaging the length and width. The GGO ratio was assessed by 3 experienced radiologists (K.-H.K., C.-K.C. and H.-H.H.). The GGO was defined as an area of slight homogeneous increase in density that did not obstruct the underlying vascular marking. Patients were categorized according to the area occupied by the GGO within the whole tumour in the CT slice with the maximal tumour area. The 2 patient groups were GGO ratio $\geq$0.75 and <0.75 [4]. When enlarged hilar or mediastinal lymph nodes of more than 10 mm in short-axis diameter were detected using conventional CT scanning, we defined them as clinical N1 or N2. Postoperative surveillance included contrast-enhanced CT scans and measurements of serum carcinoembryonic antigen level. CT scans were performed for tumour assessment every 4 months. Magnetic resonance imaging of the brain was performed as indicated clinically. Relapse (including loco-regional recurrence or distant metastasis) was documented with either imaging or histopathological diagnosis for all patients.

Statistical analysis

Descriptive data are expressed as mean ± standard deviation. The Mann–Whitney test was used to investigate continuous variables, and the χ^2 test was used to compare categorical variables between groups. Survival from the date of surgery was calculated using Kaplan–Meier survival analysis. The hazard ratios (HRs) of relapse and of the other parameters of interest were calculated by multivariable Cox regression analysis. The variables were selected for multivariable Cox regression analysis when it revealed statistical differences in χ^2 test and Mann–Whitney test. Pearson correlations were examined to determine the relationship between the GGO ratio and the maximum standard uptake value (SUV_{max}). SPSS v.18.0 software (SPSS, Inc., Chicago, IL, USA) was used for all analyses, and statistical significance was defined as *P*-value <0.05.

RESULTS

Of 789 patients, 267 (33.84%) were categorized with a GGO ratio $\geq$0.75. Significant differences were observed in gender, tumour differentiation, EGFR mutation status, smoking habits, visceral pleural invasion, lymphovascular space invasion, tumour size, SUV_{max} and serum carcinoembryonic antigen level between the 2 groups (GGO ratio $\geq$0.75 or <0.75) (Tables 1 and 2). In patients with a GGO ratio $\geq$0.75, women were dominant, tumours were well differentiated, the EGFR mutation was less prevalent and there was an absence of smoking, visceral pleural invasion and lymphovascular space invasion. In addition, tumours were smaller, the SUV_{max} was lower and there was a lower serum carcinoembryonic antigen level.

In the group with a GGO ratio <0.75, 424 (81.2%) patients underwent anatomical resection. In patients with a GGO ratio $\geq$0.75, 63.3% underwent sublobar resection (18.8% for GGO ratio <0.75, $P < 0.001$). All patients with a GGO ratio $\geq$0.75 were free from lymph node involvement. The patients had better surgical outcomes with fewer tumour relapses (2.2% for a GGO ratio $\geq$0.75, 26.8% for a GGO ratio <0.75, $P < 0.001$) and a higher 5-year survival rate (95.5% for a GGO ratio $\geq$0.75, 77.4% for a GGO ratio <0.75, $P < 0.001$) (Fig. 1A). Three patients in the GGO ratio $\geq$0.75 group died of non-cancer-related causes. The 5-year DFS rate of patients with a GGO ratio $\geq$0.75 was 95.3%, and 61.8% for patients with a GGO ratio <0.75 (log-rank $P < 0.001$) (Fig. 1B). In the GGO <0.75 group (522 patients), 140 patients had a relapse (including loco-regional recurrences and distant metastases). Of these, 85 patients developed loco-regional relapses (lung: 66; lymph node: 6; pleura seeding: 13); 33 patients developed distant metastases (bone: 9; liver: 3; brain 15; multiple organs: 6); 22 patients developed both loco-regional and distant metastases.

The 5-year OS was similar between the groups with a GGO ratio $\geq$0.75 who had anatomical or sublobar resection (for the group with a GGO ratio $\geq$0.75, the OS was 96.6% for anatomical resection and 100% for sublobar resection, log-rank $P = 0.17$). For patients with a GGO ratio <0.75, the 5-year OS was 78.0% for anatomical resection and 72.5% for sublobar resection (log-rank $P = 0.39$) (Fig. 2). The 5-year OS was no different between patients with small or large tumours ($\leq$2 cm, OS: 95.0%; >2 cm, OS: 100%); for patients with a GGO ratio $\geq$0.75, the log-rank was $P = 0.61$. In the GGO ratio <0.75 group, the 5-year OS was better for patients with small tumours ($\leq$2 cm, OS: 84.3%) than for patients with large tumours (>2 cm, 5-year OS: 72.3%, log-rank $P = 0.002$) (Fig. 3A). The 5-year OS was no different between anatomical or sublobar resection for a GGO ratio <0.75 T1a tumour. The 5-year OS was 85.9% for patients with anatomical resection and 75.4% for those who had a sublobar resection (log-rank $P = 0.42$). After tumour size

