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Original Article

Surgical result in non small cell lung cancer patients presenting with ground glass opacity predominant lesion less than 2 cm: Anatomic versus wedge resection

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ABSTRACT

Background: Image characteristics of tumor, including tumor size and component are crucial for patients' survival. Patients who presented with ground glass opacity (GGO) was found less risk of intrapulmonary lymph node metastases and good survival. However, it is difficult to get tissue prove for small GGO lesion preoperatively because of its tiny size and the accuracy of intraoperation frozen section. Some patients received another operation for anatomic resection after malignancy has been confirmed and others refused reoperation and only received wedge resection. The aim of this study was tried to compare the treatment result between anatomic and wedge resection for non small cell lung cancer patients who present as small ground glass opacity (GGO) predominant lesion in pre-operation CT.

Methods: From January 2010 to May 2014, 500 non small cell lung cancer patients who underwent tumor resection were included. Patients who presented with small GGO predominant lesion in pre-operation CT were included and medical records were reviewed retrospectively. The survival status between anatomic and wedge resection was analyzed.

Results: 37 patients received anatomic resection (Group A) and 9 patients received wedge resection (Group B). Group B showed less staple usage ($p = 0.01$) and blood loss ($p = 0.02$). From view of pathology result, only less intrapulmonary lymph nodes was dissected was identified in group B. From view of survival, similar disease free and overall survival without statistical differences in both groups.

Conclusion: Wedge resection may provide equivalent treatment result for patients who presented as peripheral GGO or GGO predominant lesions that less than 2 cm in size.

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At a glance of commentary

Scientific background on the subject

Management of benign and malignant lesion were quite different. For patients with benign lesion, sub-lobar resection is indicated for lesion removal. For patients with malignant lesion, anatomic resection with mediastinal lymph node dissection. However, it is difficult to choose proper management for patients who present as small ground glass opacity predominant lesion without pre-operative and intra-operative diagnosis. The necessity of complete anatomic resection may be considered after final pathology has been confirmed. This would lead patients to receive repeat surgery and prolong post-operation rehabilitation and suffering.

What this study adds to the field

The aim of this study is to analyze the treatment result between anatomic and wedge resection for non small cell lung cancer patients who present as small GGO predominant lesion in pre-operation CT in order to determine the necessity of complete anatomic resection.

Lung cancer is the leading cause of cancer-related death [1,2]. The incidence of cancer death in Taiwan is 39.9 per 100,000 population [3]. Because of poor prognosis in advanced lung cancer, lung cancer screening has been proposed in order to find asymptomatic lung cancer patients [4,5]. Although the lung cancer detection rate is already low [6,7], lung cancer screening could decrease cancer-related mortality in high risk patients by a further 20% [5]. However, more and more undetermined ground glass opacity lesions have been identified in lung cancer screening and need to be managed. Current guidelines utilize two characteristics, including tumor size and its solid component, as the reference for ground glass opacity (GGO) management [8–11]. However, there is no consensus on management of these GGO lesions [12]. In clinical practice, it is crucial to confirm diagnosis, ie malignant or benign, prior to treatment. However, it is difficult to obtain enough tissue because of the unsolid nature of these GGO lesions. For patients with undetermined lung lesions which present as ground glass opacity, intra-operative frozen section is the only way to confirm diagnosis. For those proven as primary lung malignancy, anatomic resection with mediastinal lymph node dissection has been the standard treatment [13] However, the reported inaccuracy of intraoperative frozen section varies from 1.58% to 12.1% [14–16]. This could be correlated to the quality of tissue biopsied during the operation, sample management prior to cryosection and the lesions' morphology [14,16,17]. Incorrect intraoperative frozen section would mean patients receive complete anatomic resection and mediastinal lymph node dissection after initial surgery [16].

For patients who present as small ground glass opacity predominant lesion without pre-operative and intra-operative diagnosis, the necessity of complete anatomic resection may

be considered after final pathology has been confirmed. The aim of this study is to analyze the treatment result between anatomic and wedge resection for non small cell lung cancer patients who present as small GGO predominant lesion in pre-operation CT in order to determine the necessity of complete anatomic resection.