Table 1: Characteristics of patients with adenocarcinomas with different GGO ratios

	GGO ≥0.75 (*n* = 267, %)	GGO <0.75 (*n* = 522, %)	*P*-value[a]
Gender, *n* (%)			
Male	69 (25.8)	189 (36.2)	**0.004**
Female	198 (74.2)	333 (53.8)	
Operation, *n* (%)			
Anatomical resection	98 (36.7)	424 (81.2)	**<0.001**
Wedge resection	129 (48.3)	75 (14.4)	
Segmentectomy	40 (15.0)	23 (4.4)	
Differentiation, *n* (%)			
Good	198 (74.1)	189 (36.2)	**<0.001**
Moderate	68 (25.5)	245 (46.9)	
Poor	1 (0.4)	88 (16.9)	
EGFR, *n* (%)			
Mutation	86 (43.4)	191 (57.4)	**0.002**
Wild type	112 (56.6)	142 (42.6)	
Subtype, *n* (%)			
Acinar	98 (36.7)	142 (27.2)	**<0.001**
Lepidic	82 (30.7)	42 (8.0)	
Papillary	3 (1.1)	24 (4.6)	
Micropapillary	8 (3.0)	55 (10.5)	
Solid	4 (1.5)	37 (7.1)	
Others	72 (27.0)	222 (42.5)	
Location, *n* (%)			
Central	123 (46.1)	287 (55.0)	0.017
Peripheral	144 (53.9)	235 (45.0)	
Adjuvant chemotherapy, *n* (%)			
Yes	43 (16.1)	226 (43.3)	**<0.001**
No	224 (83.9)	296 (56.7)	
Adjuvant radiotherapy, *n* (%)			
Yes	1 (0.4)	54 (10.3)	**<0.001**
No	266 (99.6)	468 (89.7)	
Smoking, *n* (%)			
Yes	14 (5.2)	36 (6.9)	**<0.001**
No	228 (85.4)	382 (73.2)	
Ex-smoker	25 (9.4)	104 (19.9)	
LVSI, *n* (%)			
Absent	264 (98.9)	459 (87.9)	**<0.001**
Present	3 (1.1)	63 (12.1)	
VPI, *n* (%)			
Absent	261 (97.8)	487 (93.3)	0.006
Present	6 (2.2)	35 (6.7)	
p-stage, *n* (%)			
0	16 (6.0)	1 (0.2)	**<0.001**
I	208 (77.9)	359 (68.8)	
II	24 (9.0)	78 (14.9)	
III	19 (7.1)	67 (12.8)	
IV	0 (0)	17 (3.3)	

P-values <0.05 are boldfaced.
[a]Significance was assessed using the χ^2 test.
EGFR: epidermal growth factor receptor; GGO: ground-glass opacity; LVSI: lymphovascular space invasion; p-stage: pathology stage; VPI: visceral pleural invasion.

was stratified, we analysed 299 patients who had a tumour >2 cm. The 5-year OS was no different between anatomical or sublobar resection for a GGO ratio ≥0.75 (5-year OS: 100% for both anatomical and sublobar resection groups). In contrast, the OS was better for patients with a GGO ratio <0.75 who had anatomical resection (5-year OS: 72.7%) than for those who had sublobar resection (OS: 66.2%) (log-rank $P = 0.025$) (Fig. 3B). Of 522 patients with a GGO <0.75, 94 were categorized as having pure solid tumours. The 5-year OS was 100% for patients with tumours <1 cm and 62.10% for patients with tumours ≥1 cm.