Materials and methods

Patients

From January 2010 to May 2014, 500 non small cell lung cancer patients who underwent tumor resection were enrolled. 440 patients received anatomic resection and mediastinal lymph node dissection and the remainder (60 patients) received wedge resection and mediastinal lymph node sampling. In order to compare the treatment result of different surgical approaches for patients presenting with ground glass opacity predominant lesion less than 2 cm, characteristics of chest tomography, pathology and clinical data were collected and reviewed retrospectively. Only patients who presented as GGO predominant lesion less than 2 cm and who received tumor resections were included for further analysis. The exclusion algorithm is shown in Fig. 1. The study was approved by the Institutional Review Board of Chang Gung Medical Foundation under the IRB number 103–5631B.

Pre-operation evaluation

Image survey of disease severity and pulmonary reserve were included in patients' pre-operation evaluation. For patients with confirmed malignancy, complete disease severity survey was done for evaluation of resectability. Chest CT was done in order to clarify tumor size and location, mediastinal lymph involvement status and possible liver or adrenal metastases.

Positron emission-computed tomography (PET-CT) was done for extrapulmonary metastases survey and brain magnetic resonance imaging (MRI) or CT were arranged to exclude brain metastases. For those who presented with possible N3 lesion, ie. contralateral mediastinal or ipsilateral neck lymph node, endobronchial ultrasonography or excision biopsy was done.

For those without preoperative diagnosis, resectability survey, including chest CT, PET-CT and brain MRI or CT were arranged. All patients received pulmonary reserve evaluation and spirometry was arranged in order to confirm adequate pulmonary reserve. Cardiac echo and consultation with an anesthesiologist were reserved for patients with multiple comorbidities.

Operation and post-operation adjuvant therapy

Patients who presented as resectable disease with adequate pulmonary reserve underwent anatomic resection and mediastinal lymph node dissection. Patients who could not confirm diagnosis by pre-operation or intra-operation frozen reserve received wedge resection and mediastinal lymph node sampling first and wait for final pathology. Patients who refused completion anatomic resection was enroll into wedge resection