Table 2: Characteristics of patients with adenocarcinomas with different GGO ratios

Variables	GGO ≥0.75 (*n* = 267)	GGO < 0.75 (*n* = 522)	*P*-value[a]
Age (years), mean ± SD	59.94 ± 9.45	62.57 ± 10.99	0.001
SUV_{max} of tumour, mean ± SD	1.37 ± 1.24	4.97 ± 4.32	**<0.001**
Tumour size (cm), mean ± SD	1.00 ± 0.57	2.45 ± 1.31	**<0.001**
CEA (ng/ml), mean ± SD	2.25 ± 3.71	5.79 ± 13.00	**<0.001**
Dissected lymph nodes, mean ± SD	9.28 ± 6.46	12.09 ± 6.90	**<0.001**
FEV_1 (%), mean ± SD	88.77 ± 15.40	86.32 ± 15.85	0. 179
DLCO (%), mean ± SD	93.21 ± 18.73	89.56 ± 19.57	0.110
Solid component (mm), mean ± SD	1.40 ± 0.67	21.80 ± 15.61	**<0.001**

P-values <0.05 are boldfaced.
[a]Significance was assessed using the Mann–Whitney test.
CEA: carcinoembryonic antigen; DLCO: diffusing capacity of the lungs for carbon monoxide; FEV_1: forced expiratory volume in 1 s; GGO: ground-glass opacity; SD: standard deviation; SUV_{max}: maximum standard uptake value of fluorodeoxyglucose.

We analysed 531 patients for the presence of an EGFR mutation. The OS was no different between patients with a wild type or an EGFR mutation for a GGO ratio ≥0.75 (5-year survival in the wild-type group: 92.9%; mutation group: 100%). In the group with a GGO ratio <0.75, the patients with an EGFR mutation tumour had a better prognosis compared with patients with a wild-type tumour (5-year survival in the wild-type group: 64.4%; in the mutation group: 87.8%) (log-rank $P = 0.04$). Multivariable Cox regression analysis revealed that a GGO ratio <0.75 (HR 3.96) and a poorly differentiated tumour (HR 3.19) were independent factors predictive of postoperative relapse. The EGFR mutation status and tumour size had no significant impact on postoperative relapse after adjusting for other factors (Table 3).

We excluded patients with a second primary lung cancer. We evaluated the incidence of a second primary lung cancer in our institution. Of all 954 patients with lung cancer resected between January 2004 and December 2015, 14 (1.5%) patients had a second resection for primary lung cancer. Most of these operations were limited resections.

DISCUSSION

Lung cancer remains the leading cause of cancer-related deaths. Despite advances in molecular markers and new drugs, the long-term survival rate is unsatisfactory. Anatomical lobectomy is the gold standard for surgical treatment of patients with resectable NSCLC. Deaths following surgical resection are most often associated with tumour relapse [10, 11]. Following the introduction of the lung cancer screening project [1], increasingly more GGO nodules have been detected by CT scans. The management of pulmonary nodules with GGO characteristics is a challenge with some controversial issues. In the past, a favourable prognostic outcome was related to the presence of GGO nodules [3]. The cut-off point of the GGO ratio in the determination of whether to perform surgery was inconsistent in different studies. The oncological outcome of sublobar resection remains controversial. One study showed that this approach had a trend for equal OS

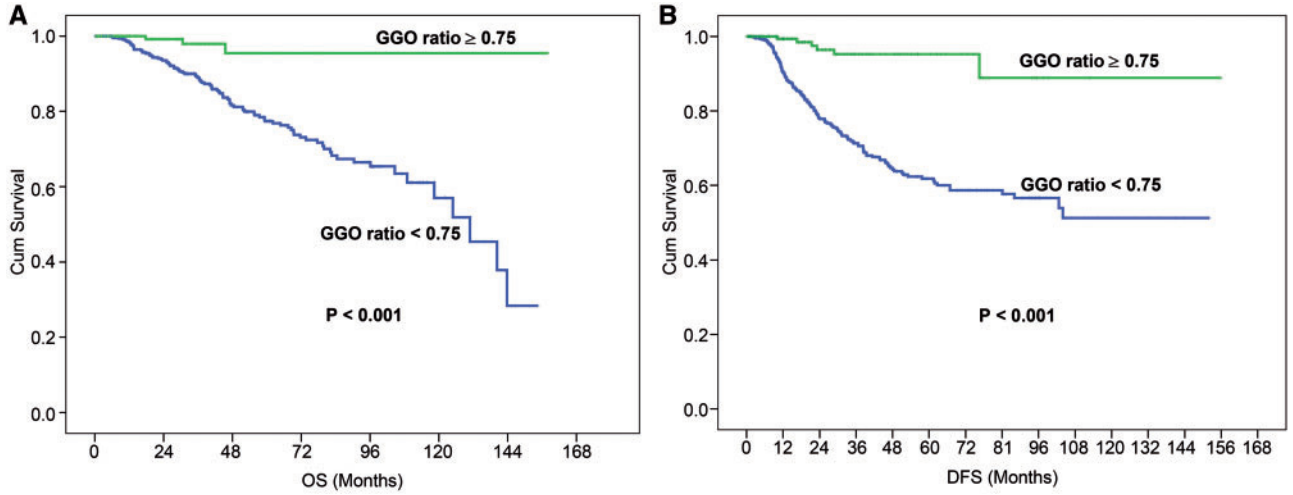

Figure 1: (**A**) OS curves for the GGO ratio ≥0.75 group and the GGO ratio <0.75 group; 5-year OS of 95.5% for GGO ratio ≥0.75, 77.4% for GGO ratio <0.75, $P < 0.001$. (**B**) DFS curves for the GGO ratio ≥0.75 and GGO ratio <0.75 groups. The 5-year DFS of patients with a GGO ratio ≥0.75 was 95.3% and 61.8% for patients with GGO ratio <0.75, log-rank $P < 0.001$. DFS: disease-free survival; GGO: ground-glass opacity; OS: overall survival.

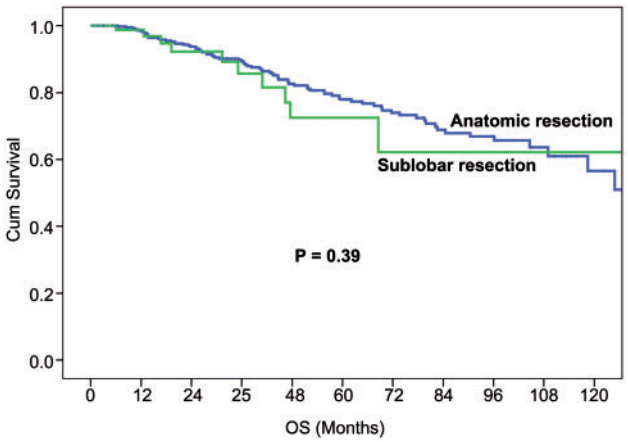

Figure 2: OS curves of patients with tumours with a ground-glass opacity ratio <0.75 who underwent anatomical resection or sublobar resection. The 5-year OS was 78.0% for anatomical resection and 72.5% for sublobar resection, log-rank $P = 0.39$. OS: overall survival.

and DFS [12]. This study, which included wedge resection and segmentectomy, enrolled patients with T1a tumours that were ≤2 cm. Khullar *et al.* [13] reported that a high recurrence rate was associated with sublobar resection in patients with tumours >2 cm (loco-regional recurrence rate of 1.9% for tumours ≤2 cm compared with 33% in patients with tumours >2 cm). Tumour size is important for postoperative outcome in anatomical or sublobar resection. In our study, the 5-year OS and DFS were better in patients with a GGO ratio ≥0.75. Sublobar resection or anatomical resection made no difference in postoperative outcome when the GGO ratio was ≥0.75. There was no significant difference in the 5-year OS between the 2 GGO ratio groups. Patients who underwent sublobar resection tended to have a better prognosis after follow-up at 60 months. Because this was a retrospective study, selective bias could have compromised the validity of the results. Therefore, we assessed the effect of tumour size for clarification. There was no difference in postoperative outcome between anatomical or sublobar resection for tumours with a GGO ratio ≥0.75, even for tumours >2 cm. Is sublobar resection indicated for a tumour larger than 2 cm with a high GGO ratio? Park and colleagues [14] reported that patients with GGO-predominant nodules of 3 cm had a fair outcome. Further studies should be conducted to clarify the surgical outcome of a GGO ratio ≥0.75 with a tumour >2 cm. In the group with a GGO ratio <0.75, patients with T1a lesions had a better prognosis than those with a tumour >2 cm. Next, we tried to determine if we would have the same results with a tumour >2 cm. The 5-year OS was no different between anatomical or sublobar resection of tumours with a GGO ratio ≥0.75. In contrast, patients with T1a lesions with a GGO ratio <0.75 who had sublobar resection had a fair prognosis. Sublobar resection should be carefully considered for patients with tumours >2 cm who have a GGO ratio <0.75 because of the poor 5-year postoperative OS.