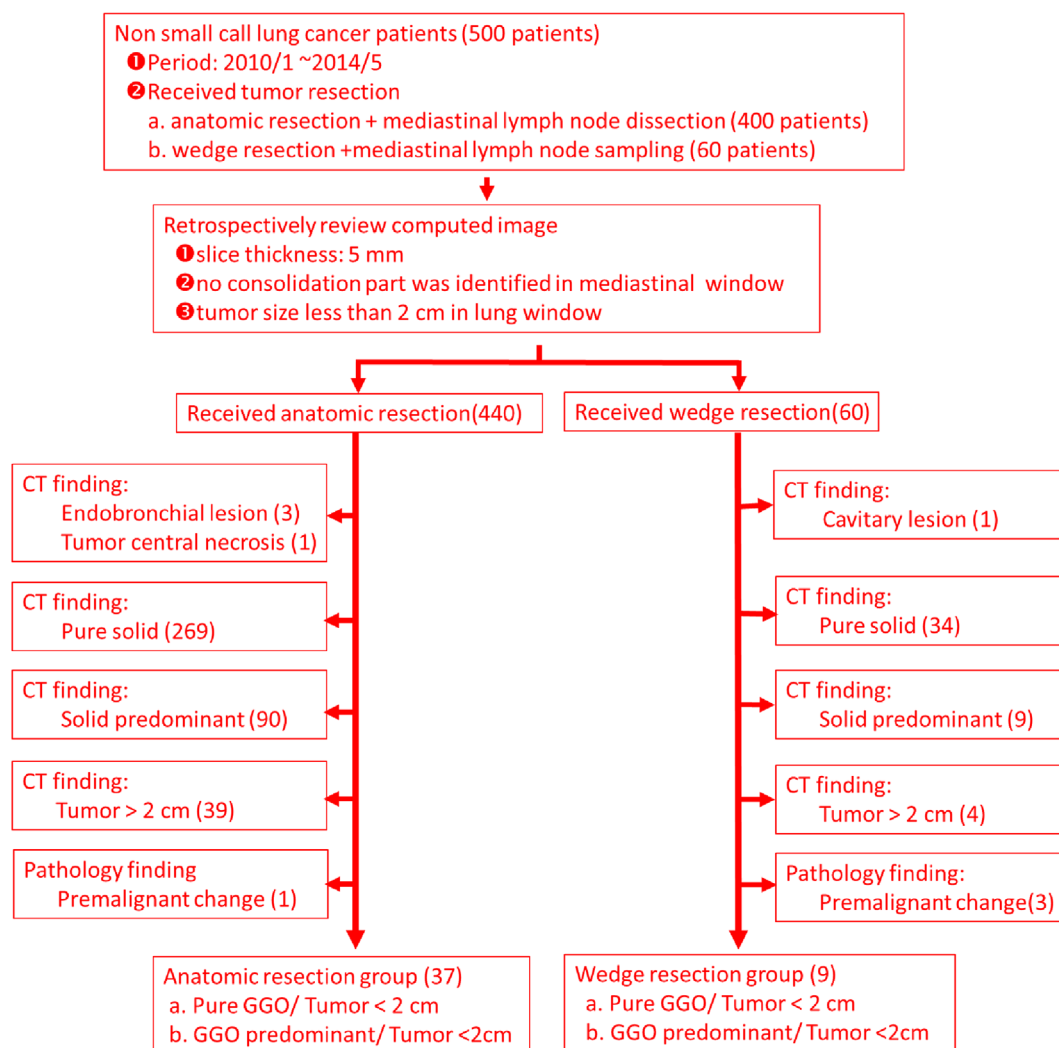


Fig. 1 Inclusion and exclusion criteria.

group. All procedures were intended to be performed by video-assisted thoracoscopic surgery (VATS) technique. Only patients with huge tumor size, severe adhesion, or vessel injuries were shifted to thoracotomy to complete resection. Pathologic staging was based on the 7th AJCC TNM staging system. Post-operative adjuvant therapy was given corresponding to the pathologic stage and recommendations of the NCCN guideline.

Follow up and surveillance

All patients underwent regular surveillance in the outpatient service every 3 months. Chest CT, from lower neck to upper abdomen, was utilized as a surveillance tool in 3–6 month-intervals.

The slice thickness of chest CT was 5 mm and all images were reviewed by clinical practitioners, including physicians, surgeons and radiologists. The definition of last follow up date was the last date that patients come back to the outpatient service. The relapse date was defined as the date of disease relapse, as confirmed by image or repeat biopsy. The expiry date was defined as date of death or critical discharge against advice. The disease-free survival period

was defined as the period between diagnostic date (1st pathology or image confirmation date) and date of disease relapse. The overall survival period was defined as lasting from diagnostic date (1st pathology or image confirmation date) to last OPD or expiry date.

Statistics

All collected clinico-pathologic factors were evaluated by univariate analysis. Categorical variables were compared using chi-squared tests and Fisher's exact test while continuous variables were compared using the two sample t-test. Survival status was represented with a Kaplan–Meier curve and compared using the log-rank test. A p -value < 0.05 was considered statistically significant. All analyses were performed using SAS, version 9 (SAS Institute, Cary, NC).

Results

From January 2010 to May 2014, 500 patients underwent tumor resection. Only patients who presented as GGO predominant

Table 1 Clinical characteristics.

Variables (Mean ± SD)/Mean (%)	Group A = 37	Group B = 9	p-value
Age	58.8 ± 10.8	59.9 ± 9.9	0.89
Gender Female	24 (64.9)	7 (70.0)	0.69
Body height	158.8 ± 8.2	159.4 ± 9.9	0.95
Body weight	59.5 ± 10.5	62.6 ± 9.4	0.55
FEV ₁	2.1 ± 0.5	2.1 ± 0.6	0.81
FVC	2.7 ± 0.6	2.5 ± 0.7	0.65
FEV ₁ /FVC	0.8 ± 0.1	0.8 ± 0.03	0.08
CT finding Tumor size	1.3 ± 0.4	1.1 ± 0.5	0.36
CT tumor component			0.69
Pure GGO	24 (64.9)	7 (77.8)	
GGO predominant	13 (35.2)	2 (22.2)	
GGO location			0.08
Peripheral	27	9	
Central	10	0	
Co-morbidities			0.38
Cardiovascular	3 (8.1)	0	0.48
Pulmonary	2 (5.4)	0	0.62
Gastrointestinal	1 (2.7)	0	–
Renal	0	0	0.62
Wound	1 (2.7)	0	
VATS/Thoracotomy			0.62
VATS	36 (97.3)	9 (100)	
Thoracotomy	1 (2.7)	0	
Total staples	9.4 ± 3.5	5.4 ± 1.6	0.01
Blood Loss (ml)	49.9 ± 47.2	10.00 ± 0	0.02
Operation time (min)	205.8 ± 57.7	245.4 ± 62.6	0.16
Post OP days	6.7 ± 4.9	5.4 ± 0.9	0.82
Total hospital days	10.0 ± 6.4	9.0 ± 5.7	0.48
Median follow up period	1303.3 ± 455.7	1303.2 ± 314.6	0.97