PET scans are part of the standard workup for the assessment of lung cancer. High SUV_{max} was correlated with tumour stage, recurrence and survival [15]. A SUV_{max} ≥10 was an independent predictor of DFS and OS. The ^{18}F-fluorodeoxyglucose metabolic activity of tumours has been shown to contribute significant prognostic information for patients with solid tumours [16]. The role of SUV_{max} in GGO tumours is not clearly understood. The GGO component on CT scans reflects the pathological non-invasive component of the tumour. As the whole tumour increases in size, the SUV_{max} tends to increase because of the decrease in the GGO component [17]. The tumour disappearance ratio on CT and the SUV_{max} on PET were significantly different. Both contributed to the prognostic impact in patients with lung adenocarcinoma. In our study, a GGO ratio ≥0.75 had a significantly lower SUV_{max}. Linear regression showed a positive correlation between the GGO ratio and the SUV_{max}. However, the Pearson correlation coefficient was quite low. A SUV_{max} cut-off value of 3.3 based on our previous study did not show statistical significance in predicting postoperative recurrence [18]. In the present study, Cox regression analysis revealed that SUV_{max} (3.3) was not an independent prognostic factor for resected lung adenocarcinoma. For the GGO tumour, the SUV_{max} on the PET scan revealed no predictive value for postoperative recurrence. In addition, the internal composition of the tumour was heterogeneous. From this study, SUV_{max} does not appear to reflect the aggressiveness of the GGO lesion. Different measurements, such as the mean and

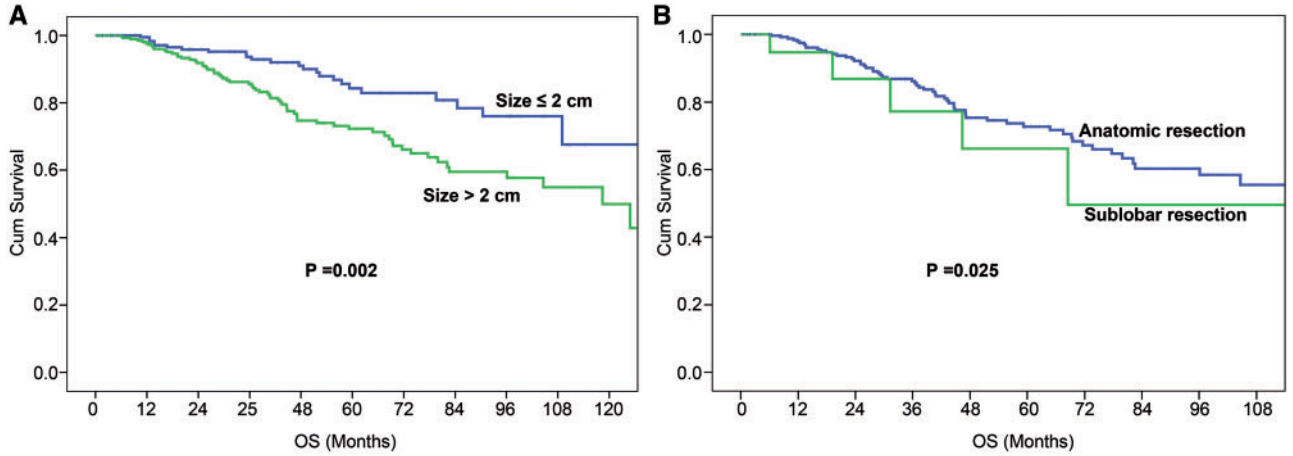

Figure 3: (**A**) OS curves of patients with tumours with a ground-glass opacity ratio <0.75. The 5-year OS was 84.3% for patients with small tumours (≤2 cm) and 72.3% for patients with large tumours (>2 cm), log-rank $P = 0.002$. (**B**) OS curves of patients with a ground-glass opacity ratio <0.75 and a tumour >2 cm who underwent sublobar or anatomical resection. The 5-year OS was 72.7% in the anatomical resection group and 66.2% for the sublobar resection group, respectively, log-rank $P = 0.025$. OS: overall survival.

Table 3: Multivariable Cox regression model for patients with lung adenocarcinoma with or without relapse

Factors	Hazard ratio (95% CI)	*P*-value
GGO ratio <0.75	3.96 (0.93–16.87)	**0.013**
Tumour >2 cm	1.15 (0.50–1.51)	0.61
Operation		
Anatomical resection	1	
Sublobar resection	1.23 (0.35–1.87)	0.62
EGFR mutation	0.91 (0.56–1.47)	0.71
SUV_{max} >3.3	1.57 (0.91–2.71)	0.11
Differentiation		
Good	1	
Moderate	2.12 (1.32–3.41)	**0.003**
Poor	3.19 (1.84–5.53)	**0.002**
LVSI	0.82 (0.44–1.52)	0.52
VPI	2.12 (0.76–5.91)	0.15
Adenocarcinoma subtype		
Acinar/lepidic	1	
Others	1.26 (0.44–1.44)	0.45
Female gender	0.94 (0.50–1.75)	0.84
Smoking (non-smoking)	1.39 (0.54–3.63)	0.50

P-values <0.05 are boldfaced.

CI: confidence interval; EGFR: epidermal growth factor receptor; GGO: ground-glass opacity; LVSI: lymphovascular space invasion; SUV_{max}: maximum standard uptake value; VPI: visceral pleural invasion.

median of the SUV, should be included to clarify the role of PET in GGO lesions.

The number of lymph nodes dissected is crucial in lung cancer surgery [18, 19]. Systemic mediastinal lymphadenectomy does not improve DFS or OS for patients with early-stage NSCLC [20]. The extent of lymph node dissection needed remains controversial for early-stage lung cancer with a GGO component. In the present study, tumours with a GGO ratio ≥0.75 did not present hilar or mediastinal nodal involvement. In patients with a GGO ratio ≥0.75, there were fewer dissected lymph nodes compared with patients who had a GGO ratio <0.75. Selective lymph node sampling did not compromise the postoperative outcome. This result was compatible with that of a published study [21]. There was no statistically significant difference in OS, local recurrence or distant metastasis between mediastinal lymph node dissection or sampling. Because this was a retrospective study, it depended on the surgeon's decision to choose either mediastinal lymph node dissection or sampling, which has biased the discussion on this issue. In conclusion, mediastinal lymph node sampling resulted in a fair outcome in GGO-predominant lung cancer. Fewer complications of systemic mediastinal dissection are encountered with advanced thoracoscopic surgery. No study has argued for the crucial role of mediastinal dissection in lung cancer surgery. With advancement in lung cancer screening, mediastinal sampling was appropriate in selected patients. The results of this study indicate that patients with tumours with a GGO ratio ≥0.75 could be considered. Further prospective studies should be conducted.

The molecular study of lung cancer has been an important issue in dealing with targeted therapy in recent years. EGFR is a transmembrane receptor tyrosine kinase involved in the signaling pathway that regulates cell proliferation, apoptosis, angiogenesis and invasion [22]. The role of the EGFR mutation as a predictive factor for tyrosine kinase inhibitor therapy in the management of NSCLC was established by the Iressa Pan-Asia Study (IPASS trial) [23]. Most EGFR mutations have been found in adenocarcinomas, women, non-smokers and Asians [24, 25]. There are no differences between tumours with or without GGO characteristics and EGFR mutations in patients with NSCLC [26]. The EGFR mutation was significantly higher in tumours of part-solid GGOs compared with pure ones. However, the proportion of GGO component and EGFR mutation was not clearly identified. In a meta-analysis, there was no significant difference between different GGO ratios (less or more than 0.5) and EGFR mutations [26]. In our study, the proportion of GGO had a reciprocal correlation with EGFR mutations. The EGFR mutation is a driver mutation that occurs in the early stage of pulmonary carcinogenesis. It is reasonable to find a high EGFR mutation rate for tumours with a GGO ratio <0.75. Although the EGFR mutation is a predictive marker for tyrosine kinase inhibitor therapy, it is not a prognostic factor in lung adenocarcinoma. Therefore, EGFR mutation status cannot be used to predict the postoperative prognosis [27]. In this study, the HR of postoperative relapse was 0.91 (95% confidence interval 0.56–1.47) for EGFR mutations. The tumours with a GGO ratio <0.75 had a high possibility of having EGFR mutations. Mutation

status cannot predict postoperative outcomes. The role of EGFR mutations and the details of their molecular mechanisms in early-stage lung adenocarcinoma should be assessed in a molecular study.

Limitations

This study did have some limitations. The sample size was small, and it was a single-institution retrospective study. Further studies combined with the histopathological characteristics of the tumours and molecular biomarkers might provide more convincing results.

CONCLUSIONS

A GGO ratio ≥0.75 proved to be of value in indicating a favourable prognosis in patients with resected lung adenocarcinoma. Sublobar resection and lymph node sampling resulted in a fair outcome regardless of tumour size. Anatomical resection is still standard for patients with tumours with a GGO ratio <0.75, size >2 cm.

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