lesion less than 2 cm and received tumor resections were included in further analysis. 37 patients who presented as GGO predominant lesions less than 2 cm and underwent anatomic resection and mediastinal lymph node dissection were assigned to the anatomic resection group. 9 patients who presented as GGO predominant lesions less than 2 cm and underwent wedge resection and mediastinal lymph node sampling were assigned to the wedge resection group. The mean ages of the anatomic and wedge resection groups were 58.84 ± 10.80 and 59.89 ± 9.92 years, respectively. Both groups were predominantly female with similar body size and pre-operative pulmonary reserve was identified. The mean tumor sizes presenting in CT of the anatomic and wedge resection groups were 1.27 ± 0.43 and 1.12 ± 0.45 cm, respectively. Most resections were done by video-assisted thoracoscopic surgery and only one patient underwent thoracotomy. Similar presentations were identified in both groups except for a lower staple number ($p = 0.01$) and blood loss ($p = 0.02$) in the wedge resection group. Similar post-operative hospital stay was also identified for both groups [Table 1].

From the pathology point of view, all patients in both groups were confirmed as adenocarcinoma. Tumor sizes in the anatomic and wedge resection groups were 1.26 ± 0.48 and 1.14 ± 0.44 cm, respectively ($p = 0.58$). In the anatomic resection group, one patient was identified as visceral pleural invasion ($p = 0.62$) and 5 patients were found with

Table 2 Pathologic characteristics.

Pathologic characteristics	Group A = 37	Group B = 9	p-value
Cell type			–
Adenocarcinoma	37 (100)	9 (100.00)	
Predominant component			0.23
Bronchioalveolar	7 (18.9)	1 (11.1)	
Acinar	14 (37.8)	7 (77.8)	
Papillary	7 (18.9)	1 (11.1)	
Micropapillary	7 (18.9)	0 (0)	
Solid	2 (5.4)	0 (0)	
Pathologic tumor size	1.3 ± 0.5	1.1 ± 0.4	0.58
Visceral pleural invasion	1 (2.70)	0	0.62
Angiolymphatic invasion	1 (2.7)	1 (11.1)	0.36
Grade			0.07
Well differentiated	32 (86.5)	9 (100.00)	
Moderately differentiated	5 (13.5)	0 (0)	
Lymph node status			
Non-metastatic LN No.	18.5 ± 0.70	9.1 ± 7.9	0.01
Total LN No.	18.6 ± 8.7	9.1 ± 7.9	0.01
Metastatic N1 LN No.	0.02 ± 0.2	0 ± 0	0.69
Non-metastatic N1 LN No.	5.1 ± 3.1	0.8 ± 1.0	0.0002
Metastatic N2 LN No.	0.03 ± 0.2	0 ± 0	0.69
Non-metastatic N2 LN No.	13.2 ± 7.3	8.4 ± 7.2	0.10
Pathologic stage			0.71
stage 1a	32 (86.5)	9 (100)	
stage 1b	1 (2.70)	–	
stage 2a	–	–	
stage 2b	2 (5.4)	–	
stage 3a	2 (5.4)	–	

moderate tumor cell differentiation ($p = 0.07$), however, this was not statistically significant in either group. Since patients in both groups were adenocarcinoma, the predominant cell components were also compared. In the wedge resection group, neither micropapillary nor solid components were identified. Only marginally significant differences were identified in cell components between anatomic and wedge resection group. ($p = 0.04$) In addition, fewer dissected intrapulmonary ($p = 0.0002$) and total lymph nodes ($p = 0.01$) were identified in the wedge resection group. From the point of view of pathologic staging, all patients in the wedge resection group presented as stage Ia. 5 patients in the anatomic resection group were confirmed with a more advanced stage, including stages 1b, 2b and 3a [Table 2]. From the point of view of disease free survival, patients who received anatomic resection showed inferior disease-free survival, which may be due to 5 patients whose pathologic stage was greater than stage 1a [Fig. 2A]. However, excellent disease free survival was confirmed in both groups after excluding patients who presented with greater than pathologic stage 1a [Fig. 2B]. From the point of view of overall survival, only one patient in the anatomic resection group died due to nasopharyngeal carcinoma progression. Similar survival curves were identified in both groups [Fig. 3A]. For patients whose image presented as GGO predominant lesion less than 2 cm and pathologic stage was confirmed as

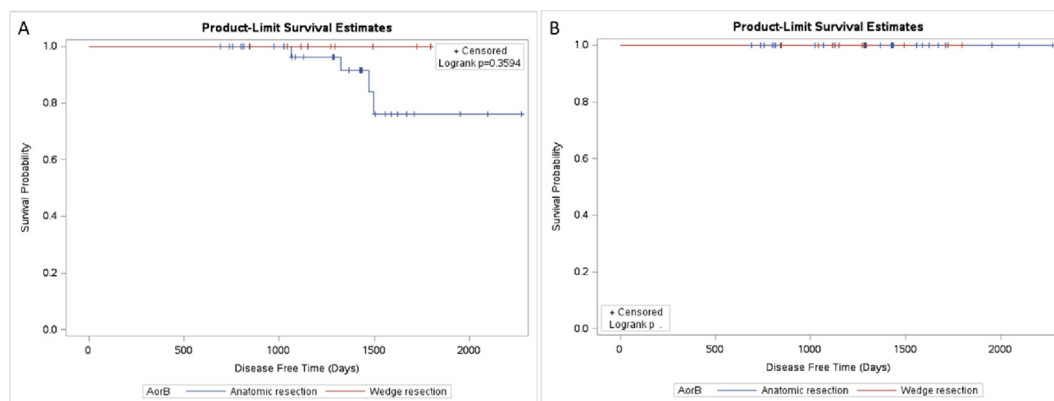


Fig. 2 Disease free survival (A) Patient presented as GGO predominant lesion less than 2 cm (Clinical 1a) [Lobectomy (37) versus wedge resection (9)]. (B) Pathologic 1a patients who presented as GGO predominant lesion less than 2 cm [Lobectomy (31) versus wedge resection (9)] 6 patients of anatomic resection group were excluded. 5 patients were excluded due to pathologic stage greater than Ia, while one was excluded after he died due to nasopharyngeal carcinoma progression. Due to no disease relapse that correlated to lung cancer, both groups show identical disease free survival and no p value was obtained.

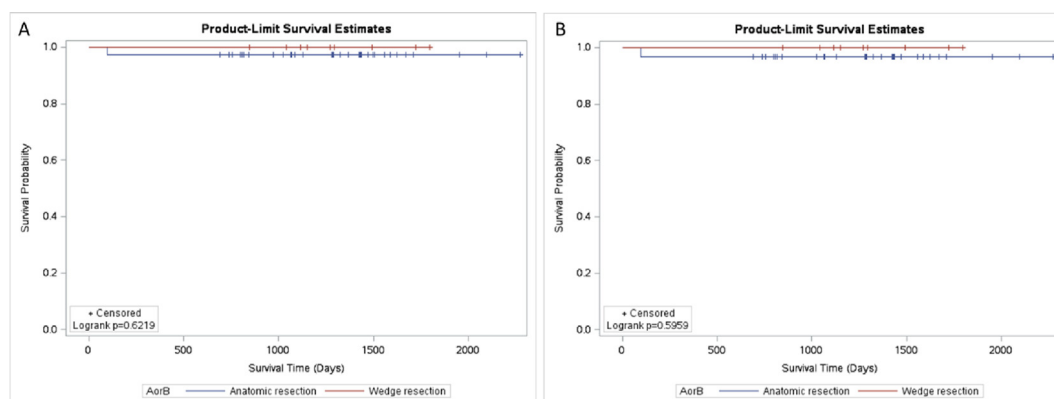


Fig. 3 Overall survival. (A) Patient presented as GGO predominant lesion less than 2 cm (Clinical 1a). [Lobectomy (37) versus wedge resection (9)]. (B) Pathologic 1a patients who presented as GGO predominant lesion less than 2 cm [Lobectomy (32) versus wedge resection (9)] 6 patients of anatomic resection group were excluded. 5 patients were excluded due to pathologic stage greater 1a.

pathologic stage 1a, similar overall survival curves were identified in both groups [Fig. 3B].

Discussion

Lung cancer remains the leading cause of cancer-related death. For patients with more advanced disease, ie. stages 3a and 4, multimodal therapies for disease control are crucial [18,19]. From the literature review, only patients presenting with earlier disease have better disease-free and overall survival. Therefore, the earlier the stage of lung cancer is identified, the better the disease-free survival to be expected. This is the reason that lung cancer screening has been proposed and carried out for high risk patients in recent years [4,5]. However, more and more small ground glass opacity lesions were identified in lung cancer screening. These lesions make it difficult to get pre-operation tissue samples, due to their small size. Intra-operative frozen section is the only way to get a definite diagnosis for these patients. However, the reported inaccuracy of

intra-operative frozen section varies from 1.58 to 12.1% [14–16]. This might mean patients receive completion anatomic resection and mediastinal lymph node dissection after initial surgery [16]. However, the possibility of mediastinal lymph node metastases is low and the necessary [17] for completion anatomic resection and mediastinal lymph node dissection need further investigation. Our study was focused on the issue and tried to compare the treatment result between wedge resection and lobectomy in patients whose lesion presented as GGO or GGO predominant lesion that less than 2 cm.

From the literature review, sublobar resection leads to higher risk for disease relapse because of inadequate lymph node dissection [20–27]. Wedge resection could not approach the lymph node that located around segmental bronchus and vessel and only hilar lymph node could be sampled. In our study, we tried to analyze the treatment efficacy of wedge resection based on clinical and pathologic characteristics. All patients were non small cell cancer patients and received tumor resection, and tumor components were reviewed. This excludes confounding caused by benign lesions or

pre-malignant change, such as atypical adenomatous hyperplasia. In the lobectomy group, we identified patients who presented with GGO predominant lesion less than 2 cm still had a risk of lymph node metastases (10.8%; 4/37) and visceral pleura invasion (2.7%; 1/37). In addition, as long as no lymph node metastases were found in the final pathologic examination, excellent disease-free survival was identified. Only one patient died because of nasopharyngeal cancer progression. In the wedge resection group, patients could not be identified by definite diagnosis during operation and only wedge resection and mediastinal lymph node sampling were done. These patients showed excellent disease-free and overall survival compared with the lobectomy group. The clinical characteristics between lobectomy and wedge resection group revealed less staple usage ($p = 0.01$) and blood loss ($p = 0.02$). From the point of view of cell type, all patients in both groups were adenocarcinoma with similarly differentiated status. However, the analysis of cell components were not done because of limited cases and all patient presented as multiple cell components. The pathologic characteristics between lobectomy and wedge resection group were similar except for fewer total non metastatic lymph nodes ($p = 0.01$), total lymph nodes ($p = 0.01$) and non metastatic intrapulmonary lymph nodes ($p = 0.0002$). This difference was only reflected in the difference of both operation methods in range of mediastinal lymph node dissection.

Several studies have shown that sublobar resection is equivalent to lobectomy from the pathologic point of view [28–30]. However, these studies were conducted in different clinical settings, including large tumor size, heterogeneity of cell type and different definition of sublobar resection. In addition, these studies did not incorporate pre-operation tumor image and could not clearly clarify the efficacy of specific procedures in lung cancer patients with specific presentations. Cho et al. found that wedge resection may play a role in clinical stage Ia lung cancer patients who present with a consolidation-tumor ratio less than 0.25 [31]. However, the result could not explain the survival impact of lymph node metastases. From the literature review, this remains a controversial issue, with some articles showing no lymph node metastases in sub-centimeter tumor [32,33] and others revealing 7–15% nodal metastases [34,18]. In this study, all clinical and pathologic characteristics were included and wedge resection was found to have equivalent disease free and overall survival in adenocarcinoma patients with GGO predominant lesions less than 2 cm located in peripheral lung parenchyma. For these patients whose diagnosis cannot be confirmed by pre-operative biopsy and intra-operative frozen section, surgeon might adopt a close follow strategy in the place with anatomic resection if patients refused to receive secondary operation.

Some limitations remain. First, this is a retrospective study with small sample size. However, the highly homogeneous study population leads to a more convincing result, despite the small sample size. Second, only adenocarcinoma was included in this study. Other cell types, such as squamous cell carcinoma were not analyzed in this study. This may be correlated to different image presentation of these cell types and further investigation is warranted. Third, cell components of adenocarcinoma were not further analyzed to

identify the survival impact of more invasive cell components, such micropapillary and solid pattern [35–37]. Further investigation may be warranted in order to clarify their survival impact. Although these limitations remain, our study has revealed that wedge resection may provide equivalent survival result for patients who presented as peripheral GGO or GGO predominant lesions that less than 2 cm in size.

Conclusion

Image characteristics of tumor, including tumor size and component are crucial for patients' survival. Patients with lung lesions which were identified as ground glass opacity (GGO) in CT was identified less risk of intrapulmonary lymph node metastases and good survival. Wedge resection may provide equivalent treatment result for patients who presented as peripheral GGO or GGO predominant lesions that less than 2 cm in size.

Conflicts of interest

The authors declared no conflicts of interest.

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